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Tetrahedron

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Applications of catalysis in academia and industry

Guest editor: Michael J. Krische

University of Texas at Austin, Chemistry & Biochemistry Department, 1 University Station A5300, Austin, TX 78712-0165, USA

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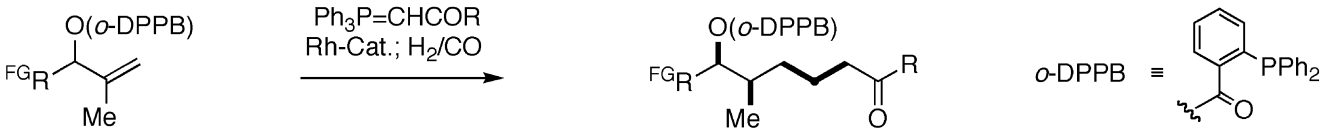

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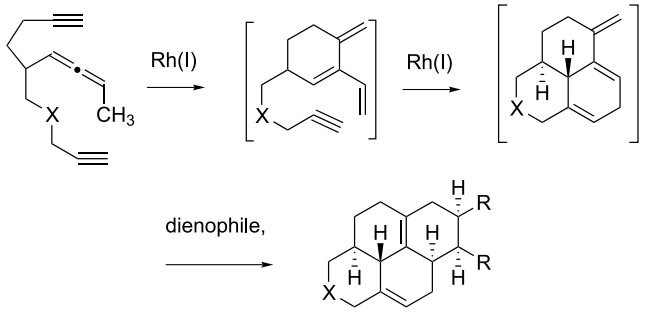

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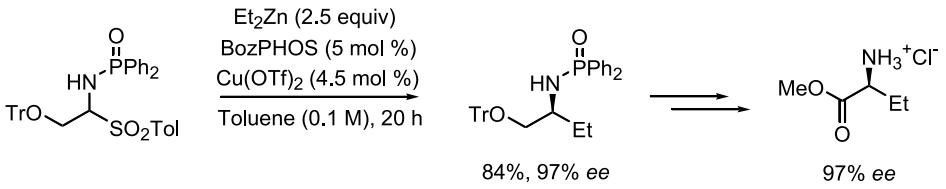
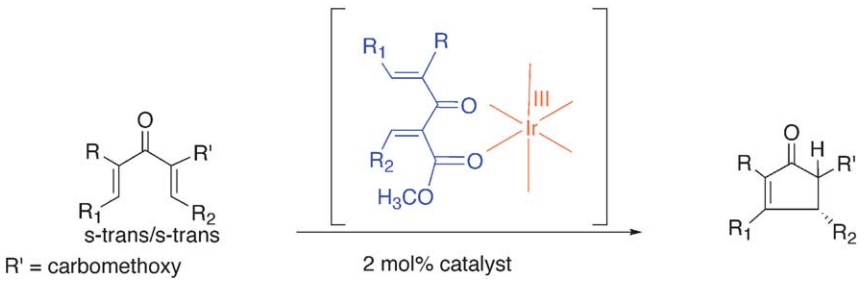
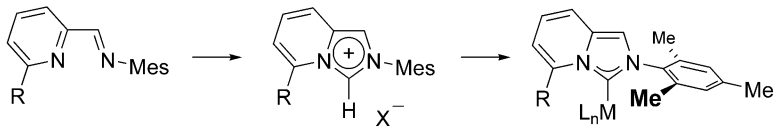
Jean-Nicolas Desrosiers, Alexandre Côté and André B. Charette*



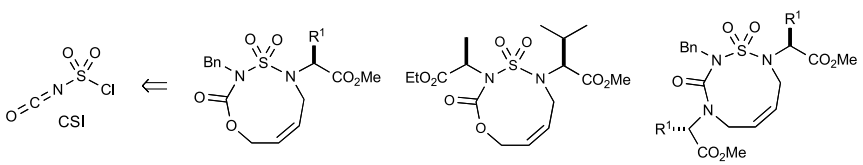
Preorganization in the Nazarov cyclization: the role of adjacent coordination sites in the highly Lewis acidic catalyst [IrMe(CO)(dppe)(DIB)](BAr$^{f}_{4}$)$_2$ **pp 6193–6206**
Mesfin Janka, Wei He, Alison J. Frontier,* Christine Flaschenriem and Richard Eisenberg*



Imidazo[1,5-*a*]pyridine-3-ylidenes—pyridine derived N-heterocyclic carbene ligands **pp 6207–6217**
Christian Burstein, Christian W. Lehmann and Frank Glorius*

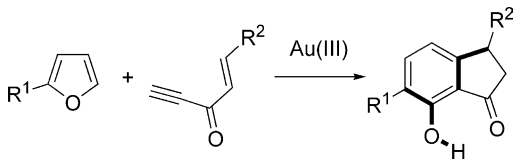


Synthesis of cyclic sulfamoyl carbamates and ureas via ring-closing metathesis **pp 6218–6230**
Joseph M. Dougherty, María Jiménez and Paul R. Hanson*



Synthetic routes to a diverse set of cyclic sulfamoyl carbamates and ureas are reported. These routes utilize 3-component coupling, Mitsunobu alkylation, and ring-closing metathesis using the second-generation Grubbs catalyst to achieve the synthesis of the target *S*-heterocyclic compounds. Cyclic *S*-heterocycles ranging from 9- to 11-membered rings have been obtained.

Gold catalysis: five new bonds by a domino hydroarylation/cycloisomerization **pp 6231–6236**
A. Stephen K. Hashmi* and Li Grundl



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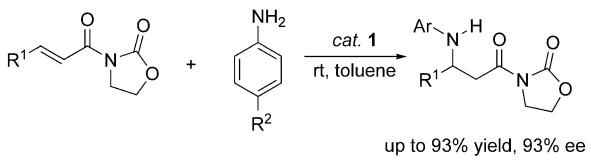
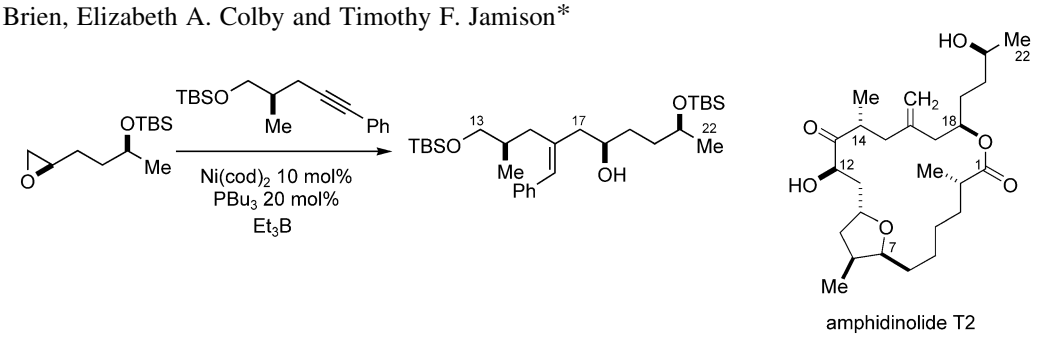
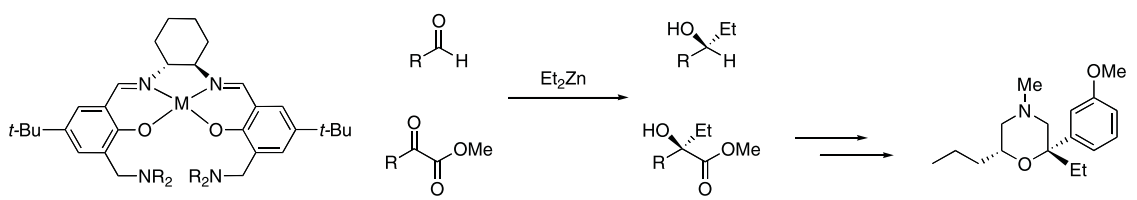
Kelin Li, Pim Huat Phua and King Kuok (Mimi) Hii*



Synthesis of C13–C22 of amphidinolide T2 via nickel-catalyzed reductive coupling of an alkyne and a terminal epoxide **pp 6243–6248**
Karen C. O'Brien, Elizabeth A. Colby and Timothy F. Jamison*

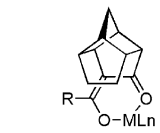


Mechanism and scope of salen bifunctional catalysts in asymmetric aldehyde and α-ketoester alkylation **pp 6249–6265**
Michael W. Fennie, Erin F. DiMauro, Erin M. O'Brien, Venkatachalam Annamalai and Marisa C. Kozlowski*

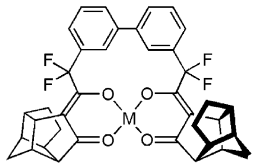


Chiral β-diketonate ligands of 'pseudo planar chiral' topology: enantioselective synthesis and transition metal complexation pp 6266-6275
Brian M. Bocknack, Long-Cheng Wang, Freddie W. Hughes and Michael J. Krische*

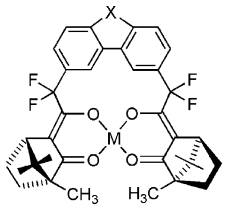
A practical enantioselective synthesis of chiral β-diketonate ligands **1a**–**1d**, which are of 'pseudo planar-chiral' topology, is described. Additionally, the first chiral bis(diketonates) **2a**–**2c**, ligands of C_2-symmetry that are isoelectronic with respect to related salen ligand systems, have been prepared. Protocols for the metallation of ligands **1a**–**1d**, **2b** and **2c** are reported.



1a, R = Ph 1c, R = CF_3
1b, R = ^{t}Bu 1d, R = $(CF_2)_3CF_3$

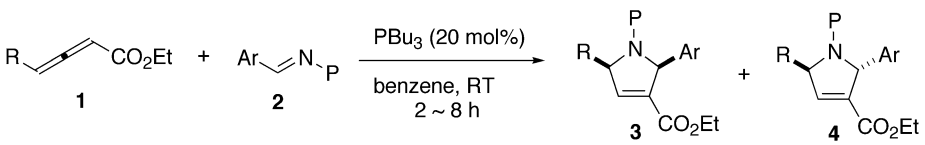


bis(diketonate) 2a



bis(diketonate) 2b, X = H2
bis(diketonate) 2c, X = O

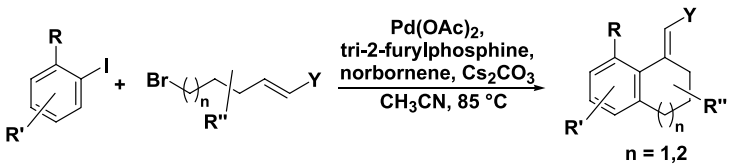
A highly diastereoselective synthesis of 3-carbethoxy-2,5-disubstituted-3-pyrrolines by phosphine catalysis pp 6276–6282
Xue-Feng Zhu, Christopher E. Henry and Ohyun Kwon*



R = alkyl, aryl
P = Ts, *p*-Ns, SES

yield = 89 ~ 100 %
cis/trans = 10:1 ~ 100:0

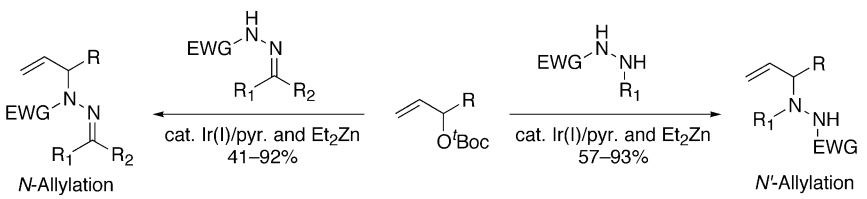
Palladium-catalyzed sequential alkylation–alkenylation reactions: application towards the synthesis of polyfunctionalized fused aromatic rings pp 6283–6297
Dino Alberico, Jean-François Paquin and Mark Lautens*



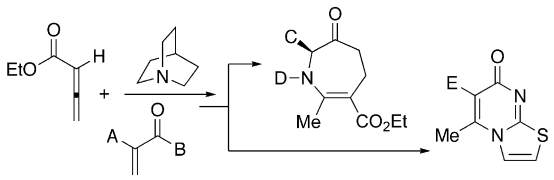
n = 1,2

The synthesis of polyfunctionalized fused aromatic carbo- and heterocycles from aryl iodides and bromoenoates via a tandem palladium-catalyzed aromatic substitution intramolecular Heck sequence is reported. Using $Pd(OAc)_2$ and tri-2-furylphosphine in the presence of norbornene and Cs_2CO_3 in CH_3CN at 85 °C gave a variety of functionalized bi- and tricyclic fused aromatic rings in good yield.

Iridium-catalyzed selective *N*-allylation of hydrazines pp 6298–6308
Robert Matunas, Amy J. Lai and Chulbom Lee*

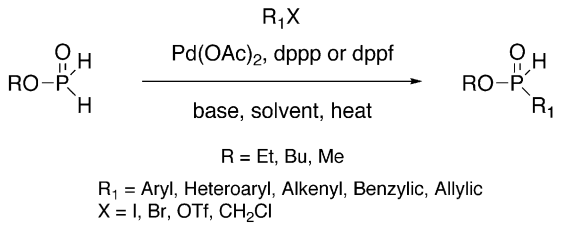


Diversity-generation from an allenoate–enone coupling: syntheses of azepines and pyrimidones from common precursors pp 6309–6314
Catherine A. Evans, Bryan J. Cowen and Scott J. Miller*



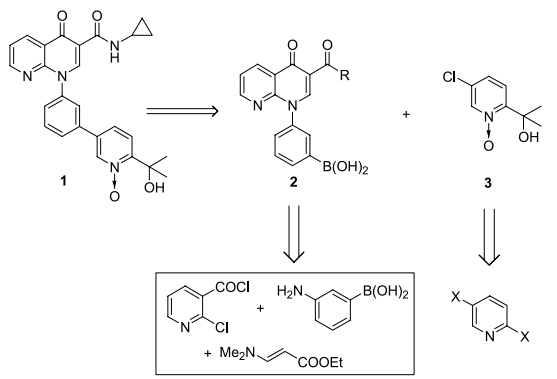
Palladium-catalyzed phosphorus–carbon bond formation: cross-coupling reactions of alkyl phosphinates with aryl, heteroaryl, alkenyl, benzylic, and allylic halides and triflates pp 6315–6329
Karla Bravo-Altamirano, Zhihong Huang and Jean-Luc Montchamp*

The palladium-catalyzed cross-coupling of alkyl phosphinates with various electrophiles is presented. Various H-phosphinate esters can be prepared conveniently in a single step. The reactions of alkenyl and allylic halides are studied for the first time. Some mechanistic aspects of the reaction are also discussed.



Practical application of new catalytic methods: a concise synthesis of a potent PDE IV inhibitor pp 6330–6336
Jennifer Albaneze-Walker,* Jerry A. Murry, Arash Soheili, Scott Ceglia, Shawn A. Springfield, Charles Bazaral, Peter G. Dormer and David L. Hughes

An efficient synthesis of a potent PDE IV inhibitor **1** is described. The synthesis is highlighted by two practical and efficient catalytic reactions: a highly selective catalytic palladium mediated carbonylation of the pyridine side chain and an efficient palladium-catalyzed Suzuki–Miyaura coupling of a chloropyridine-*N*-oxide.



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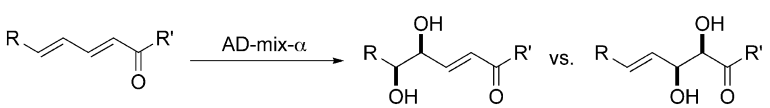
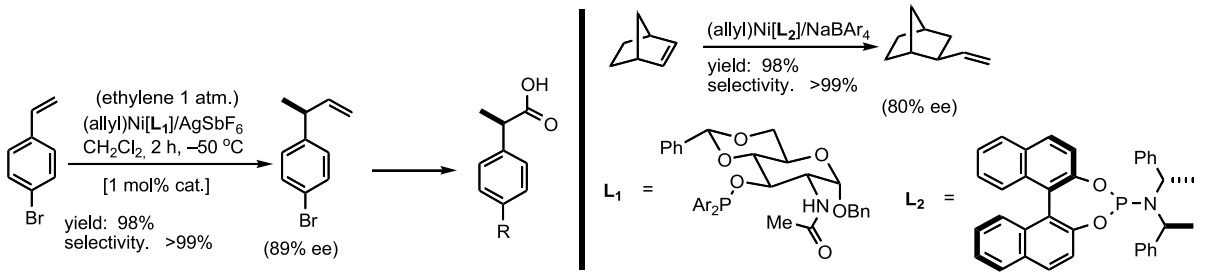
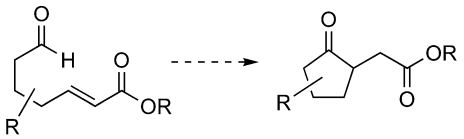
Yan Zhang and George A. O'Doherty*



Tunable phosphinite, phosphite and phosphoramidite ligands for the asymmetric hydrovinylation reactions pp 6352–6367
Haengsoon Park, Ramaiah Kumareswaran and T. V. RajanBabu*



The effect of pre-existing stereocenters in the intramolecular asymmetric Stetter reaction pp 6368–6378
Nathan T. Reynolds and Tomislav Rovis*



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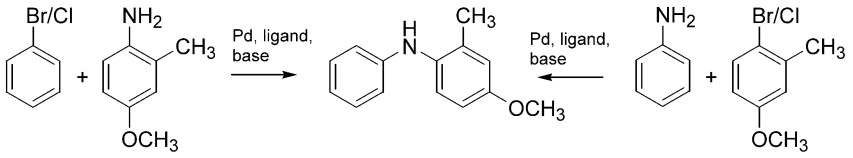
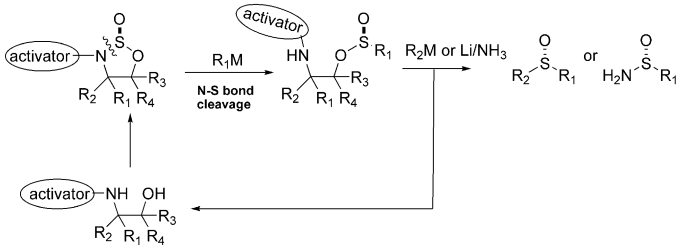
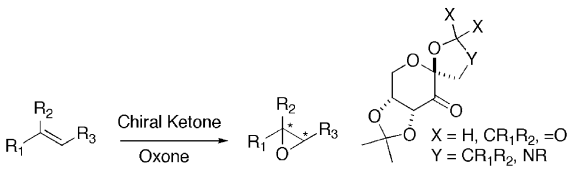
Ulrich Scholz* and Björn Schlummer



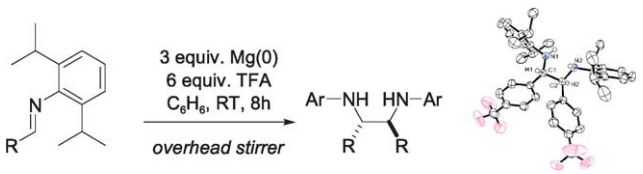
Practical and highly stereoselective technology for preparation of enantiopure sulfoxides and sulfinamides utilizing activated and functionally differentiated *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide derivatives pp 6386–6408
Zhengxu Han,* Dhileepkumar Krishnamurthy, Paul Grover, Q. Kevin Fang, Xiping Su, H. Scott Wilkinson, Zhi-Hui Lu, Daniel Magiera and Chris H. Senanayake*



Exploring structural effects of ketone catalysts on asymmetric epoxidation of olefins **pp 6409–6417**
Zackary Crane, David Goeddel, Yonghong Gan and Yian Shi*

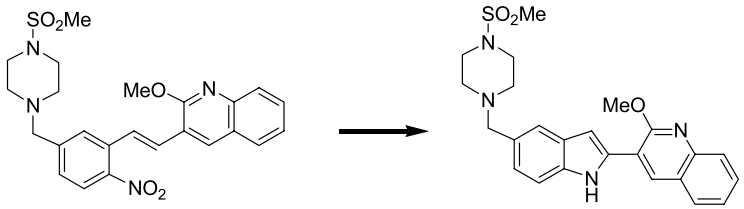


Intermolecular reductive coupling of hindered *N*-aryl imines towards the modular synthesis of chiral *N*-heterocyclic carbenes **pp 6418–6424**
Gregory J. Mercer, Megan Sturdy, David R. Jensen and Matthew S. Sigman*

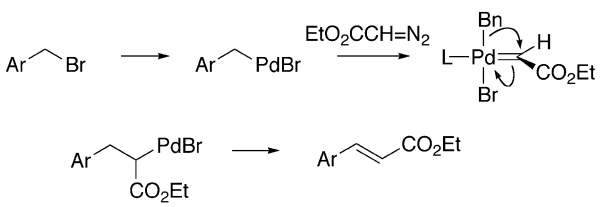


A highly active catalyst for the reductive cyclization of *ortho*-nitrostyrenes under mild conditions **pp 6425–6437**
Ian W. Davies,* Jacqueline H. Smitrovich, Rick Sidler, Chuanxing Qu, Venita Gresham and Charles Bazaral

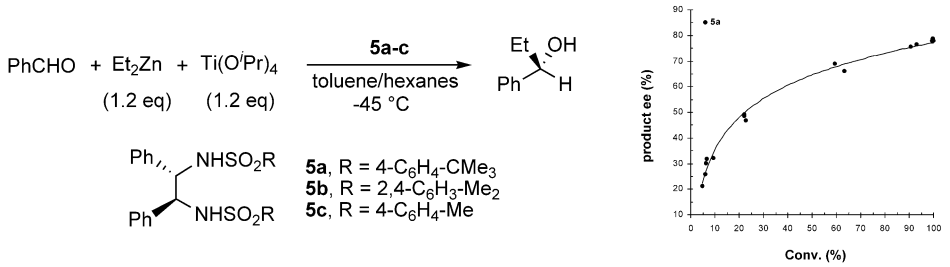
A mild and efficient method for the palladium-catalyzed reductive cyclization of *ortho*-nitrostyrenes to afford indoles is reported. Treatment of *ortho*-nitrostyrenes **3** with 0.1 mol% palladium (II) trifluoroacetate [$Pd(TFA)_2$] and 0.7 mol% 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) in DMF at 15 psig CO and 80 °C gives indole **2** in 98% yield. The mechanism of the reaction was explored in detail.



Palladium-catalyzed carbene insertion into benzyl bromides **pp 6438–6441**
Kevin L. Greenman and David L. Van Vranken*

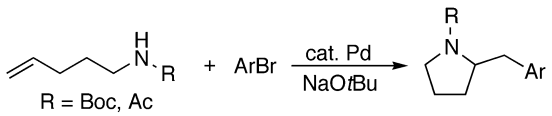


Dramatic catalyst evolution in the asymmetric addition of diethylzinc to benzaldehyde **pp 6442–6446**
Anna M. Costa, Celina García, Patrick J. Carroll and Patrick J. Walsh*

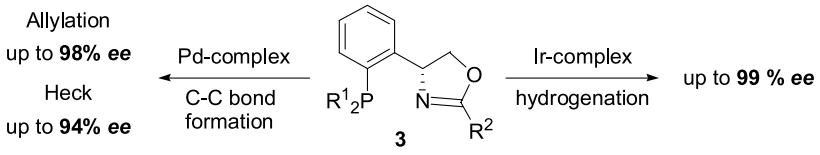


Large changes in enantioselectivity are observed during the asymmetric addition of diethylzinc to benzaldehyde catalyzed by bis(sulfonamide) ligands **5a–c**.

Stereoselective synthesis of *N*-protected pyrrolidines via Pd-catalyzed reactions of γ-(*N*-acylamino) alkenes and γ-(*N*-Boc-amino) alkenes with aryl bromides **pp 6447–6459**
Myra Beaudoin Bertrand and John P. Wolfe*



A new class of readily available and conformationally rigid phosphino-oxazoline ligands for asymmetric catalysis **pp 6460–6471**
Duan Liu, Qian Dai and Xumu Zhang*



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Instructions to contributors **pp III–VI**

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Hypophosphorous compounds ($ROP(O)H_2$) can be used in novel palladium-catalyzed phosphorus-carbon bond-forming reactions. The picture shows examples of H-phosphinic acid products obtained through hydrophosphinylation (in red) or cross-coupling (in blue), and the two corresponding catalytic cycles. *Tetrahedron* **2005**, *61*, 6315–6329.

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts. Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei Compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch

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Tetrahedron Symposia-in-Print

Series Editor
Professor H. H. Wasserman, Department of Chemistry, Yale University, P.O. Box 208107, New Haven, CT 06520-8107, U.S.A.

Tetrahedron Symposia-in-Print comprise collections of original research papers covering timely areas of organic chemistry.

Each symposium is organized by a Symposium Editor who will invite authors, active in the selected field, to submit original articles covering current research, complete with experimental sections. These papers will be rapidly reviewed and processed for publication by the Symposium Editor under the usual refereeing system.

Authors who have not already been invited, and who may have obtained recent significant results in the area of the announced symposium, may also submit contributions for Editorial consideration and possible inclusion. Before submitting such papers authors should send an abstract to the Symposium Editor for preliminary evaluation. Firm deadlines for receipt of papers will allow sufficient time for completion and presentation of ongoing work without loss of the freshness and timeliness of the research results.

Symposia-in-Print—already published

1. Recent trends in organic photochemistry, Albert Padwa, Ed. *Tetrahedron* **1981**, *37*, 3227–3420.
2. New general synthetic methods, E. J. Corey, Ed. *Tetrahedron* **1981**, *37*, 3871–4119.
3. Recent developments in polycyclopentanoid chemistry, Leo A. Paquette, Ed. *Tetrahedron* **1981**, *37*, 4357–4559.
4. Biradicals, Josef Michl, Ed. *Tetrahedron* **1982**, *38*, 733–867.
5. Electron-transfer initiated reactions, Gary B. Schuster, Ed. *Tetrahedron* **1982**, *38*, 1025–1122.
6. The organic chemistry of animal defense mechanisms, Jerrold Meinwald, Ed. *Tetrahedron* **1982**, *38*, 1853–1970.
7. Recent developments in the use of silicon in organic synthesis, Hans Reich, Ed. *Tetrahedron* **1983**, *39*, 839–1009.
8. Linear tetrapyrroles, Ray Bonnett, Ed. *Tetrahedron* **1983**, *39*, 1837–1954.
9. Heteroatom-directed metallations in heterocyclic synthesis, George R. Newkome, Ed. *Tetrahedron* **1983**, *39*, 1955–2091.
10. Recent aspects of the chemistry of β-lactams, J. E. Baldwin, Ed. *Tetrahedron* **1983**, *39*, 2445–2608.
11. New spectroscopic techniques for studying metabolic processes, A. I. Scott, Ed. *Tetrahedron* **1983**, *39*, 3441–3626.
12. New developments in indole alkaloids, Martin E. Kuehne, Ed. *Tetrahedron* **1983**, *39*, 3627–3780.
13. Recent aspects of the chemistry of nucleosides, nucleotides and nucleic acids, Colin B. Reese, Ed. *Tetrahedron* **1984**, *40*, 1–164.
14. Bioorganic studies on receptor sites, Koji Nakanishi, Ed. *Tetrahedron* **1984**, *40*, 455–592.
15. Synthesis of chiral non-racemic compounds, A. I. Meyers, Ed. *Tetrahedron* **1984**, *40*, 1213–1418.
16. Control of acyclic stereochemistry, Teruaki Mukaiyama, Ed. *Tetrahedron* **1984**, *40*, 2197–2344.
17. Recent aspects of anthracyclinone chemistry, T. Ross Kelly, Ed. *Tetrahedron* **1984**, *40*, 4537–4794.
18. The organic chemistry of marine products, Paul J. Scheuer, Ed. *Tetrahedron* **1985**, *41*, 979–1108.
19. Recent aspects of carbene chemistry, Matthew Platz, Ed. *Tetrahedron* **1985**, *41*, 1423–1612.
20. Recent aspects of singlet oxygen chemistry of photooxidation, Isao Saito and Teruo Matsuura, Eds. *Tetrahedron* **1985**, *41*, 2037–2236.
21. Synthetic applications of dipolar cycloaddition reactions. Wolfgang Oppolzer, Ed. *Tetrahedron* **1985**, *41*, 3447–3568.
22. Selectivity and synthetic applications of radical reactions, Bernd Giese, Ed. *Tetrahedron* **1985**, *41*, 3887–4302.
23. Recent aspects of organoselenium chemistry, Dennis Liotta, Ed. *Tetrahedron* **1985**, *41*, 4727–4890.
24. Application of newer organometallic reagents to the total synthesis of natural products, Martin Semmelhack, Ed. *Tetrahedron* **1985**, *41*, 5741–5900.
25. Formal transfers of hydride from carbon–hydrogen bonds, James D. Wuest, Ed. *Tetrahedron* **1986**, *42*, 941–1208.
26. Synthesis of non-natural products: challenge and reward, Philip E. Eaton, Ed. *Tetrahedron* **1986**, *42*, 1549–1916.
27. New synthetic methods—II, F. E. Ziegler, Ed. *Tetrahedron* **1986**, *42*, 2777–3028.
28. Structure and reactivity of organic radical ions, Heinz D. Roth, Ed. *Tetrahedron* **1986**, *42*, 6097–6350.
29. Organic chemistry in anisotropic media, V. Ramamurthy, J. R. Scheffer and N. J. Turro, Eds. *Tetrahedron* **1987**, *43*, 1197–1746.
30. Current topics in sesquiterpene synthesis, John W. Huffman, Ed. *Tetrahedron* **1987**, *43*, 5467–5722.
31. Peptide chemistry: design and synthesis of peptides, conformational analysis and biological functions, Victor J. Hruby and Robert Schwyzer, Eds. *Tetrahedron* **1988**, *44*, 661–1006.
32. Organosilicon chemistry in organic synthesis, Ian Fleming, Ed. *Tetrahedron* **1988**, *44*, 3761–4292.
33. α-Amino acid synthesis, Martin J. O'Donnell, Ed. *Tetrahedron* **1988**, *44*, 5253–5614.
34. Physical-organic/theoretical chemistry: the Dewar interface, Nathan L. Bauld, Ed. *Tetrahedron* **1988**, *44*, 7335–7626.
35. Recent developments in organocopper chemistry, Bruce H. Lipshutz, Ed. *Tetrahedron* **1989**, *45*, 349–578.
36. Organotin compounds in organic synthesis, Yoshinori Yamamoto, Ed. *Tetrahedron* **1989**, *45*, 909–1230.

37. Mycotoxins, Pieter S. Steyn, Ed. *Tetrahedron* **1989**, *45*, 2237–2464.
38. Strain-assisted syntheses, Léon Ghosez, Ed. *Tetrahedron* **1989**, *45*, 2875–3232.
39. Covalently linked donor–acceptor species for mimicry of photosynthetic electron and energy transfer, Devens Gust and Thomas A. Moore, Eds. *Tetrahedron* **1989**, *45*, 4669–4912.
40. Aspects of modern carbohydrate chemistry, S. Hanessian, Ed. *Tetrahedron* **1990**, *46*, 1–290.
41. Nitroalkanes and nitroalkenes in synthesis, Anthony G. M. Barrett, Ed. *Tetrahedron* **1990**, *46*, 7313–7598.
42. Synthetic applications of anodic oxidations, John S. Swenton and Gary W. Morrow, Eds. *Tetrahedron* **1991**, *47*, 531–906.
43. Recent advances in bioorganic chemistry, Dale L. Boger, Ed. *Tetrahedron* **1991**, *47*, 2351–2682.
44. Natural product structure determination, R. B. Bates, Ed. *Tetrahedron* **1991**, *47*, 3511–3664.
45. Frontiers in natural products biosynthesis. Enzymological and molecular genetic advances, D. E. Cane, Ed. *Tetrahedron* **1991**, *47*, 5919–6078.
46. New synthetic methods—III, S. E. Denmark, Ed. *Tetrahedron* **1992**, *48*, 1959–2222.
47. Organotitanium reagents in organic chemistry, M. T. Reetz, Ed. *Tetrahedron* **1992**, *48*, 5557–5754.
48. Total and semi-synthetic approaches to taxol, J. D. Winkler, Ed. *Tetrahedron* **1992**, *48*, 6953–7056.
49. Synthesis of optically active compounds—prospects for the 21st century, Kenji Koga and Takayuki Shioiri, Eds. *Tetrahedron* **1993**, *49*, 1711–1924.
50. Peptide secondary structure mimetics, Michael Kahn, Ed. *Tetrahedron* **1993**, *49*, 3433–3689.
51. Transition metal organometallics in organic synthesis, Anthony J. Pearson, Ed. *Tetrahedron* **1993**, *49*, 5415–5682.
52. Palladium in organic synthesis, Jan-E. Bäckvall, Ed. *Tetrahedron* **1994**, *50*, 285–572.
53. Recent progress in the chemistry of enediyne antibiotics, Terrence W. Doyle and John F. Kadow, Eds. *Tetrahedron* **1994**, *50*, 1311–1538.
54. Catalytic asymmetric addition reactions, Stephen F. Martin, Ed. *Tetrahedron* **1994**, *50*, 4235–4574.
55. Mechanistic aspects of polar organometallic chemistry, Manfred Schlosser, Ed. *Tetrahedron* **1994**, *50*, 5845–6128.
56. Molecular recognition, Andrew D. Hamilton, Ed. *Tetrahedron* **1995**, *51*, 343–648.
57. Recent advances in the chemistry of zirconocene and related compounds, Ei-ichi Negishi, Ed. *Tetrahedron* **1995**, *51*, 4255–4570.
58. Fluoroorganic chemistry: synthetic challenges and biomedicinal rewards, Giuseppe Resnati and Vadim A. Soloshonok, Eds. *Tetrahedron* **1996**, *52*, 1–330.
59. Novel applications of heterocycles in synthesis, A. R. Katritzky, Ed. *Tetrahedron* **1996**, *52*, 3057–3374.
60. Fullerene chemistry, Amos B. Smith III, Ed. *Tetrahedron* **1996**, *52*, 4925–5262.
61. New synthetic methods—IV. Organometallics in organic chemistry, István E. Markó, Ed. *Tetrahedron* **1996**, *52*, 7201–7598.
62. Cascade reactions, Ron Grigg, Ed. *Tetrahedron* **1996**, *52*, 11385–11664.
63. Applications of solid-supported organic synthesis in combinatorial chemistry, James A. Bristol, Ed. *Tetrahedron* **1997**, *53*, 6573–6706.
64. Recent applications of synthetic organic chemistry, Stephen F. Martin, Ed. *Tetrahedron* **1997**, *53*, 8689–9006.
65. Chemical biology, Gregory L. Verdine and Julian Simon, Eds. *Tetrahedron* **1997**, *53*, 11937–12066.
66. Recent aspects of S, Se, and Te chemistry, Richard S. Glass and Renji Okazaki, Eds. *Tetrahedron* **1997**, *53*, 12067–12318.
67. Modern organic chemistry of polymerization, H. K. Hall Jr., Ed. *Tetrahedron* **1997**, *53*, 15157–15616.
68. New synthetic methods—V, John L. Wood, Ed. *Tetrahedron* **1997**, *53*, 16213–16606.
69. New developments in organonickel chemistry, Bruce H. Lipshutz and Tien-Yau Luh, Eds. *Tetrahedron* **1998**, *54*, 1021–1316.
70. Solution phase combinatorial chemistry, David L. Coffen, Ed. *Tetrahedron* **1998**, *54*, 3955–4150.
71. Heterocycles in asymmetric synthesis, Alexandre Alexakis, Ed. *Tetrahedron* **1998**, *54*, 10239–10554.
72. Recent advances of phase-transfer catalysis, Takayuki Shioiri, Ed. *Tetrahedron* **1999**, *55*, 6261–6402.
73. Olefin metathesis in organic synthesis, Marc L. Snapper and Amir H. Hoveyda, Eds. *Tetrahedron* **1999**, *55*, 8141–8262.
74. Stereoselective carbon–carbon bond forming reactions, Harry H. Wasserman, Stephen F. Martin and Yoshinori Yamamoto, Eds. *Tetrahedron* **1999**, *55*, 8589–9006.
75. Applications of combinatorial chemistry, Miles G. Siegel and Stephen W. Kaldor, Eds. *Tetrahedron* **1999**, *55*, 11609–11710.
76. Advances in carbon–phosphorus heterocyclic chemistry, François Mathey, Ed. *Tetrahedron* **2000**, *56*, 1–164.
77. Transition metal organometallics in organic synthesis, Kenneth M. Nicholas, Ed. *Tetrahedron* **2000**, *56*, 2103–2338.
78. Organocopper chemistry II, Norbert Krause, Ed. *Tetrahedron* **2000**, *56*, 2727–2904.
79. Carbene complexes in organic chemistry, James W. Herndon, Ed. *Tetrahedron* **2000**, *56*, 4847–5044.
80. Recent aspects of the chemistry of β-lactams—II, Marvin J. Miller, Ed. *Tetrahedron* **2000**, *56*, 5553–5742.
81. Molecular assembly and reactivity of organic crystals and related structures, Miguel A. Garcia-Garibay, Vaidhyanathan Ramamurthy and John R. Scheffer, Eds. *Tetrahedron* **2000**, *56*, 6595–7050.
82. Protein engineering, Richard Chamberlin, Ed. *Tetrahedron* **2000**, *56*, 9401–9526.
83. Recent advances in peptidomimetics, Jeffrey Aubé, Ed. *Tetrahedron* **2000**, *56*, 9725–9842.
84. New synthetic methods—VI, George A. Kraus, Ed. *Tetrahedron* **2000**, *56*, 10101–10282.
85. Oxidative activation of aromatic rings: an efficient strategy for arene functionalization, Stéphane Quideau and Ken S. Feldman, Eds. *Tetrahedron* **2001**, *57*, 265–424.
86. Lewis acid control of asymmetric synthesis, Keiji Maruoka, Ed. *Tetrahedron* **2001**, *57*, 805–914.
87. Novel aromatic compounds, Lawrence T. Scott and Jay S. Siegel, Eds. *Tetrahedron* **2001**, *57*, 3507–3808.
88. Asymmetric synthesis of novel sterically constrained amino acids, Victor J. Hruby and Vadim A. Soloshonok, Eds. *Tetrahedron* **2001**, *57*, 6329–6650.
89. Recognition-mediated self-assembly of organic systems, Vincent M. Rotello, Ed. *Tetrahedron* **2002**, *58*, 621–844.
90. Synthesis of marine natural products containing polycyclic ethers, Masahiro Hirama and Jon D. Rainier, Eds. *Tetrahedron* **2002**, *58*, 1779–2040.

91. Fluorous chemistry, John A. Gladysz and Dennis P. Curran, Eds. *Tetrahedron* **2002**, *58*, 3823–4132.
92. Recent developments in chiral lithium amide base chemistry, Peter O'Brien, Ed. *Tetrahedron* **2002**, *58*, 4567–4734.
93. Beyond natural product synthesis (Tetrahedron Prize for Creativity in Organic Chemistry 2001 - Yoshito Kishi), Harry H. Wasserman and Stephen F. Martin, Eds. *Tetrahedron* **2002**, *58*, 6223–6602.
94. Strained heterocycles as intermediates in organic synthesis, Amy R. Howell, Ed. *Tetrahedron* **2002**, *58*, 6979–7194.
95. Molecular design of Lewis and Brønsted acid catalysts—the key to environmentally benign reagents (Tetrahedron Chair 2002), Hisashi Yamamoto, Ed. *Tetrahedron* **2002**, *58*, 8153–8364.
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97. Art, science and technology in total synthesis (Tetrahedron Prize for Creativity in Organic Chemistry 2002 - K. C. Nicolaou), Stephen F. Martin and Harry H. Wasserman, Eds. *Tetrahedron* **2003**, *59*, 6667–7070.
98. New synthetic methods—VII, Brian M. Stoltz, Ed. *Tetrahedron* **2003**, *59*, 8843–9030.
99. Oxiranyl and aziridinyl anions as reactive intermediates in synthetic organic chemistry, S. Florio, Ed. *Tetrahedron* **2003**, *59*, 9683–9864.
100. Recent advances in rare earth chemistry, Shū Kobayashi, Ed. *Tetrahedron* **2003**, *59*, 10339–10598.
101. Biocatalysts in synthetic organic chemistry, S. M. Roberts, Ed. *Tetrahedron* **2004**, *60*, 483–806.
102. Recent advances in the chemistry of zirconocenes, Keisuke Suzuki and Peter Wipf, Eds. *Tetrahedron* **2004**, *60*, 1257–1424.
103. Atropisomerism, Jonathan Clayden, Ed. *Tetrahedron* **2004**, *60*, 4325–4558.
104. Chemistry of biologically and physiologically intriguing phenomena, Daisuke Uemura, Ed. *Tetrahedron* **2004**, *60*, 6959–7098.
105. Olefin metathesis: a powerful and versatile instrument for organic synthesis (Tetrahedron prize for creativity in organic chemistry 2003 – R. H. Grubbs), Stephen F. Martin and Harry H. Wasserman, Eds. *Tetrahedron* **2004**, *60*, 7099–7438.
106. From synthetic methodology to biomimetic target assembly (Tetrahedron prize for creativity in organic chemistry 2003 – D. Seebach), Léon A. Ghosez, Ed. *Tetrahedron* **2004**, *60*, 7439–7794.
107. Solid and solution phase combinatorial chemistry, Rolf Breinbauer and Herbert Waldmann, Eds. *Tetrahedron* **2004**, *60*, 8579–8738.
108. Catalytic tools enabling total synthesis (Tetrahedron Chair 2004), Alois Fürstner, Ed. *Tetrahedron* **2004**, *60*, 9529–9784.
109. Synthesis and applications of non-racemic cyanohydrins and α-amino nitriles, Michael North, Ed. *Tetrahedron* **2004**, *60*, 10371–10568.
110. Synthetic receptors as sensors, Eric V. Anslyn, Ed. *Tetrahedron* **2004**, *60*, 11041–11316.
111. Functionalised organolithium compounds, Carmen Nájera and Miguel Yus, Eds. *Tetrahedron* **2005**, *61*, 3125–3450.
112. Applications of catalysis in academia and industry, Michael J. Krische, Ed. *Tetrahedron* **2005**, *61*, 6155–6472.

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Preface

A brief perspective on catalysis from its origins and at the threshold of the 21st century

The roots of catalysis reach back to the very origins of civilization. With humankinds ever increasing understanding of catalysis, so has the course of human events been shaped ever more profoundly by catalysis. Beginning with the production of alcohol through fermentation, the first examples of catalysis appeared long before any sophisticated concepts of structure and bonding were in place. Hence, the earliest period of catalysis is one characterized by empiricism, largely associated with the production of foods.

In the early 1800s, a series of key discoveries culminated in the phenomenological recognition of 'catalysis'. Sir Humphrey Davy, in an 1817 lecture to the royal society of London, revealed that mixtures of coal gas and air over platinum wire cause the wire to glow. This heterogeneous catalytic oxidation enabled the invention of a safety lamp for miners. In 1822, Johann Wolfgang Döbereiner disclosed a method for the production of acetic acid and water, involving the air oxidation of alcohol in the presence of platinum. This innovation formed the basis of the 'Schtitzenbach Quick Vinegar Process.' One year later, Döbereiner reported that mixtures of hydrogen and air ignite in presence of platinum sponge. The creation of fire without flint and tinder immediately captured international attention, and the 'Döbereiner lighter' served as the prototype for legion devices used for the self-ignition of coal-gas burners.

Recognition that certain chemical reactions will only take place in the presence of specific substances was articulated by Eilhard Mitscherlich (*Ann. Phys. Chem.* **1834**, *31*, 273). However, it was the Swedish chemist Berzelius who first recognized that certain substances, termed 'catalysts', will alter reaction rate and yet remain unchanged themeselves (*Ann. Chim. Phys. (Paris)* **1836**, *61*, 146). Interestingly, Berzelius also coined the term 'organic' to define chemical substances characteristic of living organisms, and it was his student Wohler who contributed to the genesis of organic chemistry (and demise of vitalism) by completing the total synthesis of urea in 1828. From their origins, catalysis and organic chemistry were closely linked—a bond that persists to this day!

Numerous catalytic processes were developed in the following decades. Although, they were not fully understood, their impact was felt globally as the era of industrial catalysis emerged. Positive and negative repercussions were apparent, as new technologies were applied to constructive and destructive ends. A poignant example is represented by the catalytic production of ammonia from elemental hydrogen and atmospheric nitrogen reported by Haber in 1895. In WWI, the German military's supply of imported nitrates, which were required for the production of explosives, was tenuous. The Haber process was implemented, and the ammonia obtained was oxidized to nitric acid using a catalytic process developed by Ostwald in 1902. Although Haber's innovation fueled human conflict, it also enabled cost-effective routes to nitrogenous fertilizer, increasing worldwide food production to unprecedented levels. In recognition of this achievement, Haber received the Nobel Prize in Chemistry in 1918.

Significant achievements were made in the years that followed, including such milestones as the Fischer–Tropsch reaction (1922), the first industrial steam reforming process (1930), the Houdry process for petroleum cracking (1936), Ziegler–Natta olefin polymerization (1953) and the Wacker process (1958)—methods still in use today. Wilkinson's development of rhodium-based homogenous hydrogenation catalysts (*Proc. Chem. Soc.* **1964**, 284) was a key contribution, as it catapulted homogeneous catalysis to the forefront of research. The study of well defined homogeneous catalysts combined with fundamental advances in the understanding of structure, bonding and reactivity enabled a vital progression from empiricism to exquisite levels of rational design. Indeed, entrance into the 21st century is marked by the 2001 Nobel Prize in Chemistry awarded to Knowles (*Chem. Commun.* **1968**, 1445) and Noyori (*J. Am. Chem. Soc.* **1980**, *102*, 7932) 'for their work on chirally catalysed hydrogenation reactions', which encompassed a variation of Wilkinson's original homogenous hydrogenation, and Sharpless (*J. Am. Chem. Soc.* **1980**, *102*, 4263) 'for his work on chirally catalysed oxidation reactions'.

At the threshold of the 21st century, a new set of challenges is defined by the need to develop sustainable means of providing chemical commodities demanded by society. Hence, such concepts as atom economy, step economy, and 'green chemistry' play an increasingly important role. It is clear that catalysis holds the key, and that these very challenges will fan the flames of discovery. In this

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Tetrahedron Symposium-in-Print, we find a collection of works comprising a portrait of catalysis *circa* 2000. At this time, homogeneous transition metal catalyzed transformations and biocatalytic processes are reaching ever higher levels of sophistication, the use of small organic catalysts has achieved critical mass giving rise to the field of asymmetric organocatalysis, and new catalysis concepts continue to emerge and find traction. Ostwald once wrote that 'there is probably no chemical reaction which cannot be influenced catalytically', and it now appears that his prophecy is valid. Given our steep trajectory, the future of catalysis seems as bright as the Döbereiner lighter must have appeared nearly two centuries ago!

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Domino hydroformylation–Wittig olefination–hydrogenation

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Abstract—Rhodium-catalyzed hydroformylation in the presence of stabilized phosphorus ylides initiates a domino hydroformylation–Wittig olefination process. When mono-substituted acceptor-stabilized phosphorus ylides were employed, a hydrogenation step succeeds the Wittig olefination to give a domino hydroformylation–Wittig olefination hydrogenation process. For the hydroformylation key step both, linear regioselective hydroformylation of terminal alkenes based on catalyst control as well as diastereoselective hydroformylation based on *ortho*-diphenylphosphanylbenzoate (*o*-DPPB)-directed active substrate control could be employed.

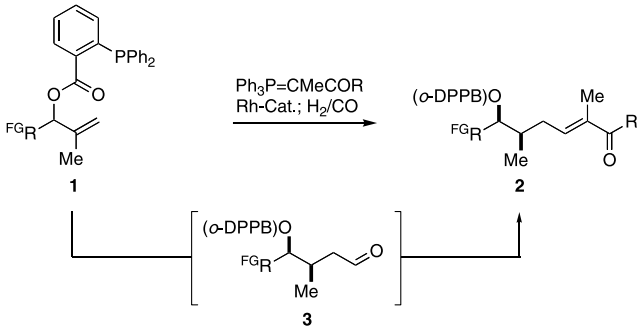
1. Introduction

Key transformations in organic synthesis are those allowing the coupling of two complex fragments in the course of a convergent synthesis. Among the reactions, useful for this purpose the Wittig olefination occupies a prominent position.[1] One of the reaction partners required for the Wittig olefination is a carbonyl derivative such as an aldehyde. Because of the intrinsically high reactivity of the aldehyde function it is typically generated just prior to use employing either deprotection strategies or alternatively, making use of redox processes. However, these reactions all belong to the class of functional group interconversions, which are not deemed synthetically efficient because they do not contribute to an elaboration towards the target skeleton.[2] Thus, skeleton expanding operations such as C/C bond formation which simultaneously generate the aldehyde in an atom economical fashion would be ideal.[3] Synthetically even more useful would be skeleton expanding reactions which simultaneously install new stereogenic centers in a controllable and selective manner.[4] Hence, a reaction meeting all these requirements would be a merged regio- and stereoselective hydroformylation–Wittig olefination process.[5] We herein report in full detail on the realization of the first, domino hydroformylation–Wittig olefination as well as the first, domino hydroformylation–Wittig olefination–hydrogenation reactions.[6]

2. Results and discussion

We recently, showed that attachment of the *ortho*-diphenylphosphanylbenzoate function (*o*-DPPB) to a methallylic alcohol enables a directed regio- and diastereoselective hydroformylation to give the corresponding *syn*-aldehydes **3** in good to excellent yield and diastereoselectivity.[7] It was envisioned that hydroformylation of an alkene in the presence of a carbon nucleophile compatible with the hydroformylation conditions might allow for an instantaneous trapping of the aldehyde with concomitant carbon–carbon bond formation. As interesting carbon nucleophiles stabilized phosphorus ylides were selected for study.

When *o*-DPPB esters **1** were subjected to hydroformylation conditions (0.7 mol% $[RhH(CO)(PPh_3)_3]$, 20 bar CO/H_2 (1:1), toluene, 90 °C) in the presence of the alkyl-substituted stabilized ylides **5** and **7** the α,β-unsaturated carbonyl



Scheme 1. Domino hydroformylation–Wittig olefination.

Keywords: Hydroformylation; Tandem catalysis; Wittig olefination; Catalyst-directing group.
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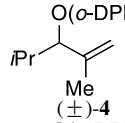
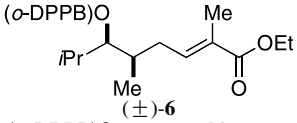
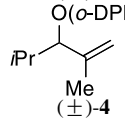
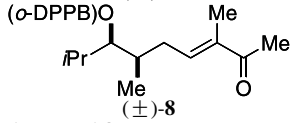
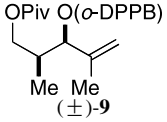
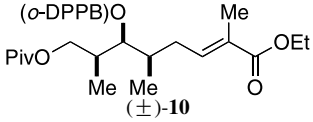
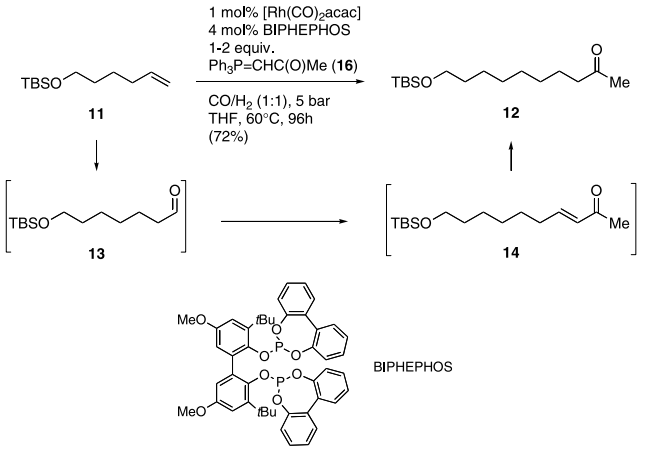
Table 1. Results of the *o*-DPPB-directed diastereoselective domino hydroformylation–Wittig olefination reaction

Entry[a]	Substrate	Ylide	Major product	dr (*syn*/*anti*)[b]	Yield %[c]
1	 (±)-**4**	$Ph_3P{=}CMeC(O)OEt$ (**5**)	 (±)-**6**	96:4	75
2	 (±)-**4**	$Ph_3P{=}CMeC(O)Me$ (**7**)	 (±)-**8**	93:7	78
3	 (±)-**9**	$Ph_3P{=}CMeC(O)OEt$ (**5**)	 (±)-**10**	92:8	60

[a] Reaction conditions: 1.1 equiv ylide **5** or **7**, 0.7 mol% $[Rh(H)(CO)(PPh_3)_3]$, toluene, 90 °C, 48 h, 20 bar H_2/CO (1:1).
[b] Determined through NMR of the crude reaction mixture.
[c] Isolated yield after chromatographic purification.

derivatives **2** were formed in good yield and diastereoselectivity (Scheme 1, Table 1). Hence, these products arise through a domino hydroformylation–Wittig olefination sequence. Thus, a new carbon–carbon single bond as well as a new carbon–carbon double bond were formed concomitant with the installation of a new stereogenic center based on acyclic stereocontrol. The *syn*-diastereocontrol is the result of a directed hydroformylation step relying on the catalyst-directing ability of the *o*-DPPB group.[8] The *E*-selectivity of the olefination step stems from the intrinsically high *E*-preference of stabilized phosphorus ylides.[1]

An interesting observation was made when mono-substituted ylide **16** was employed. Thus, subjection of the TBS–ether functionalized terminal alkene **11** to the conditions of a linear-regioselective hydroformylation with the Rh(I)/BIPHEPHOS catalyst[9] in the presence of ylide **16**, a single product was formed which was identified as the saturated methylketone **12** (Scheme 2). Hence, a domino process involving three separate steps had occurred. The initial step is a linear selective hydroformylation to give aldehyde **13** followed by Wittig olefination to furnish enone **14**. However, the reaction does not stop at this stage as observed for the disubstituted Wittig ylides (Scheme 1, Table 1).



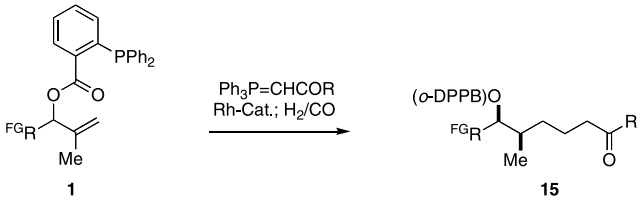
Scheme 2. Regioselective domino hydroformylation–Wittig olefination.

Presumably, due to less steric hindrance, the 1,2-disubstituted double bond of enone **14** undergoes a final hydrogenation reaction to give the saturated ketone **12**. Thus, the same catalyst, that had catalyzed the initial hydroformylation step, acted as a hydrogenation catalyst in the final hydrogenation reaction of this three step domino process.

In order to probe whether the directed hydroformylation may be employed as the key step for a similar hydroformylation–Wittig olefination–hydrogenation sequence methallylic-*o*-DPPB esters **1** were subjected to the reaction conditions of the domino process (Scheme 3, Table 2). Thus, using conditions similar to the hydroformylation–Wittig olefination process but employing the mono-substituted ylides **16** and **21** furnished the saturated *syn*-1,6-oxygen functionalized ketones **15** in good yield and with high levels of acyclic stereocontrol.

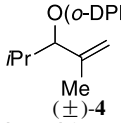
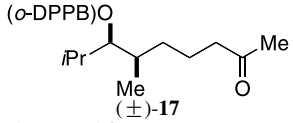
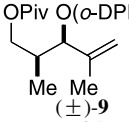
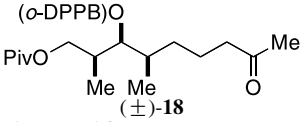
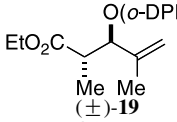
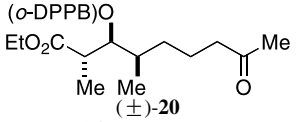
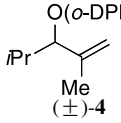
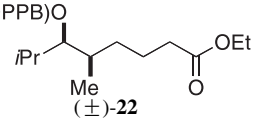
Additionally, homomethallylic *o*-DPPB esters could be employed. In this case 1,3-asymmetric induction transmitted through the catalyst-directing *o*-DPPB group lead to the formation of the *anti*-diastereomer **24** as the major product (Scheme 4).[10]

In these cases (Scheme 3 and 4) 'active' substrate control is operative in which a suitable functional group (here, the *o*-DPPB function) of the substrate generates attractive interactions between the catalyst and the substrate causing an intramolecular catalyst trajectory. Alternatively, if a substrate passes a reactive conformation in which one of the two diastereotopic alkene faces is more or less blocked based on repulsive catalyst/substrate interactions, a 'passive' substrate control is operative. In both cases high



Scheme 3. Domino hydroformylation–Wittig olefination–hydrogenation.

Table 2. Results of the *o*-DPPB-directed diastereoselective domino hydroformylation–Wittig olefination–hydrogenation reaction

Entry[a]	Substrate	Ylide	Major product	dr (*syn*/*anti*)[b]	Yield %[c]
1	 (±)-**4**	$Ph_3P{=}CHC(O)Me$ (**16**)	 (±)-**17**	94:6	70
2	 (±)-**9**	$Ph_3P{=}CHC(O)Me$ (**16**)	 (±)-**18**	96:4	68
3	 (±)-**19**	$Ph_3P{=}CHC(O)Me$ (**16**)	 (±)-**20**	94:6	60
4	 (±)-**4**	$Ph_3P{=}CHC(O)OEt$ (**21**)	 (±)-**22**	94:6	36

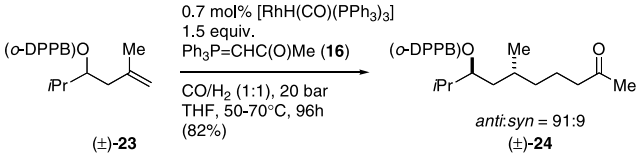
[a] Reaction conditions: 1.5 equiv ylide **16** or **21**, 0.7 mol% $[Rh(H)(CO)(PPh_3)_3]$, toluene, 90 °C, 48 h, 20 bar H_2/CO (1:1).
[b] Determined through NMR of the crude reaction mixture.
[c] Isolated yield after chromatographic purification.

levels of diastereoselectivity may be obtained. An example for passive substrate control is the hydroformylation of alkene (±)-**25**.[11] Subjection of **25** to the conditions of the domino process furnished the all-*anti*-stereotriad building block **26** with excellent acyclic stereocontrol (Scheme 5).

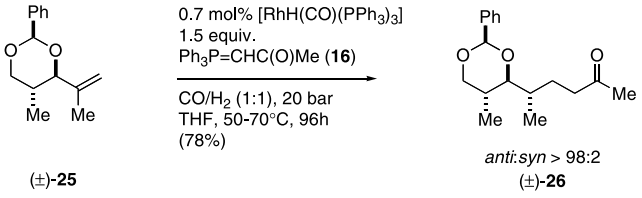
In order to prove the relative configuration of the domino reaction products the known aldehyde **27**[7,8] was transferred via enone **28** to the saturated ketone **17** (Scheme 6) which was identical in all respects (analytical and spectroscopical data) with the product obtained through the domino process (Table 2, entry 1). Hence, the domino reaction conditions do not influence the known stereochemical courses of the hydroformylation step.

Previous research from these laboratories has established the role of the *o*-DPPB group to act as a catalyst-directing group which controls the reaction diastereoselectivity.[7,8] Additionally, a significant rate acceleration of the *o*-DPPB-directed hydroformylation relative to a corresponding non-directed hydroformylation was observed.[8] In theory a similar effect may be excerted by the *o*-DPPB group in the course of the enone hydrogenation step to give saturated ketones **15**. In order to probe the role of the *o*-DPPB group for the final hydrogenation step of the domino hydroformylation–Wittig olefination–hydrogenation processes, enone derivative **33** was prepared. Thus, exchanging the phosphorus atom of the *o*-DPPB group through a CH increment should suppress the ability of the benzoate function to bind to the metal catalyst while keeping the steric influence comparable. Thus, aldehyde **27** which stems from *o*-DPPB directed diastereoselective hydroformylation of methallylic *o*-DPPB ester **4** was protected as the dimethylacetal. Alkaline hydrolysis allowed the removal and recovery of the *o*-DPPB group as the corresponding carboxylic acid. Alcohol **30** was esterified employing the Steglich conditions to give CH-ester **31**.[12] Acetal deprotection followed by Wittig olefination of the resulting aldehyde **32** with ylide **16** gave the desired enone substrate **33**. Rhodium catalyzed hydrogenation afforded the saturated CH-ketone **34** (Scheme 7).

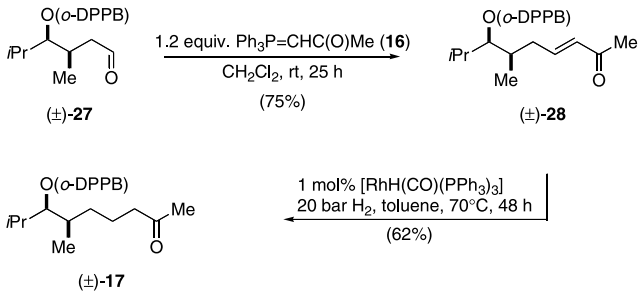
In order to probe the role of the *o*-DPPB group in the course of the enone hydrogenation step a competition experiment was initiated. Thus, a 1:1 mixture of enones **28** and **33** was



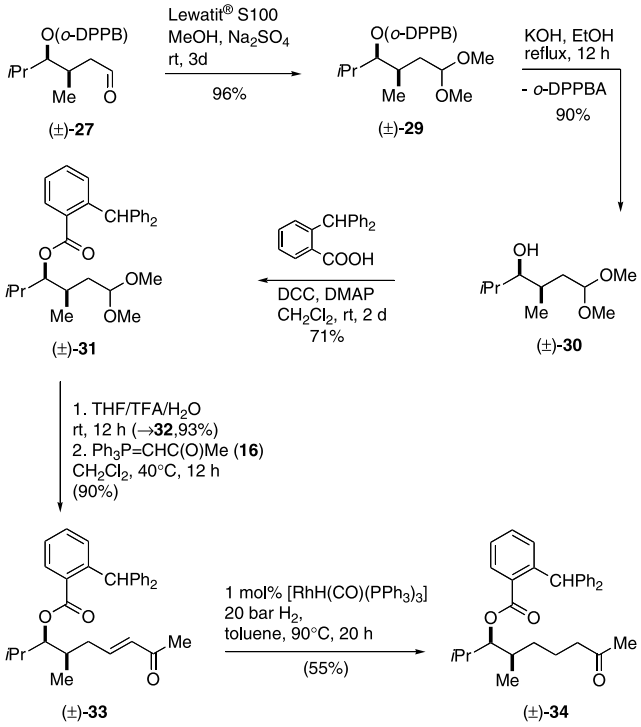
Scheme 4. 1,3-Asymmetric induction in the course of the domino hydroformylation–Wittig olefination–hydrogenation.



Scheme 5. All-*anti* stereotriad synthesis through domino hydroformylation–Wittig olefination–hydrogenation.



Scheme 6. Synthesis of domino product **17** starting from the known aldehyde (±)-**27**.

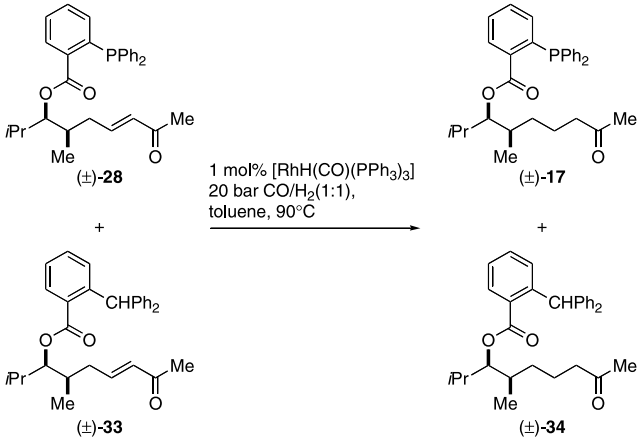


Scheme 7. Preparation of CH-enoate **33**.

subjected to the same reaction conditions which were used in the domino process. Conversion was monitored as a function of time employing ^{1}H NMR spectroscopy (Table 3, Fig. 1, for details see Section 4).

With the assumption that the hydrogenation rate is independent from substrate concentration up to a conversion of ca. 80% linear regression provides the corresponding rate constants (Fig. 1). These results show that the hydrogenation of the P-enone **28** proceeds about 1.3 times faster in comparison to the CH-enone **33** hydrogenation. Hence, this

Table 3. Competition experiment



t (min)	Conversion of **28** (%)	Conversion of **33** (%)
0	0	0
30	10	6
90	35	27
180	72	64

Results of hydrogenation of a 1:1 mixture of P-enone **28** and CH-enone **33**.

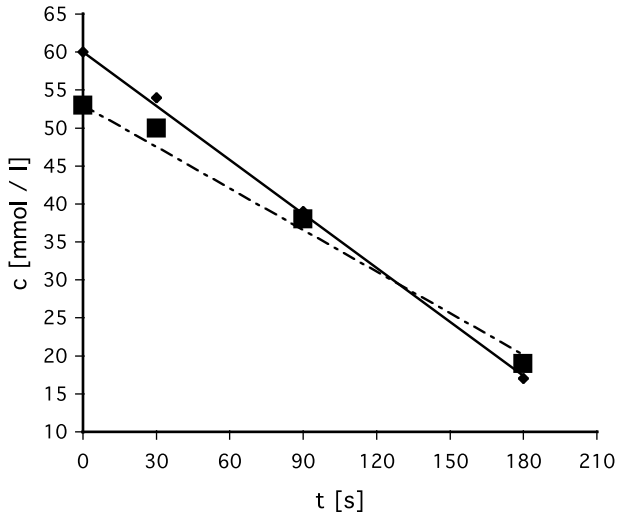


Figure 1. Competition experiment. Concentration of enones **28** (◆) and **33** (■) versus time (for P-enone **28**: $y=-0.237x+60$, $R^2=0.9987$ gives k_{H2} (**28**) $=-0.237$ mmol l^{-1}s^{-1}; for CH-enone **33**: $y=0.1804x+53$, $R^2=0.9815$ gives k_{H2} (**33**) $=-0.180$ mmol l^{-1}s^{-1}).

small differences in rate constants suggests that the hydrogenation step of the domino hydroformylation–Wittig olefination–hydrogenation reaction does not involve active participation of the *o*-DPPB function as a catalyst-directing group.

3. Conclusion

Stabilized Wittig ylides have proven as synthetically interesting carbon nucleophiles which are compatible with conditions of a rhodium-catalyzed hydroformylation. This observation paved the way for the development of efficient domino processes in which the hydroformylation as an atom economic carbon–carbon bond forming process was employed as the key step to generate the aldehyde component of a succeeding Wittig olefination. With disubstituted stabilized Wittig ylides the domino process stops at the olefin stage. However, with mono-substituted stabilized ylides the two step domino process was followed by a hydrogenation reaction of the acceptor substituted alkene. Thus, depending on the substitution pattern of the ylide, domino hydroformylation–Wittig olefination and domino hydroformylation–Wittig olefination–hydrogenation processes could be realized. Both, regioselective hydroformylation and diastereoselective hydroformylation based on active and passive substrate control can be employed as initial steps of these new domino processes.

4. Experimental

4.1. General

Reactions were performed in flame-dried glassware either under argon (purity >99.998%) or under nitrogen. The solvents were dried by standard procedures, distilled and stored under nitrogen. ^{1}H, ^{13}C NMR spectra: Bruker ARX-200, Bruker AC-300, Bruker WH-400, Bruker AMX-500 with tetramethylsilane (TMS), chloroform ($CHCl_3$) or

benzene (C_6H_6) as internal standards. ^{31}P NMR spectra: Bruker WH 400 (161.978 MHz) with 85% H_3PO_4 as external standard. Elemental analyses: CHN-rapid analyzer (Heraeus). Flash chromatography: Silica gel Si 60, E. Merck AG, Darmstadt, 40–63 μm. Hydroformylation reactions were performed in 100 and 200 ml stainless-steel autoclaves equipped with magnetical stirrers. Gases: Carbon monoxide 2.0 (Messer-Griesheim), hydrogen 3.0 (Messer-Griesheim). The following compounds were prepared according to literature procedures: Methallylic *o*-DPPB esters (±)-**4**[7], (±)-**9**[7], (±)-**19**[7], homomethallylic *o*-DPPB ester (±)-**23**[10], benzylidene acetal (±)-**25**[11], 2-diphenylmethyl benzoic acid.[13]

4.1.1. Preparation of 1-*tert*-butyldimethylsilyloxy-5-hexene (11). To a solution of 5-hexene-1-ol (1.50 g, 15.0 mmol) in DMF (25 ml) were added imidazol (1.12 g, 16.5 mmol) and *tert*-butyl dimethyl chlorosilane (2.37 g, 15.8 mmol). The reaction mixture was allowed to stir at rt for 30 h until TLC showed complete consumption of starting material. Water (50 ml) and *tert*-butyl methyl ether (100 ml) were added and the organic phase separated. The organic phase was washed with water (3×50 ml), dried ($MgSO_4$) and the solvent removed in vacuo. Purification through flash chromatography gave 2.51 g (78%) of the TBDMS ether **11** as a colorless oil. ^1H NMR (500.130 MHz, $CDCl_3$): δ=0.02 (s, 6H, Me_2Si), 0.87 (s, 9H, *t*-Bu), 1.38–1.44 (m, 2H), 1.48–1.55 (m, 2H), 2.04 (q, J=7.0 Hz, 2H), 3.59 (t, J=6.7 Hz, 2H, CH_2O), 4.92 (d, J=10.0 Hz, 1H, =CH_2), 4.97 (d, J=17.4 Hz, 1H, =CH_2), 5.77 (m_c, 1H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ=−5.3 (2C), 18.3, 25.2, 26.0 (3C), 32.3, 33.5, 63.1, 114.3, 138.9. $C_{12}H_{26}OSi$ (214.4). Calcd C 67.22, H 12.22; found C 67.05, H 12.22.

4.2. General procedure for the domino hydroformylation–Wittig olefination and domino hydroformylation–Wittig olefination–hydrogenation reaction

To a solution of [RhH(CO)(PPh_3)$_3$] (6.4 mg, 0.007 mmol) in toluene (3 ml) was added at rt the alkene (1.0 mmol, 1.0 equiv) and the reaction mixture was stirred for further, 5 min. Subsequently, the corresponding ylide (1.0–1.5 mmol, 1.0–1.5 equiv) was added and the reaction mixture was transferred with additional toluene (2 ml) into a stainless steel autoclave. The pressure was adjusted to 20 bar synthesis gas (CO/H_2 1:1) and heated to 90 °C until TLC showed complete consumption of starting material (1–3 d). After cooling to rt the autoclave was depressurized and an appropriate amount of silica gel was added. The solvent was removed in vacuo to dryness. The residue was added onto a silica column (3×1.5 cm) and eluted with *tert*-butyl-methyl ether (50–100 ml). After removal of solvent in vacuo the crude product was analyzed by NMR to determine the diastereoselectivity of the reaction. The crude products were purified by flash chromatography with petroleum ether (40–60)/*tert*-butyl methyl ether (9:1) or petroleum ether (40–60)/ethyl actetate (8:2), depending on the polarity of the product, to give the products as highly viscous colorless to yellowish oils.

4.2.1. (1*R,2*R**,4*E*)-(±)-5-(Ethyloxycarbonyl)-1-isopropyl-2-methyl-4-hexenyl-[2-(diphenylphosphanyl)]-benzoate ((±)-6).** From *o*-DPPB ester (±)-**4** (402 mg, 1.0 mmol) and ylide **5** (399 mg, 1.1 mmol) was obtained after 3 d 391 mg (75%) of enoate (±)-**6** (dr (*syn*/*anti*)=95:5). ^1H NMR (300 MHz, $CDCl_3$): δ=0.66–0.75 (m, 9H, 3×CH_3), 1.14 (t, J=7.1 Hz, 3H, CH_3CH_2), 1.61 (s, 3H, CH_3), 1.73 –2.01 (m, 4H), 4.03 (q, J=7.1 Hz, 2H, OCH_2), 4.72 (dd, J=7.6, 3.7 Hz, 1H), 6.58 (m_c, 1H, CH-olefin.), 6.79 (m_c, 1H, Ar-H), 7.11–7.16 (m, 10H, Ar-H), 7.23 (m_c, 2H, Ar-H), 7.99 (m_c, 1H, Ar-H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ=12.2, 13.3, 13.9, 17.9, 18.8, 29.4, 32.7, 34.3, 60.0, 81.9, 127.8, 128.0 (d, $^3J_{C,P}$=7.1 Hz, 2C), 128.08 (d, $^3J_{C,P}$=7.2 Hz, 2C), 128.25 (2C), 128.52, 130.10, 131.5 (2C), 133.5 (d, $^2J_{C,P}$=20.8 Hz, 2C), 133.7 (d, $^3J_{C,P}$=21.0 Hz, 2C), 133.93, 137.7 (d, $^1J_{C,P}$=12.5 Hz), 137.8 (d, $^1J_{C,P}$=11.9 Hz), 139.8, 140.9 (d, $^2J_{C,P}$=28.2 Hz), 165.92, 167.60. ^{31}P NMR (161.978 MHz, $CDCl_3$): δ=−2.9 (s). $C_{32}H_{37}O_4P$ (516.6). Calcd C 74.49, H 7.22; found C 74.61, H 7.34.

4.2.2. (1*R,2*R**,4*E*)-(±)-1-Isopropyl-2,5-dimethyl-6-oxo-4-heptenyl-[2-(diphenylphosphanyl)]benzoate ((±)-8).** From *o*-DPPB ester (±)-**7** (402 mg, 1.0 mmol) and ylide **7** (499 mg, 1.5 mmol) was obtained after 2 d 378 mg (78%) of enone (±)-**8** (dr (*syn*/*anti*)=94:6). ^1H NMR (300 MHz, $CDCl_3$): δ=0.74–0.83 (m, 9H, 3×CH_3), 1.60 (s, 3H, CH_3), 1.81–2.08 (m, 5H), 4.79 (dd, J=8.0, 3.7 Hz, 1H), 6.50 (m_c, 1H, CH-olefin.), 6.85 (m_c, 1H, Ar-H), 7.18–7.24 (m, 10H, Ar-H), 7.32 (m_c, 2H, Ar-H), 8.05 (m_c, 1H, Ar-H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ=11.2, 13.7, 18.4, 19.0, 25.3, 26.9, 33.3, 34.5, 81.6, 128.0 (2C), 128.1–128.4 (5 C), 128.8 (α-C-olefin.), 130.2 (d, $^3J_{C,P}$=2.0 Hz), 133.5 (d, $^2J_{C,P}$=20.6 Hz, 2C), 133.8 (d, $^2J_{C,P}$=20.8 Hz, 2C), 134.2, 137.9 (d, $^1J_{C,P}$=13.0 Hz), 138.0 (d, $^1J_{C,P}$=12.3 Hz), 138.4, 141.0 (d, $^2J_{C,P}$=28.4 Hz), 141.0 (d, $^2J_{C,P}$=28.4 Hz), 141.3 (β-C-olefin.), 166.1, 199.5. ^{31}P NMR (81.015 MHz, $CDCl_3$): δ=−3.2 (s). $C_{31}H_{35}O_3P$ (486.6). Calcd C 76.52, H 7.52; found C 76.65, H 7.56.

4.2.3. (1*R,2*S**,4*E*)-(±)-1-[(1*R**)-2-*tert*-Butylcarbonyloxy)-1-methylethyl]-5-(ethyloxycarbonyl)-2-methyl-4-hexenyl-[2-(diphenylphosphanyl)]benzoate ((±)-10).** From *o*-DPPB ester (±)-**9** (352 mg, 0.7 mmol), (380 mg, 1.05 mmol) ylide **5** (380 mg, 1.05 mmol), [RhH(CO)(PPh_3)$_3$] (4.5 mg, 0.0049 mmol) was obtained after 26 h 250 mg (60%) of enoate (±)-**10** (dr (*syn*/*anti*)=92:8). ^1H NMR (300 MHz, $CDCl_3$): δ=0.87–0.89 (m, 6H, 2×CH_3), 1.17 (s, 9H, 3×CH_3), 1.30 (t, J=7.0 Hz, 3H), 1.76 (s, 3H, CH_3), 1.92–2.19 (m, 4H), 3.80–3.92 (m, 2H, CH_2OPiv), 4.16 (q, J=7.1 Hz, 2H, CH_2O), 5.10 (m_c, 1H), 6.67 (m_c, 1H, =CH), 6.93 (m_c, 1H, Ar-H), 7.22–7.36 (m, 10H, Ar-H), 7.39 (m_c, 2H, Ar-H), 8.10 (m_c,1H, Ar-H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ=12.4, 14.1, 14.4, 27.0 (3×CH_3), 32.6, 34.5, 34.8, 38.6, 49.2, 60.3, 65.9, 77.6, 128.0, 128.3 (d, $^3J_{C,P}$=12.2 Hz, 4C), 128.4, 129.0 (d, $^3J_{C,P}$=14.0 Hz), 130.4, 131.7–131.9 (6 Ar-C), 133.2, 133.7 (d, $^2J_{C,P}$=20.8 Hz), 133.8 (d, $^2J_{C,P}$=21.0 Hz), 134.2, 137.9, 139.4, 165.9, 167.7, 178.1. ^{31}P NMR (81.015 MHz, $CDCl_3$): δ=−3.2 (s). $C_{37}H_{45}O_6P$ (616.7). Calcd C 72.06, H 7.35; found C 71.90, H 6.91.

4.2.4. (1*R,2*R**)-(±)-1-Isopropyl-2-methyl-6-oxoheptyl-[2-(diphenylphosphanyl)]benzoate ((±)-17).** From *o*-DPPB ester (±)-**4** (402 mg, 1.0 mmol), ylide **16** (478 mg, 1.5 mmol), [RhH(CO)(PPh_3)$_3$] (6.4 mg,

0.007 mmol) was obtained after 24 h 328 mg (70%) of ketone (±)-**17** (dr (*syn*/*anti*)=94:6). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.67–0.82 (m, 9H, 3×CH_3), 0.97 (m_c, 1H), 1.08 (m_c, 1H), 1.43 (m_c, 2H), 1.65 (m_c, 1H), 1.80 (m_c, 1H), 1.97 (s, 3H, $CH_3C(O)$), 2.10–2.20 (m, 2H, CH_2), 4.72 (dd, J=7.8, 4.1 Hz, 1H), 6.82 (m_c, 1H, Ar-H), 7.10–7.20 (m, 10H, Ar-H), 7.26 (m_c, 2H, Ar-H), 8.01 (m_c, 1H, Ar-H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ=13.6, 18.3, 19.1, 21.3, 29.1, 29.4, 33.1, 34.2, 43.6, 81.8, 128.0, 128.1–128.5 (5C), 128.9, 130.2, 131.7, 133.3 (d, $^2J_{C,P}$=21.5 Hz, 2C), 133.9, 134.0 (d, $^2J_{C,P}$=25.8 Hz, 2C), 134.2, 138.0 (d, $^1J_{C,P}$=10.3 Hz), 138.2 (d, $^1J_{C,P}$=11.8 Hz), 141.0 (d, $^2J_{C,P}$27.9 Hz), 166.3, 208.7. ^{31}P NMR (81.015 MHz, $CDCl_3$): δ=−2.9 (s). $C_{30}H_{35}O_3P$ (474.58). Calcd C 75.93, H 7.43; found C 75.91, H 7.72.

4.2.5. (1*R,2*S**)-(±)-1-[(1*R**)-2-*tert*-Butylcarbonyloxy)-1-methyl-ethyl]-2-methyl-6-oxoheptyl-[2-(diphenylphosphanyl)]benzoate ((±)-18).** From *o*-DPPB ester (±)-**9** (352 mg, 0.7 mmol), ylide **16** (334 mg, 1.05 mmol), [RhH(CO)(PPh_3)$_3$] (4.5 mg, 0.0049 mmol) was obtained after 28 h 274 mg (68%) of ketone (±)-**18** (dr (*syn*/*anti*)=96:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.84 (d, J=6.8 Hz, 3H, CH_3), 0.88 (d, J=6.8 Hz, 3H, CH_3), 1.14–1.26 (m, 10H, CH, C(CH_3)$_3$), 1.44–1.77 (m, 3H), 2.09 (s, 3H, CH_3), 2.14 (m_c, 1H, CH), 2.26–2.35 (m, 3H), 3.77–3.91 (m, 2H, OCH_2), 5.04 (m_c, 1H), 6.90 (m_c, 1H, Ar-H), 7.21–7.32 (m, 10H, Ar-H), 7.40 (m_c, 2H, Ar-H), 8.06 (m_c,1H, Ar-H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ=12.7, 14.3, 21.2, 27.2 (3×CH_3), 33.0, 34.5, 34.7, 38.7, 43.7, 49.4, 66.2, 77.8, 128.0, 128.1–128.5 (7 Ar-C), 128.6, 130.5, 131.9, 133.9 (d, $^2J_{C,P}$=20.6 Hz, 4C), 134.3, 137.9 (d, $^1J_{C,P}$=12.0 Hz), 141.0 (d, $^2J_{C,P}$=28.0 Hz), 166.0 (d, $^3J_{C,P}$=2.7 Hz), 178.2, 208.7. ^{31}P NMR (81.015 MHz, $CDCl_3$): δ=−3.1 (s). $C_{35}H_{43}O_5P$ (574.7). Calcd C 73.15, H 7.54; found C 73.02, H 7.60.

4.2.6. (1*R,2*S**)-(±)-1-[(1*R**)-1-(Ethyloxycarbonyl)-ethyl]-2-methyl-6-oxoheptyl-[2-(diphenylphosphanyl)]-benzoate ((±)-20).** From *o*-DPPB ester (±)-**12** (461 mg, 1.0 mmol), ylide **16** (414 mg, 1.3 mmol), [RhH(CO)(PPh_3)$_3$] (6.4 mg, 0.007 mmol) was obtained after 23 h 316 mg (59%) of ketone (±)-**20** (dr (*syn*/*anti*)=94:6). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.82 (d, J=6.8 Hz, 3H, CH_3), 1.07–1.13 (m, 8H), 1.55 (pseudo quint., J=7.9 Hz, 2H), 1.75 (m_c, 1H), 2.10 (s, 3H, $CH_3C(O)$), 2.29 (m_c, 2H), 2.83 (m_c, 1H), 3.97 (m_c, 2H), 5.23 (dd, J=8.3, 3.9 Hz, 1H), 6.90 (m_c, 1H, Ar-H), 7.19–7.32 (m, 10H, Ar-H), 7.37 (m_c, 2H, Ar-H), 8.08 (m_c, 1H, Ar-H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ=13.5, 13.9, 14.0, 21.4, 27.0, 32.9, 34.3, 42.3, 43.7, 60.6, 77.7, 128.0, 128.2–128.4 (8 Ar-C), 130.5, 131.8, 133.7 (d, $^2J_{C,P}$=20.7 Hz, 2C), 133.9 (d, $^2J_{C,P}$=21.0 Hz, 2C), 134.2, 138.0 (d, $^1J_{C,P}$=12.4 Hz), 138.2 (d, $^1J_{C,P}$=12.7 Hz), 165.5, 173.6, 208.8. ^{31}P NMR (81.015 MHz, $CDCl_3$): δ=−3.7 (s). $C_{32}H_{37}O_5P$ (532.6). Calcd C 72.16, H 7.00; found C 71.99, H 6.91.

4.2.7. (1*R,2*R**)-(±)-5-(Ethyloxycarbonyl)-1-isopropyl-2-methylpentyl-[2-(diphenylphosphanyl)]benzoate ((±)-22).** From *o*-DPPB ester (±)-**4** (402 mg, 1.0 mmol), ylide **21** (523 mg, 1.5 mmol), [RhH(CO)(PPh_3)$_3$] (6.4 mg, 0.007 mmol) was obtained after 24 h 328 mg (36%) of ester (±)-**22** (dr (*syn*/*anti*)=95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.66 – 0.80 (m, 9H, 3×CH_3), 0.97 (m_c, 1H), 1.13 (t, J=7.1 Hz, 3H), 1.50 (m_c, 2H), 1.68 (m_c, 1H), 1.82 (m_c, 1H), 2.00–2.09 (m, 3H), 4.00 (q, J=7.1 Hz, 2H, CH_2O), 4.71 (dd, J=7.5, 4.4 Hz, 1H), 6.82 (m_c, 1H, Ar-H), 7.14–7.22 (m, 10H, Ar-H), 7.28 (m_c, 2H, Ar-H), 8.00 (m_c, 1H, Ar-H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ=3.5, 13.9, 17.9, 19.2, 22.2, 29.3, 32.8, 33.9, 34.0, 59.8, 81.7, 127.7, 128.0–128.2 (7 C), 130.4 (d, $^3J_{C,P}$=1.8 Hz), 131.4, 133.5 (d, $^2J_{C,P}$=19.4 Hz, 2C), 133.8 (d, $^2J_{C,P}$=21.2 Hz, 2C), 133.9, 137.9 (d, $^1J_{C,P}$=12.6 Hz), 138.0 (d, $^1J_{C,P}$=12.1 Hz), 140.9 (d, $^2J_{C,P}$=28.1 Hz), 166.0 (d, $^3J_{C,P}$=2.9 Hz), 173.2 (CO_2Et). ^{31}P NMR (81.015 MHz, $CDCl_3$): δ=−3.0 (s). $C_{31}H_{37}O_4P$ (504.6). Calcd C 73.79, H 7.39; found C 73.60, H 7.54.

4.2.8. (1*R,3*S**)-(±)-1-Isopropyl-2-methyl-7-oxooctyl-[2-(diphenylphosphanyl)]benzoate ((±)-24).** From *o*-DPPB ester (±)-**23** (458 mg, 1.1 mmol), ylide **16** (525 mg, 1.65 mmol), [RhH(CO)(PPh_3)$_3$] (7.1 mg, 0.0077 mmol) was obtained after 48 h at 50 °C and 48 h at 70 °C 441 mg (82%) of ketone (±)-**24** (dr (*anti*/*syn*)=91:9). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.76 (d, J=6.4 Hz, 3H, CH_3), 0.82 (d, J=6.8 Hz, 6H, 2×CH_3), 1.08–1.79 (m, 8H), 2.08 (s, 3H, CH_3), 2.36 (pt, J=7.5 Hz, 2H), 4.98 (m_c, 1H), 6.90 (m_c, 1H, Ar-H), 7.24–7.33 (m, 10H, Ar-H), 7.39 (m_c, 2H, Ar-H), 8.06 (m_c, 1H, Ar-H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ=17.9, 18.4, 19.2, 21.2, 29.1, 29.8, 32.2, 37.2, 38.1, 44.0, 77.4, 128.1, 128.4–128.5 (8 Ar-C), 130.5, 131.7, 133.9 (d, $^2J_{C,P}$=20.8 Hz, 2C), 134.1 (d, $^2J_{C,P}$=20.8 Hz, 2C), 134.3, 138.3 (d, $^1J_{C,P}$=12.1 Hz, 2C), 167.8 (d, $^3J_{C,P}$=3.0 Hz), 208.9. ^{31}P NMR (81.015 MHz, $CDCl_3$): δ=−3.3 (s). $C_{31}H_{37}O_3P$ (488.6). Calcd C 76.20, H 7.63; found C 75.96, H 7.42.

4.2.9. (6*S)-(±)-6-[(2*R**,4*S**,5*R**)-5-Methyl-2-phenyl-[1,3]-dioxan-4-yl]-heptan-2-one ((±)-26).** From benzylidene acetal (±)-**25** (218 mg, 1.0 mmol), ylide **16** (478 mg, 1.5 mmol), [RhH(CO)(PPh_3)$_3$] (6.4 mg, 0.007 mmol) was obtained after 48 h at 50 °C and 48 h at 70 °C 174 mg (78%, based on 77% conversion) of ketone (±)-**26** (dr (*anti*/*syn*)=>98:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.76 (d, J=6.7 Hz, 3H, CH_3), 1.08 (d, J=6.9 Hz, 3H, CH_3), 1.26–1.59 (m, 3H), 1.66–1.84 (m, 3H), 2.00–210 (m, 1H), 2.13 (s, 3H, $CH_3C(O)$), 2.43 (pt, J=7.1 Hz, 2H), 3.35 (dd, J=10.0 Hz, 1H), 3.48 (pt, J=11.0 Hz, 1H), 5.45 (s, 1H), 7.31–7.38 (3H, Ar-H), 7.46–7.49 (2H, Ar-H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ=12.2, 17.0, 22.1, 29.2, 29.8, 30.6, 33.8, 44.0, 73.2, 87.7, 101.2, 126.0 (2C), 128.1 (2C), 128.5, 139.0, 209.4. $C_{18}H_{26}O_3$ (290.4). Calcd C 74.45, H 9.02; found C 74.40, H 8.92.

4.3. Regioselective domino hydroformylation–Wittig olefination–hydrogentation of silylether 11

4.3.1. Preparation of 10-(*tert*-butyldimethylsilyloxy)-decane-2-one (12). To a solution of [Rh(CO)$_2$acac] (1.3 mg, 0.005 mmol) in THF (2 ml) was added at rt BIPHEPHOS (15.7 mg, 0.002 mmol). Subsequently alkene **11** (106 mg, 0.5 mmol) and ylide **16** (191 mg, 0.6 mmol) was added. The resulting solution was transferred with additional THF (2 ml) into the autoclave. Hydroformylation was performed during 4 d at 60 °C to give after the usual workup 103 mg (72%) of the methylketone **12** (rs≥98:2) as

a colorless oil. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ=0.02 (s, 6H, Me_2Si), 0.87 (s, 9H, *t*-Bu), 1.25–1.27 (m, 8H), 1.45–1.57 (m, 4H), 2.11 (s, 3H, CH_3CO), 2.40 (t, J=7.4 Hz, 2H, CH_2CO), 3.57 (t, J=6.6 Hz, 2H, CH_2O). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ=−5.3 (2C), 23.8, 25.7, 26.0 (3C), 28.7, 29.1, 29.2, 29.4, 29.8, 32.8, 43.8, 63.2, 209.3. $C_{16}H_{34}O_2Si$ (286.5). Calcd C 67.07, H 11.96; found C 66.86, H 12.11.

4.3.2. (1*R,2*R**,4*E*)-(±)-1-Isopropyl-2-methyl-6-oxo-4-heptenyl-[2-benzhydryl]benzoate ((±)-28).** To a solution of aldehyde (±)-**27** (162 mg, 0.39 mmol) in dichloromethane (4 ml) was added ylide **16** (186 mg, 0.59 mmol). The reaction mixture was heated during 12 h to 40 °C in a Schlenk pressure vessel. Removal of the solvent in vacuo and purification through flash chromatography with petroleum ether (40–60)/*tert*-butyl methyl ether (4:1) gave 160 mg (90%) of the unsaturated ketone (±)-**28** as a colorless highly viscous oil. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ=0.76 (d, J=6.7 Hz, 3H, CH_3), 0.82 (d, J=6.8 Hz, 3H, CH_3), 0.86 (d, J=6.9 Hz, 3H, CH_3), 1.76 (m_c, 1H), 1.90 (m_c, 1H), 2.03 (m_c, 1H), 2.21 (s, 3H, CH_3), 4.79 (dd, J=8.1, 3.8 Hz, 1H), 5.96 (d, J=16.0 Hz, 1H, α-olefin.-H), 6.67 (m_c, 1H, β-olefin.-H), 6.81 (s, 1H, $CHPh_2$), 7.00–7.15 (m, 5H, Ar-H), 7.14–7.19 (m, 2H, Ar-H), 7.20–7.26 (m, 5H, Ar-H), 7.31 (m_c, 1H, Ar-H), 7.40 (m_c, 1H, Ar-H), 7.88 (d, J=7.5 Hz, 1H, Ar-H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ=13.3, 18.4, 19.1, 26.9, 29.7, 34.2, 36.8, 51.7, 81.1, 126.2 (2C), 128.18 (2C), 128.20 (2C), 129.7 (2C), 129.8 (2C), 130.2, 130.6, 131.1, 131.5, 132.7 (2C), 143.7, 143.8, 148.1, 146.1, 167.2, 198.4. $C_{30}H_{33}O_3P$ (472.6). Calcd C 76.25, H 7.04; found C 76.02, H 7.26.

4.4. Hydrogenation of enone (±)-28

To a solution of $[RhH(CO)(PPh_3)_3]$ (29.3 mg, 0.032 mmol) in toluene (3 ml) was added enone (±)-**28**. This solution was transferred with further, toluene (1 ml) into a stainless steel autoclave. The autoclave was pressurized with hydrogen gas (20 bar) and warmed to 70 °C. After 48 h under these conditions the autoclave was cooled, depressurized, and the solvent removed in vacuo. Purification through flash chromatography with petroleum ether (40–60)/ethyl acetate (7:3) gave 938 mg (62%) of the saturated ketone (±)-**17**. Spectroscopical and analytical data were identical to those obtained from the ketone product (±)-**17** of the domino process.

4.4.1. (1*R,2*R**)-(±)-1-Isopropyl-4,4-dimethoxy-2-methyl-butyl-[2-(diphenylphosphanyl)]benzoate ((±)-29).** To a solution of aldehyde (±)-**27** (2.27 g, 5.25 mmol) in methanol (40 ml) was added sodium sulfate (3 g), acidic ion exchange resin Lewatit® S100 (740 mg). The reaction was stirred for 3 d at rt and subsequently filtered through basic aluminium oxide. Removal of all volatile components in vacuo gave 2.4 g (96%) of the dimethylacetal (±)-**29** as a colorless, highly viscous oil. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ=0.77 (d, J=6.6 Hz, 3H, CH_3), 0.84 (d, J=6.8 Hz, 3H, CH_3), 0.89 (d, J=7.0 Hz, 3H, CH_3), 1.30 (m_c, 1H), 1.60 (m_c, 1H), 1.87–2.00 (m, 2H), 3.21 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 4.44 (pt, J=5.9 Hz, 1H, $CH(OMe)_2$), 4.80 (dd, J=7.9 Hz, 4.1 Hz, 1H), 6.92 (m_c, 1H, Ar-H), 7.23–7.30 (m, 10H, Ar-H), 7.35–7.41 (m, 2H, Ar-H), 8.11 (m_c, 1H, Ar-H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ=13.8, 18.4, 19.2, 29.4, 30.5, 36.4, 53.0, 53.1, 82.1, 102.7, 128.1, 128.3–128.5 (6 Ar-C), 130.5, 131.9, 133.8 (d, $^2J_{C,P}$=20.8 Hz, 2C), 134.0 (d, $^2J_{C,P}$=21.0 Hz, 2C), 134.1 (d, $^2J_{C,P}$=17.0 Hz), 134.3, 138.1 (d, $^1J_{C,P}$=11.6 Hz), 138.2 (d, $^2J_{C,P}$=12.3 Hz), 141.1 (d, $^2J_{C,P}$=28.0 Hz), 166.3 (d, $^3J_{C,P}$=2.8 Hz). ^{31}P NMR (202.456 MHz, $CDCl_3$): δ=−4.5 (s). $C_{29}H_{35}O_4P$ (478.6). Calcd C 72.78, H 7.37; found C 72.53, H 7.30.

4.4.2. (3*R,4*R**)-(±)-6,6-Dimethoxy-2,4-dimethyl-hexan-3-ol ((±)-30).** Dimethylacetal ester (±)-**29** (2.25 g, 4.7 mmol) was dissolved in ethanolic KOH (sat.) and heated to reflux for 12 h. Water (50 ml) was added and the mixture was extracted with *tert*-butyl methyl ether (3× 30 ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed in vacuo. Flash chromatography of the residue with petroleum ether (40–60)/*tert*-butyl methyl ether (4:1) furnished 810 mg (90%) of alcohol (±)-**30** as a pale yellow oil.

Recovery of the ortho-diphenylphosphanylbenzoic acid. The above obtained aqueous phase was acidified to pH 1 with sulphuric acid (1 N) and subsequently extracted with dichloromethane (3×30 ml). The combined organic phases were dried ($MgSO_4$) and the solvent was removed in vacuo. Filtration through a plug of silica with *tert*-butyl methyl ether and removal of the solvent in vacuo gave 1.22 g (85%) of the acid as pale yellow crystals.

Spectroscopic data of alcohol (±)-**30**. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ=0.87 (d, J=7.2 Hz, 3H, CH_3), 0.89 (d, J=7.1 Hz, 3H, CH_3), 0.89 (d, J=7.0 Hz, 3H, CH_3), 1.54–1.60 (m, 1H), 1.68–1.76 (m, 3H), 1.85 (m_c, 1H), 3.10 (m_c, 1H), 3.33 (s, 3H, OMe), 3.34 (s, 3H, OMe), 4.48 (dd, J=6.6, 4.8 Hz, 1H, $CH(OMe)_2$). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ=12.7, 19.2, 19.3, 30.9, 31.5, 37.1, 52.4, 53.0, 79.7, 103.3.

4.4.3. (1*R,2*R**)-(±)-1-Isopropyl-4,4-dimethoxy-2-methyl-butyl-2-benzhydryl benzoate ((±)-31).** To a solution of alcohol (±)-**30** (390 mg, 2.0 mmol) in dichloromethane (25 ml) was added successively 2-diphenylmethyl benzoic acid (577 mg, 2.0 mmol), DMAP (244 mg, 2.0 mmol) and DCC (412 mg, 2.0 mmol). After stirring for 48 h at rt the reaction mixture was filtered with additional dichloromethane (50 ml) through celite®. All volatile components were removed in vacuo and the residue was purified through flash chromatography with petroleum ether (40–60)/*tert*-butyl ethyl ether (9:1) to give 650 mg (71%) of ester (±)-**31** as a colorless highly viscous oil. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ=0.66 (d, J=6.6 Hz, 3H, CH_3), 0.84 (d, J=6.8 Hz, 6H, 2×CH_3), 1.30 (m_c, 1H), 1.60 (m_c, 1H), 1.89 (m_c, 1H), 1.96 (m_c, 1H), 3.26 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 3.26 (pt, J=5.7 Hz, 1H), 4.78 (dd, J=7.8, 4.1 Hz, 1H), 6.77 (s, 1H), 7.04 (m_c, 1H, Ar-H), 7.14–7.29 (m, 7H, Ar-H), 7.39 (m_c, 1H, Ar-H), 7.88 (d, J=7.7 Hz, 1H, Ar-H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ=13.8, 18.2, 19.2, 29.5, 30.5, 36.4, 51.7, 52.6, 52.9, 81.6, 102.8, 126.1 (2C), 126.2, 128.1 (2C), 128.2 (2C), 129.7 (4C), 130.3, 130.8, 131.2, 131.4, 143.89, 143.90, 144.9, 167.4. $C_{30}H_{36}O_4$ (460.6). Calcd C 78.27, H 7.88; found C 78.31, H 7.81.

4.4.4. (1*R,2*R**)-(±)-3-Formyl-1-isopropyl-2-methyl-propyl-[2-benzhydryl]benzoate ((−)-32).** To a solution of dimethylacetal (±)-**31** (152 mg, 0.33 mmol) in THF (3 ml) was added water (1 ml) and trifluoro acetic acid (1 ml) and the reaction mixture was allowed to stir for 12 h at rt. Subsequently, the mixture was added to aqueous. sat. $NaHCO_3$ (20 ml). The aqueous phase was extracted with *tert*-butyl methyl ether (2×30 ml) and the combined organic phases were dried ($MgSO_4$). Removal of the solvent in vacuo and flash chromatography with petroleum ether (40–60)/*tert*-butyl methyl ether (4:1) furnished 127 mg (93%) of aldehyde (±)-**32** as a colorless highly viscous oil. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ=0.78 (d, J=6.6 Hz, 3H, CH_3), 0.80 (d, J=6.8 Hz, 3H, CH_3), 0.90 (d, J=6.9 Hz, 3H, CH_3), 1.81 (ddd, J=17.8, 8.1, 1.4 Hz, 1H), 1.90 (m_c, 1H), 2.05 (dd, J=17.8, 5.4 Hz, 1H), 2.41 (m_c, 1H), 4.74 (dd, J=8.9, 3.1 Hz, 1H), 6.84 (s, 1H), 6.98 (d, J=7.7 Hz, 1H, Ar-H), 7.04 (m_c, 4H, Ar-H), 7.13–7.18 (m, 2H, Ar-H), 7.21–7.30 (m, 5H, Ar-H), 7.37 (m_c, 1H, Ar-H), 7.87 (d, J=7.7 Hz, 1H, Ar-H), 9.51 (s, 1H, CHO). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ=13.2, 18.8, 18.9, 28.6, 29.6, 47.8, 51.7, 81.1, 126.16, 126.17, 126.20, 128.17 (2C), 128.20 (2C), 129.7 (2C), 129.8 (2C), 130.2, 130.5, 131.0, 131.5, 143.8, 144.0, 145.1, 167.3, 201.3. HRMS (FAB$^+$) Calcd for $C_{28}H_{30}O_5$ (M^+ +H) 415.2273; found 415.2275.

4.4.5. (1*R,2*R**,4*E*)-(±)-1-Isopropyl-2-methyl-6-oxo-4-heptenyl-[2-benzhydryl]benzoate ((±)-33).** To a solution of aldehyde (±)-**32** (162 mg, 0.39 mmol) in dichloromethane (4 ml) was added ylide **16** (186 mg, 0.59 mmol). After heating the reaction mixture for 12 h at 40 °C in a Schlenk pressure vessel, silica gel (1 g) was added and all volatile components were removed in vacuo. Flash chromatography with petroleum ether (40–60)/*tert*-butyl methyl ether (4:1) furnished 160 mg (90%) of unsaturated ketone (±)-**33** as a colorless highly viscous oil. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ=0.76 (d, J=6.7 Hz, 3H, CH_3), 0.82 (d, J=6.8 Hz, 3H, CH_3), 0.86 (d, J=6.9 Hz, 3H, CH_3), 1.76 (m_c, 1H), 1.90 (m_c, 1H), 2.03 (m_c, 1H), 2.21 (s, 3H, CH_3), 4.79 (dd, J=8.1, 3.8 Hz, 1H), 5.96 (d, J=16.0 Hz, 1H, α-olefin.-H), 6.67 (m_c, 1H, β-olefin.-H), 6.81 (s, 1H, $CHPh_2$), 7.00–7.15 (m, 5H, Ar-H), 7.14–7.19 (m, 2H, Ar-H), 7.20–7.26 (m, 5H, Ar-H), 7.31 (m_c, 1H, Ar-H), 7.40 (m_c, 1H, Ar-H), 7.88 (d, J=7.5 Hz, 1H, Ar-H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ=13.3, 18.4, 19.1, 26.9, 29.7, 34.2, 36.8, 51.7, 81.1, 126.2 (2C), 128.18 (2C), 128.20 (2C), 129.7 (2C), 129.8 (2C), 130.2, 130.6, 131.1, 131.5, 132.7 (2C), 143.7, 143.8, 148.1, 146.1, 167.2, 198.4. HRMS (FAB) Calcd for $C_{31}H_{34}O_5$ (M^+ +H): 455.2586; found 455.2604.

4.4.6. Hydrogenation of (±)-33: preparation of (1*R,2*R**,4*E*)-(±)-1-Isopropyl-2-methyl-6-oxo-4-heptenyl-[2-benzhydryl]benzoate ((±)-34).** To a solution of [RhH(CO)(PPh_3)$_3$] (0.9 mg, 0.001 mmol) in toluene (1 ml) was added enone (±)-**33**. This solution was transferred with further, toluene (0.5 ml) into a stainless steel autoclave. The autoclave was pressurized with hydrogen (20 bar) and warmed to 90 °C. After 20 h under these conditions the autoclave was cooled, depressurized, and the solvent removed in vacuo. Purification through flash chromatography with petroleum ether (40–60)/*tert*-butyl methyl ether (9:1) gave 25 mg (55%) of the saturated ketone (±)-**34**. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ=0.61 (d, J=6.7 Hz, 3H, CH_3), 0.72 (d, J=6.8 Hz, 3H, CH_3), 0.75 (d, J=6.8 Hz, 3H, CH_3), 0.89–0.95 (m, 1H), 1.07–1.12 (m, 1H), 1.43–1.51 (m, 2H), 1.67 (m_c, 1H), 1.80 (m_c, 1H), 2.03 (s, 3H, CH_3), 2.23 (m_c, 2H), 4.71 (dd, J=7.8, 4.2 Hz, 1H), 6.71 (s, 1H, $CHPh_2$), 6.94–6.98 (m, 5H, Ar-H), 7.07–7.12 (m, 2H, Ar-H), 7.15–7.23 (m, 5H, Ar-H), 7.31 (m_c, 1H, Ar-H), 7.81 (d, J=7.5 Hz, 1H, Ar-H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ=13.6, 18.2, 19.2, 21.4, 29.5, 29.8, 33.2, 34.3, 43.8, 51.7, 81.6, 126.1, 126.2, 128.17 (2C), 128.18 (2C), 129.72 (2C), 129.76 (2C), 130.3, 130.6, 131.0, 131.1, 131.3, 143.9, 144.0, 144.9, 167.4, 208.9. HRMS (FAB) Calcd for $C_{31}H_{37}O_5$ (M^+ +H): 457.2743; found 457.2747.

4.5. Competition experiment: hydrogenation of a 1:1 mixture of (±)-28 and (±)-33

To a solution of [RhH(CO)(PPh_3)$_3$] (2.3 mg, 0.0025 mmol) in toluene (2 ml) was added (±)-**28** (118 mg, 0.25 mmol), (±)-**33** (116 mg, 0.25 mmol) and 1,3,5-trimethoxybenzene (16 mg, 10 mol%) as internal standard. The reaction solution was transferred with additional toluene (2 ml) into a stainless steel autoclave. The autoclave was heated to 90 °C and the reaction was started upon addition of synthesis gas (CO/H_2 1:1, 20 bar). Aliquots (0.5 ml) were taken at t=0, 30, 90 and 180 min, filtrated through silica, evaporated and analyzed by NMR to determine conversion.

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References and notes

1. (a) Maercker, A. *Org. React.* **1965**, *14*, 270–490. (b) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1–30. (c) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73–253. (d) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. (e) Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 85–163. (f) Nicolaou, K. C.; Härter, M. W.; Gunzer, J. L.; Nadin, A. *Liebigs Ann. Recl.* **1997**, 1283–1301.
2. Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784–5800. (b) Hendrickson, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 5439–5450. (c) Hendrickson, J. B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1286–1295.
3. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (b) Trost, B. M. *Science* **1991**, *254*, 1471–1477.
4. Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989; Chapter 4, pp 47–57.
5. (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163. (c) Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, 1992. (d) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1332–1334.
6. Breit, B.; Zahn, S. K. *Angew. Chem., Int. Ed.* **1999**, *38*, 969–971. For the use of the Wittig olefination in other domino

processes see e.g. Raw, S. A.; Reid, M.; Roman, E.; Taylor, R. J. K. *Synlett* **2004**, 819.
7. (a) Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264–275. (b) Breit, B.; Dauber, M.; Harms, K. *Chem. Eur. J.* **1999**, *5*, 2819–2827. (c) Breit, B. *Liebigs Ann.* **1997**, 1841–1851. (d) Breit, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2835–2837.
8. Breit, B.; Heckmann, G.; Zahn, S. K. *Chem. Eur. J.* **2003**, *9*, 425–434.
9. Billig, E.; Abatjoglou, A. G.; Bryant, D. R. (UCC) U.S. Patent 4, 769, 498, 1988; *Chem. Abstr.* **1989**, *111*, 117–287. Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2066–2068.
10. (a) Breit, B. *Eur. J. Org. Chem.* **1998**, 1123–1134. (b) Breit, B. *Chem. Commun.* **1997**, 591–592.
11. (a) Breit, B.; Zahn, S. K. *J. Org. Chem.* **2001**, *66*, 4870–4877. (b) Breit, B.; Zahn, S. K. *Tetrahedron Lett.* **1998**, *39*, 1901–1904.
12. Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 602–615. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569–583.
13. Wykypiel, W.; Lohmann, J.-J.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1337–1346.

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Consecutive Rh(I)-catalyzed Alder-ene/Diels–Alder/Diels–Alder reaction sequence affording rapid entry to polycyclic compounds

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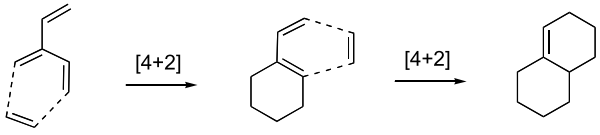
Abstract—Conversion of acyclic allenynes to polycyclic compounds using consecutive transition metal catalyzed carbon–carbon bond forming reactions in a single chemical operation is described. Reaction of an allenyne with a Rh(I) catalyst affords a cross-conjugated triene via a formal Alder-ene reaction. The triene then participates in a Rh(I)-catalyzed intramolecular [4+2] cycloaddition reaction to generate a new conjugated diene. An external dienophile is added to this diene which then undergoes a second [4+2] cycloaddition reaction to afford a complex polycyclic ring system. This reaction sequence demonstrates the synthetic potential of allenynes and cross conjugated trienes and highlights the rapid increases in molecular complexity that are possible by one-pot sequential transition metal catalyzed carbon–carbon bond forming reactions.

1. Introduction

While major advances in transition metals catalyzed reactions have been made, it remains a continuing challenge to organic chemists to efficiently produce structures of high molecular complexity from readily available starting materials. Clearly, one way this goal has been achieved is by combining two or more reactions in a single synthetic operation.[1] The inherent success of tandem or consecutive reactions is dependent upon the substrate structure and the potential for intermediates to participate in subsequent reactions. Recently, it was discovered in our group that allenynes undergo formal Rh(I)-catalyzed Alder-ene reactions to provide cross-conjugated trienes.[2] The scope of this reaction is currently being examined and a variety of substructures have been obtained in high yields with high *E*/*Z* selectivity depending upon the catalyst and substrate.

Cross-conjugated trienes represent interesting building blocks capable of undergoing a variety of reactions subsequent to their formation. For instance, it has previously been demonstrated that cross-conjugated trienes can participate in tandem Diels–Alder reactions as shown in Eq. 1. The triene reacts with a dienophile to give a vinylcyclohexene that can react with another dienophile to give a mono-unsaturated decalin ring system.



(1)

Based upon the synthetic potential of tandem Diels–Alder reactions alone, it would seem that the cross-conjugated triene moiety would be ubiquitous in organic synthesis. In fact, synthetic access and utilization of cross-conjugated trienes has been described (vide infra), but in contrast to its obvious synthetic potential, its exploitation has been limited. This appears to be mostly due to the difficulty in synthesizing this moiety. In a previous study, Tsuge prepared an acyclic triene via a condensation of 2,4-pentanedione and benzaldehyde to afford 3-benzylidene-2,4-pentadione, which upon formation of the bis-silylenol ether affords the cross-conjugated triene **1**.[3] Tsuge has reacted this triene with a variety of cyclic-, acyclic-, and heterodienophiles to give the corresponding cycloadducts (Eq. 2).[4] More recently, Fallis has effected the condensation of pentadienyl anion with an aldehyde using indium (Eq. 3).[5] Elimination of the resulting alcohol gives the cross-conjugated triene that can be trapped with a variety of dienophiles to afford the tetracyclic compounds such as **2**. Schreiber has recognized the advantages of Fallis-type trienes and has utilized them in the preparation of structurally unique scaffolds.[6]

There can be regioselectivity issues associated with

Keywords: Rh(I) allenic Alder ene; Diels–Alder reaction; Consecutive transition metal catalyzed reactions; Allenynes; Polycycles; Cross-conjugated trienes.
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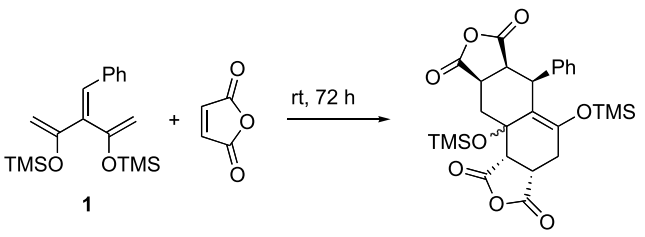
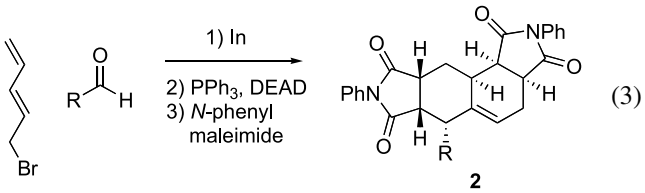
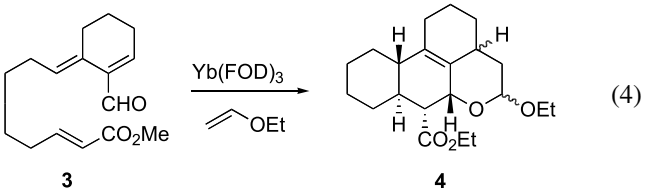
unsymmetrical acyclic trienes and mixtures of products are possible if one diene does not react selectively. Spino has resolved this issue, albeit using a dienal, by fixing one diene in a *transoid* configuration that cannot participate in the Diels–Alder reaction (Eq. 4).[7] The inverse demand ytterbium-catalyzed intermolecular hetero-Diels–Alder cycloaddition between **3** and ethyl vinyl ether affords the intermolecular hetero-Diels–Alder adduct that then participates in an *endo*-selective intramolecular Diels–Alder cycloaddition to give **4**.



(2)



(3)



(4)

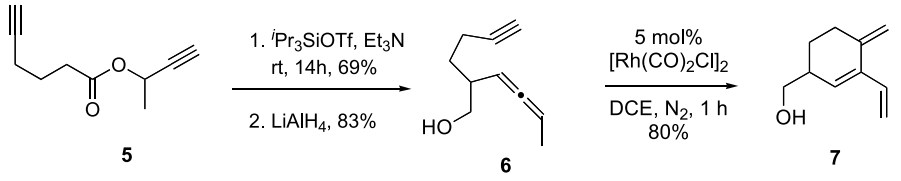
Thus, the potential to rapidly increase molecular complexity by using cross-conjugated trienes has not escaped attention of synthetic chemists. Moreover, limited access to this moiety is certainly not a result of lack of interest. Instead, the limited access appears to be due to: (1) the requirement of very specific substrates to effect the formation of the triene;[8] (2) the low stability of the trienes to the reaction conditions used to generate them; and (3) in the case of acyclic cross-conjugated trienes, the lack of regioselectivity given that there are two dienes with which the cycloaddition reaction can occur.

2. Results and discussion

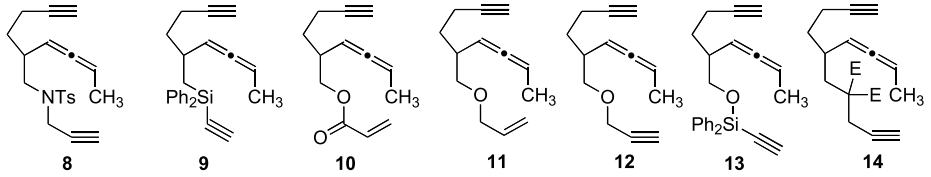
In our preliminary communication on the rhodium(I) catalyzed allenic Alder-ene reaction, we reported the transformation of alkynyl allene **6** to triene **7** in high yield (Scheme 1).[2] Alkynyl allene **6** is easily prepared from readily available starting materials in three steps involving: (1) condensation of hexynoic acid and 3-butynol-2-ol (DCC/DMAP) to afford ester **5**; (2) treating ester **5** with triisopropyl silyl triflate and triethylamine to afford an allenic silyl ester via an Ireland-Claisen rearrangement;[9] and (3) reduction of the silyl ester with $LiAlH_4$ to afford the alkynyl allene **6**. Conversion of the alkynyl allene **6** to triene **7**, catalyzed by rhodium biscarbonylchloride dimer $[Rh(CO)_2Cl]_2$, occurred at room temperature in 80% yield.

The reactions in Scheme 1 also showcase the functional group compatibility of the Rh(I) catalyst, which in this example tolerates both the hydroxymethyl group and the cross conjugated triene.[10] The hydroxymethyl group also serves as an ideal attachment point for a tethered-dienophile. In addition to the ease of synthesis and mild conditions, the triene generated in our laboratory has one of the diene moieties locked in the s-*trans* configuration which ensures that only one of the dienes participates in the initial cycloaddition reaction. More importantly, we believed the Rh(I) catalyst used to generate the triene could potentially catalyze subsequent cycloaddition reactions in a one-pot procedure.[11]

Initially, we opted to investigate [4+2] cycloaddition reactions on isolated trienes. This strategy was adopted due to the ease in which tethered dienophiles can be introduced in the allenic Alder-ene precursor and the ample precedent for effecting these formal cycloaddition reactions using Rh(I) catalysts (vide infra). Thus, the next step in our investigation involved determining the functional group compatibility of various tethered-dienophiles to the Alder-ene reaction conditions, since the dienophiles



Scheme 1. Rh(I)-catalyzed Allenic Alder-ene reaction.

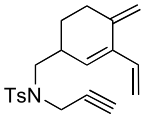
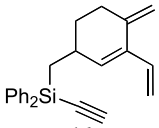
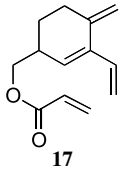
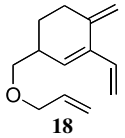
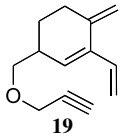
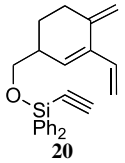
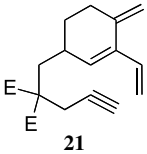


Scheme 2. Attaching dienophiles to the appending hydroxymethyl group (see text).

themselves could potentially react under the Alder-ene reaction conditions.

A series of Alder-ene precursors were prepared as follows (Scheme 2). Propargyl tosylamide **8** was prepared in 91% yield by reaction of the hydroxymethyl group of **6** with propargyl tosylamide, diisopropylazodicarboxylate and triphenylphosphine (Scheme 2). Transformation of **6** to the silicon-tethered allenediyne **9** involved a four-step protocol, where the hydroxyl group was converted to an iodide in 87% yield via initial formation of the mesylate (MsCl, NEt_3) followed by the addition of NaI. Metal–halogen exchange using *n*-BuLi affords the corresponding alkyl lithium species that was trapped by the addition of chlorodiphenylethynylsilane to give compound **9** in 68% yield. Acryloyl chloride and triethylamine were added to compound **6** affording a 76% yield of the acyclic ester **10**. Deprotonation of **6** with sodium hydride and the addition of allyl bromide and propargyl bromide afforded ethers **11** and **12**, respectively, each in 96% yield. Exposure of **6** to triethylamine and diphenylchlorosilane gave a 68% yield of silyl ether **13**. Finally, addition of the sodium anion of dimethylpropargyl malonate to the iodide prepared from **6** gave 43% yield of **14**. We were poised to examine the allenic Alder-ene reaction of substrates **8**–**14**.

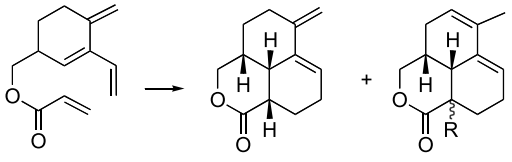
Table 1. Allenic Alder ene reaction

Entry	Allenyne	Triene	Time	Yield
1	**8**	 **15**	10 min	93%
2	**9**	 **16**	10 min	79%[a]
3	**10**	 **17**	2 h	78%
4	**11**	 **18**	2 h	83%
5	**12**	 **19**	1.5	86%
6	**13**	 **20**	20 min	85%
7	**14**	 **21**	4.5 h	79%

Conditions: 5 mol% $[Rh(CO)_2Cl]_2$, DCE, N_2, room temperature.
[a] Compound **9** and **16** both possess sillyl-containing contaminants.

Each of the alkynyl allenes was subjected to the standard allenic Alder-ene conditions, rhodium biscarbonyl chloride dimer in dichloroethane at rt.[2] The results from these studies are shown in Table 1. Conversion of the propargyl tosylamide **8** and alkynyl silanes **9** and **13** to the corresponding trienes was extremely rapid taking place in less than 20 min (entries 1, 2, and 6 Table 2). Triene formation in the presence of the acrylate ester **10** (entry 3), allyl ether **11** (entry 4), propargyl ether **12** (entry 5) and propargyl malonate **14** (entry 7) tethers was slower, but the yields remained high. Alternative rhodium(I) catalysts for effecting triene formation were briefly examined. For example, alkynyl allene **12** was reacted with 5 mol% of Wilkinson's catalyst [chlorotris(triphenylphosphine) rhodium(I)] in trifluoroethanol at 80 °C for 12 h to afford triene **19** in 48% yield. Moreover, alkynyl allene **12** was subjected to rhodium cyclooctadiene chloride dimer and silver hexafluoroantimonate to give 68% of compound **19** in 15 min. The results obtained when using these two alternative catalysts were inferior to rhodium biscarbonyl chloride dimer. Unfortunately, a spontaneous intramolecular [4+2] cycloaddition was not observed under any of these reaction conditions.

We next turned our attention to effecting the intramolecular Diels–Alder reaction of isolated trienes **15**–**21**. Initial investigations involved the [4+2] cycloaddition reaction of the acrylic ester **17**. Treatment of compound **17** with dichloromethylalane resulted in the formation of the diene **23a** in 80% yield (entry 1, Table 2), which presumably results from the isomerization of the initial cycloadduct **22** (Eq. 5). Unfortunately, all attempts to convert compound **17** to the cycloadduct **22** using other Lewis acids were unsuccessful [$BF_3 \cdot OEt_2$, $AlCl_3$, $EtAlCl_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $SnCl_4$ all gave either decomposition or recovery of the starting material]. Heating ester **17** in DCE to 140 °C in a sealed tube for 24 h gave the endoadduct **22** in 47% yield. Heating **17** at 160 °C in DMSO gave a mixture of **23a** and **23b** in a combined yield of 42%.



(5)

Table 2. Results for Diels–Alder reaction (Eq. 5)

Entry	Conditions	Yield
1	$MeAlCl_2$, toluene, −78 °C	**23a** (80%)
2	DCE, 140 °C 24 h	**22** (47%)
3	DMSO, 160 °C	**23a** (32%)
		23b (10%)

The stereochemistry of **23a** was assigned by 2D-NOESY experiments, with the main NOE enhancements in **23a**

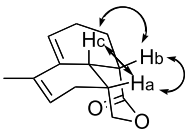
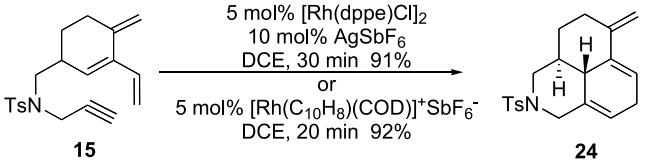


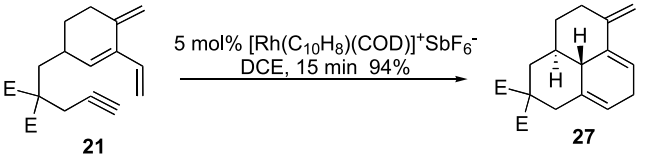
Figure 1. NOE enhancements for tricyclic compounds **23a**.

being Ha–Hc, Hb–Hc, Ha–Hb (Fig. 1). The structure of **23b** was assigned based upon similarities of the spectral data to that of **23a**.

Next, we examined the Diels–Alder reactions between electronically similar dienes and dienophiles using transition metal catalysis. For the conversion of **15** to cycloadduct **24**, conditions reported by Zhang[12] ($[Rh(dppe)Cl]_2$, $AgSbF_6$) and Wender[13] ($[Rh(C_{10}H_8)(COD)]SbF_6$) appeared to be equally effective, providing the cycloadduct **24** in 91 and 92% yields, respectively, (Eq. 6).[14] Similar results were obtained when trienyne **21** was exposed to 5 mol% $[Rh(C_{10}H_8)(COD)]SbF_6$, affording a 94% yield of cycloadduct **27** in 15 min at rt (Eq 7).



(6)

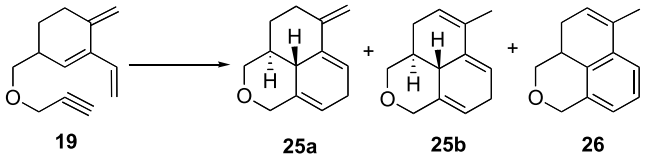


(7)

Propargyl ether **19** was subjected to the same reaction conditions as described above (Eq. 8). However, for this substrate the results were much more dependent upon the catalyst. For example, $[Rh(dppe)Cl]_2$ activated with $AgSbF_6$ gave the cycloadducts **25b** and **26** in a 10:1 ratio in a combined 77% yield (entry 1, Table 3). The best results were obtained when $[Rh(C_{10}H_8)(COD)]^+SbF_6^-$ was used in DCE, which after 20 min gave **25a** as the only product in 92% yield (entry 2, Table 3).

Table 3. Intramolecular Rh(I)-catalyzed Diels–Alder reaction

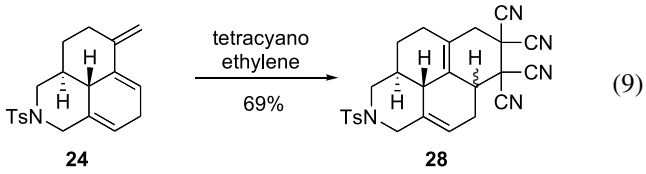
Entry	Conditions	Ratios, yield
1	5 mol% $[Rh(dppe)Cl]_2$, 10 mol% $AgSbF_6$, DCE, 1 h	**25b**:**26**, 10:1, 77%
2	5 mol% $[Rh(C_{10}H_8)(COD)]^+SF_6^-$, DCE, 20 min	**25a**, 92%



(8)

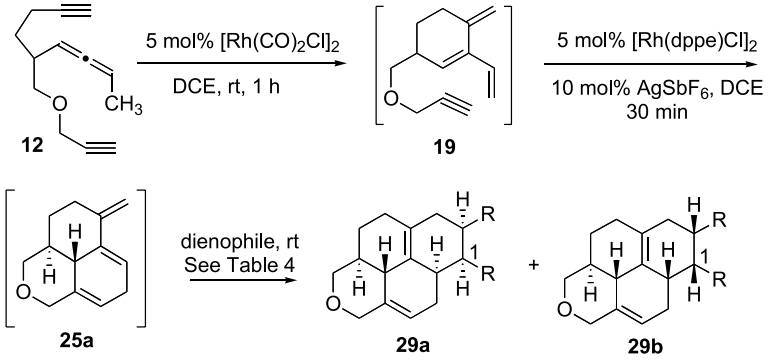
Attempts to effect the intramolecular Diels–Alder reaction on substrates **16**, **18** and **20** with either $[Rh(dppe)Cl]_2$/$AgSbF_6$ or $[Rh(C_{10}H_8)(COD)]^+SbF_6^-$ afforded none of the corresponding cycloaddition products. The recalcitrant nature of alkynyl silanes **16** and **20** toward cycloaddition is thought to be steric in nature. For substrate **18**, it is recognized that alkenes do not readily participate in transition metal catalyzed formal [4+2] cycloaddition reaction to form decalin ring systems.[15]

To examine whether the second Diels–Alder reaction could be effected, isolated diene **24** was exposed to an external dienophile. The very reactive dienophile tetracyanoethylene, underwent rapid intermolecular Diels–Alder reactions affording a 69% yield of the tetracyclic product **28** (Eq. 9).



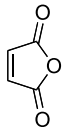
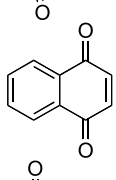
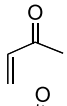
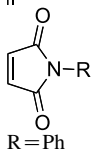
(9)

An ultimate goal of this investigation is the rapid synthesis of complex molecules via tandem reaction sequences. Thus, formation of complex polycyclic compounds via consecutive Alder-ene/Diels–Alder/Diels–Alder reactions in one pot was investigated (Scheme 3). Dialkynylallene **12** was first converted to cross-conjugated triene **19** using $[Rh(CO)_2Cl]_2$. The reaction was complete in 1 h at room temperature (as monitored by TLC). Next, 5 mol% $[Rh(dppe)Cl]_2$ and 10 mol% $AgSbF_6$ was added to the reaction flask. In 30 min, **19** had been completely converted to **25a** (as monitored by TLC).[16] A variety of external dienophiles (see Table 4) were then added at rt to give the intermolecular Diels–Alder products **29a** and **29b**. It is likely the Rh(I) catalyst functions as a Lewis acid to activate



Scheme 3.

Table 4. Consecutive reaction results from Scheme 4

Entry	Dienophile	Time (h)	Yield (%)	dr (**29a**:**29b**)
1		7	74	1:1
2		24	87	2:1
3		12	75	1:1
				
4	R=Ph	24	66	2:1
5	R=Me	24	82	5:1
6	R=H	20	68	1:2

the dienophiles since the intermolecular Diels–Alder reactions also occur at rt.[17]

The one-pot, three step reaction was used to generate a library of polycyclic compounds using different dienophiles (Table 4). Maleic anhydride (entry 1) and benzoquinone (entry 2) were added as dienophiles to give very high yields of the cycloadducts but with low diastereoselectivity. The unsymmetrical and less active dienophile methyl vinyl ketone reacted with complete regioselectivity to give the cycloadducts as a 1:1 mixture of diastereomers with the methyl ketone group at the C1 position (entry 3). In addition, we investigated the intermolecular Diels–Alder reaction with functionalized maleimides. The group on the nitrogen of the maleimide moiety played no apparent role in the rate of the cycloaddition, but did appear to effect the diastereoselectivity (entries 4–6). The stereochemical assignments shown Table 4 are based on X-ray analysis of **29a** (entry 2, Table 4) and **29b** (entry 3, Table 4).[18] Thus far attempts to effect the consecutive Alder-ene/Diels–Alder reaction with a single Rh(I) catalyst have not been successful.[19]

3. Conclusion

A consecutive one-pot Alder-ene/Diels–Alder/Diels–Alder reaction has been developed to demonstrate the potential of the cross-conjugated triene for accessing polycyclic compounds. The reaction sequence is highly chemoselective with the Alder-ene and the first Diels–Alder reaction only providing a single isomer **25a** and the intramolecular Diels–Alder reaction giving two endoaddition products resulting from addition to either face of **25a**. The transformation is highly atom-efficient with all the atoms of the starting dialkynyl allenes and dienophiles appearing in the products. Investigations are currently directed towards the application of this new method to the preparation of novel steroidal-like compounds.

Acknowledgements

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Supplementary data

Supporting information available: Spectra and experimentals for all new compounds are provided as supporting information.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.141

References and notes

1. Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, 1992.
2. (a) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186. (b) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *5*, 2245. (c) Shibata, T.; Takesue, Y.; Kadowaki, S.; Takagi, K. *Synlett* **2003**, 268.
3. Tsuge, O.; Wada, E.; Kanemasa, S. *Chem. Lett.* **1983**, 239.
4. Tsuge, O.; Wada, E.; Kanemasa, S. *Chem. Lett.* **1983**, 1525.
5. (a) Woo, S.; Squires, N.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 573. (b) Woo, S.; Legoupy, S.; Parra, S.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 1013.
6. Kwon, O.; Park, S. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 13402.
7. (a) Spino, C.; Tu, N. *Tetrahedron Lett.* **1994**, *35*, 3683. (b) Spino, C.; Liu, G.; Tu, N.; Girard, S. *J. Org. Chem.* **1994**, *59*, 5596.
8. Cross-conjugated trienes have been accessed previously using transition metal mediation. Malacria has subjected an allenyne to a cobalt(I) complex and obtained a mixture of two cross-conjugated trienes by using a *tert*-butyl group on the proximal double bond of the allene to direct the regiochemistry of the cyclization reaction to the distal double bond of the allene. (a) Lierena, D.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1996**, *37*, 7027. Sato has effected an Alder-ene reaction from an allenynol by using a two-carbon tether that favors reaction with the distal double bond of the allene. (b) Yamazaki, T.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7333. Livinghouse has observed a cross conjugated triene as a minor byproduct (21% yield) when using cobalt to catalyze a Pauson–Khand reaction. Pagenkopf, B. L.; Belanger, D. B.; O'Mahony, D. J. R.; Livinghouse, T. *Synthesis* **2000**, 1009.
9. To the best of our knowledge, this type of Ireland–Claisen rearrangement is an unprecedented protocol for the formation of allenes.
10. More recently our group has found that performing Alder-ene reactions at lower concentrations (0.05-0.01 M) gives higher yields of trienes in faster reaction times suggesting product inhibition.

11. For references regarding rhodium(I) transition metal catalyzed [4+2] cycloaddition reactions between electronically similar dienes and dienophiles, see: Gilbertson, S. R.; Hoge, G. S.; Genov, D. G. *J. Org. Chem.* **1998**, *63*, 10077. Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. Wang, B.; Cao, P.; Zhang, X. *Tetrahedron Lett.* **2000**, *41*, 8041. Paik, S.-J.; Son, S. U.; Chung, Y. K. *Org. Lett.* **1999**, *1*, 2045. Matsuda, I.; Shibata, M.; Sato, S.; Izumi, Y. *Tetrahedron Lett.* **1987**, *28*, 3361. McKinstry, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145. For a diene-allene cycloaddition, see: Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843.
12. Wang, B.; Cao, P.; Zhang, X. *Tetrahedron Lett.* **2000**, *41*, 8041.
13. Wender, P. A.; Williams, T. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4550.
14. Other catalysts were examined, but without success. Wilkinson's catalyst in trifluoroethanol, and activation of Wilkinson's catalyst with silver hexafluoroantimonate both led to decomposition while $[Rh(nbd)(dppe)]^{+}SbF_6^{-}$ gave no reaction.
15. A few groups have reported rhodium catalyzed formal [4+2] reactions using alkenes as the dienophile to form fused [6−5] ring systems. (a) Gilbertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075. (b) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. (c) Sato, Y.; Oonishi, Y.; Mori, M. *Organometallics* **2003**, *22*, 30.
16. Surprsingly, 5 mol% $[Rh(dppe)Cl]_2$/10 mol% $AgSbF_6$ gave better results than $[Rh(C_{10}H_8)(COD)]^{+}SbF_6^{-}$ for the one pot process. Compare the results of Table 3 and Scheme 3.
17. Wender, P. A.; Gamber, G. G.; Scanio, M. J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 3895.
18. The X-ray crystallographic data have been included in the supporting information as a CIF file and have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 256297 and 256298.
19. For a recent review on using a single catalyst to mediate two or more reactions, see: Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754.

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Enantioselective synthesis of β-amino alcohols and α-amino acids via a copper catalyzed addition of diorganozinc reagents to *N*-phosphinoylimines

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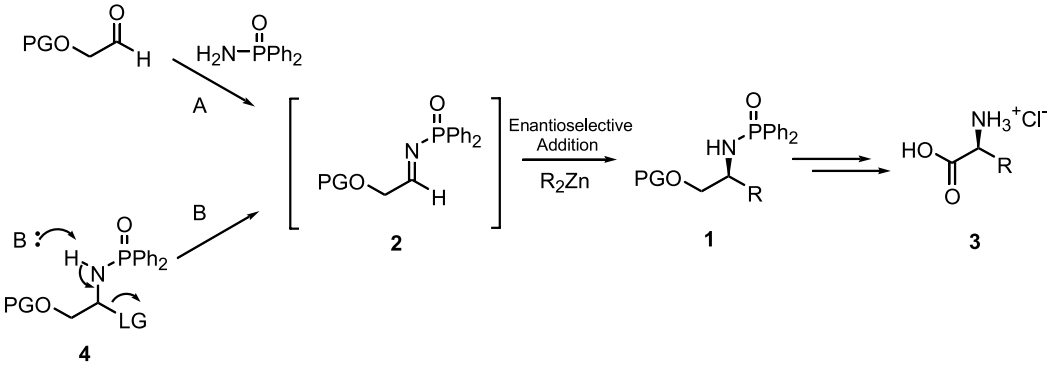
Abstract—Enantioenriched β-amino alcohols were prepared via an asymmetric addition of diethylzinc, catalyzed by the BozPHOS·Cu(I) complex, on in situ formed *N*-phosphinoylimines. The nature of the hydroxyl protecting groups was found to affect the enantioselectivities. Subsequent deprotection and oxidation of *N*-phosphinoyl β-amino alcohols afforded optically active α-amino acids (97% ee).

1. Introduction

The synthesis of β-amino alcohols is of considerable current interest as they are important sub-units commonly found in natural products, biologically active molecules, ligands, and chiral auxiliaries, or simply used as building blocks.[1] β-Amino alcohols are also potential precursors for the synthesis of non-proteinogenic α-amino acids. Incorporation of these unnatural compounds into proteins can lead to conformational changes, non-scissile peptide mimics and biologically active molecules with novel properties.[2]

The method we chose to synthesize β-amino alcohols (**1**, Scheme 1) was a nucleophilic addition of diorganozinc reagents to *N*-phosphinoylalkylimines (**2**) substituted with a β-alkoxy functionality. Subsequent oxidation of the deprotected β-amino alcohol will afford α-amino acid (**3**). The *N*-diphenylphosphinoyl protecting group was used due to its facile cleavage under mildly acidic conditions with no racemization. Diastereoselective methodologies were developed to generate β-amino alcohols.[3] One powerful method for preparing β-amino alcohols was a one-pot catalytic enantioselective reaction developed by Hoveyda and Snapper.[4] Excellent ee values were obtained, but this procedure suffered from use of an excess of diorganozinc reagents and a *N*-aryl protecting group that can be cleaved only under oxidizing conditions.



Scheme 1. Strategy to generate *N*-phosphinoylalkylimines, β-amino alcohols and α-amino acids.

Keywords: β-Amino alcohols; α-Amino acids; Enantioselective synthesis; Imines; Copper; Diorganozinc reagents.
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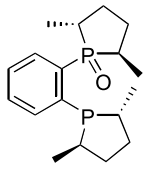
One drawback of using *N*-phosphinoylalkylimines with α-enolizable protons was the difficulty to isolate them due to their instability. Two strategies were used to solve this problem. The first one (path A) was a one-pot procedure involving generation of the imine from an in situ condensation of the aldehyde and the amide, using the diorganozinc reagent as a dehydrating agent. This approach led to excellent ee values but low conversions. The second (path B), was an in situ formation of the imine from a stable precursor **4** containing a leaving group (–OMe,[5] $-SO_2Ph$,[6] benzotriazoyl,[7] –OTMS,[8] or succinimyl[9]) on the α-position of the *N*-protected amine.

Recently, we reported an efficient methodology to generate the *N*-phosphinoylalkylimines in situ, from sulfinic acid (LG=$-SO_2Tol$) adducts, which was compatible with the BozPHOS (**5**)·Cu asymmetric catalyzed addition of diorganozinc reagents (Fig. 1).[10,11] Because it afforded excellent yields and ee values, we planned to use this strategy (path B) to generate optically active β-amino alcohols (**1**) and α-amino acids (**3**).



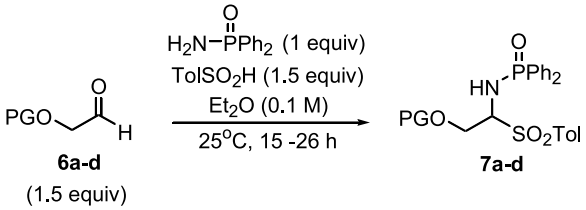
5
(*R*,*R*)-BozPHOS

Figure 1. Structure of (*R*,*R*)-BozPHOS, ((*R*,*R*)-MeDuPHOS monoxide).

2. Results and discussion

We initially identified which hydroxyl protecting group (PG) was the most suitable for the BozPHOS·Cu catalyzed asymmetric addition. Thus, sulfinic acid adducts **7** were prepared with several hydroxyl protecting groups (PG) by mixing the aldehyde **6**, diphenylphosphinic amide and *p*-toluenesulfinic acid in diethyl ether. The benzyl protected substrate **7a** was produced in the highest yield of 97% (Table 1, entry 1). It was found that strictly anhydrous conditions were mandatory to generate the adduct **7b** bearing the trityl moiety. Otherwise, acidic traces of water deprotected the α-trityloxyacetaldehyde **6b** and no desired product precipitated from the reaction mixture. The synthesis of the sulfinic acid adduct **7d** was problematic because it did not lead to any precipitation of the desired product. Consequently, the latter needed to be purified from the crude mixture by flash chromatography and it decomposed upon isolation.

Table 1. One-pot synthesis of sulfinic acid adducts **7**



6a-d
(1.5 equiv)

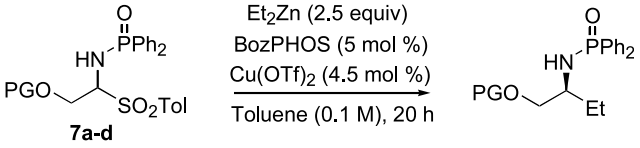
7a-d

Entry	PG	Product	Time (h)	Yield (%)
1	Bn	**7a**	20	97
2[a]	Tr	**7b**	15	70
3	Piv	**7c**	26	54
4	TBDMS	**7d**	15	38[b]

[a] Required strictly anhydrous conditions.
[b] Determined after flash chromatography.

With these compounds **7** in hand, we studied the effect of protecting groups (PG) on the level of enantiocontrol in the Cu-catalyzed diethylzinc addition (Table 2). The sulfinic acid adducts **7** were submitted to the optimized reaction conditions recently developed.[11] As the data summarized in Table 2 illustrate, the BozPHOS·Cu catalyzed addition of diethylzinc was strongly affected by the protecting group. It was found that the bulky trityl group **8b** (entries 4–7) provided best isolated yields (81–92%) and best ee values (75–97%).

Table 2. Enantioselective addition of diethylzinc to sulfinic acid adducts **7**



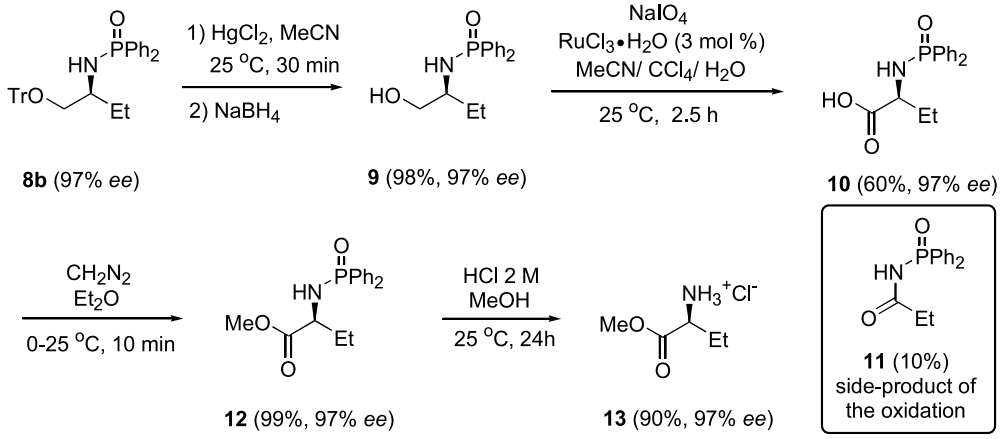
7a-d

Entry	PG	Product	Temperature (°C)	Yield (%)	ee[a] (%)
1[b]	Bn	**8a**	−20	95	84
2			−40	96	86
3			−60	83	89
4	Tr	**8b**	0	92	93
5			−40	81	95
6			−60	84	97
7			−78	89	75
8	Piv	**8c**	10	49	79
9			0	51	92
10			−20	69	87
11	TBDMS	**8d**	0	79	75[c]
12			−60	67	79[c]

[a] Enantiomeric excesses were determined by HPLC on a chiral stationary phase unless otherwise stated.
[b] Results determined after 48 h.
[c] Enantiomeric excesses were determined by SFC on a chiral stationary phase.

The temperature was another parameter that considerably affected the enantiomeric excesses. The most striking example was a 13% ee difference for a variation of 10 °C with the pivaloyl adduct **8c** (entries 8 and 9). In addition, a temperature of −60 °C was required to reach 97% ee with substrate **8b**. Finally, we changed the sulfinate leaving group by a benzotriazoyl substituent (**4**, LG=Bt). Comparable ee values were obtained but, owing to its low solubility, modest yields were obtained.

Removal of both the trityl and the *N*-diphenylphosphinoyl groups from **8b** was possible using HCl/MeOH, affording the free β-amino alcohol in quantitative yield (Scheme 2). However, our goal was to develop reaction conditions to access monoprotected α-amino acids **10** and **13**, which could be more useful in peptidic synthesis. Several conditions were screened for selective trityl deprotection (hydrogenolysis,[12] $ZnBr_2$,[13] BCl_3,[14] BBr_3, BBr_3·DMS, TFA,[15] TFA and TFAA followed by Et_3N[16] and acetyl chloride[17]) but the best procedure was a reductive

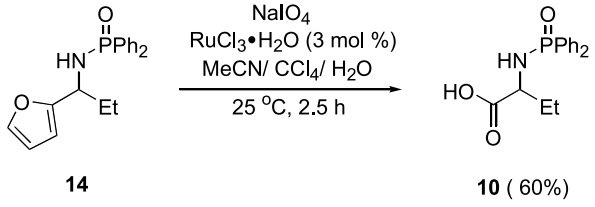


Scheme 2. Synthesis of α-amino acids from **8b**.

demercuration reported by Maltese.[18] A 10-fold excess of $HgCl_2$ was required to afford the β-amino alcohol **9** in 98% yield and 97% ee.

The next challenge was the oxidation of the β-amino alcohol **9** (Scheme 2). The complexity of this step resided in the presence of the protic acid sensitive *N*-phosphinoyl group and the possibility of the chiral center to racemize. Unsuccessful procedures tried included TEMPO free radical with sodium chlorite[19] or with trichloroisocyanuric acid,[20] IBX and 2-hydroxypyridine[21] or PDC[22] and all afforded total or partial degradation of the starting material or of the desired amino acid. The most successful procedure was the Sharpless oxidation[23] with $RuCl_3$ and $NaIO_4$ which generated the α-amino acid **10** in 60% yield without erosion in enantiomeric purity and 10% of the side-product **11** caused by over oxidation. Subsequent esterification with diazomethane and straightforward deprotection of the *N*-phosphinoyl group in mildly acidic conditions afforded the enantioenriched (97% ee) methyl ester hydrochloride derivative **13** of ethylglycine in 89% yield over two steps.

An alternative approach toward α-amino acids was to start from the addition product **14** of the *N*-phosphinoylimine derived from 2-furaldehyde (Scheme 3).[24] The enantioselective synthesis of the latter substrate from the BozPHOS·Cu catalyzed addition of diorganozinc reagents was reported by our research group.[10] By treating compound **14** with the same oxidation conditions mentioned above (Scheme 2), a similar yield of the α-amino acid **10** was obtained.



Scheme 3. Oxidative cleavage of the *N*-phosphinoylimine **14** derived from 2-furaldehyde.

3. Conclusion

In summary, based on the BozPHOS·Cu catalyzed addition of diorganozinc reagents, we have developed a practical procedure for the synthesis of enantioenriched (97% ee) β-amino alcohols.

The latter was an excellent framework for the catalytic enantioselective synthesis of optically active α-amino acids from a nucleophilic addition on imines. This method allowed generation of both enantiomers of α-amino acids, since both enantiomers of the BozPHOS ligand can be prepared, from the two commercially available enantiomers of Me-DuPHOS. We have also previously reported that the reaction was compatible with different dialkylzinc (Me_2Zn, *n*-Bu_2Zn and *i*-Pr_2Zn) or functionalized reagents.[10]

4. Experimental

4.1. General

All non-aqueous reactions were run under an inert atmosphere (argon) with rigid exclusion of moisture from reagents and glassware by using standard techniques for manipulating air-sensitive compounds. All glassware was stored in the oven and/or was flame-dried before use under an inert atmosphere of gas. Anhydrous solvents were obtained either by filtration through drying columns (ether, toluene, acetonitrile, dichloromethane) on a Glass-Contour system (Irvine, CA) or by distillation over sodium/benzophenone (toluene). Analytical TLC was performed on precoated, glass-backed silica gel (Merck 60 F_{254}). Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, ninhydrine, *p*-anisaldehyde or aqueous potassium permanganate. Flash column chromatography was performed by using 230–400 mesh silica [EM Science or Silicycle (Québec City, QC, Canada)] of the indicated solvent system according to standard technique. Melting points were obtained on a Buchi (Flawil, Switzerland) melting point apparatus and are uncorrected. NMR spectra (^1H, ^{13}C, ^{31}P) were recorded on Bruker AV 300, AMX 300, AV 400 or ARX 400 spectrometers.

Chemical shifts for ^{1}H NMR spectra are recorded in ppm with the solvent resonance as the internal standard ($CDCl_3$, δ 7.27 ppm, DMSO-d_6, δ 2.50 ppm or D_2O δ 4.80 ppm). Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; sept, septet; oc, octet; m, multiplet; br, broad), coupling constant in Hz, and integration. Chemical shifts for ^{13}C NMR spectra are recorded in ppm from tetramethylsilane by using the central peak of deuterochloroform (77.00 ppm) or deuterated DMSO (39.52 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. Infrared spectra were taken on a Perkin–Elmer Spectrum One FTIR and are reported in reciprocal centimeters (cm^{-1}). Optical rotations were determined with a Perkin–Elmer 341 polarimeter at 589 or 546 nm. Data are reported as follows: $[\alpha]_D^{temp}$, concentration (c in g/100 mL) and solvent. Combustion analyses were performed by the Elemental analysis Laboratory of the Université de Montréal.

Analytical HPLC was performed on a Hewlett–Packard analytical instrument (model 1100) equipped with a diode array UV detector. Data for determination of the enantiomeric excess are reported as follows: column type, eluent, flow rate, and retention time (t_r). Analytical Supercritical Fluid Chromatography was performed on a Berger SFC Analytical Instrument equipped with a diode array UV detector. Data are reported as follows: column type, eluent, flow rate: retention time (t_r). Analytical gas chromatography was carried out on a Hewlett–Packard 5880A gas chromatograph equipped with a splitless mode capillary injector and a flame ionization dectector. Unless otherwise noted, the injector and detector temperatures were set to 250 °C and hydrogen was used as the carrier gas (63 psi). Data are reported as follows: column type, column length, initial temperature, initial time, rate, final temperature, final time: retention time (t_r).

$Cu(OTf)_2$ and $RuCl_3 \cdot H_2O$ were purchased from Strem Chemicals (Newburyport, MA). Diazomethane was prepared from Diazald®. *p*-Toluenesulfinic acid was formed by dissolving its hydrated sodium salt in a minimum of hot 10% vol/vol HCl (the resulting pH must be lower than 3) and crystallization at 4 °C. Further filtration and drying under vacuum led to white crystals. Diethylzinc was purchased neat from Akzo Nobel and used without purification. All others starting materials were purchased from Aldrich or Alfa Aesar (Ward Hill, MA). Unless otherwise stated, commercial reagents were used without purification. Racemic samples for HPLC analysis were prepared by addition of Et_2Zn/CuCN in toluene to the sulfinic acid adducts. Ligand (*R*,*R*)-BozPHOS was prepared according to literature procedure.[10]

4.2. General procedure for preparation of sulfinic acid adducts 7

A round-bottomed flask equipped with a magnetic stirring bar, was charged with *P*,*P*-diphenylphosphinic amide (1.43 g, 6.6 mmol, 1 equiv). Diethyl ether (70 mL, ~0.1 M) was then added to the flask. The resulting suspension was stirred for 5 min and the aldehyde **6** (10 mmol, 1.5 equiv) was added, then *p*-toluenesulfinic acid (1.56 g, 10 mmol, 1.5 equiv) was added in one portion at room temperature. The reaction mixture was allowed to stir (200 rpm) under closed atmosphere for a specific period of time, during which a white precipitate was slowly formed. The mixture was filtered through a sintered glass funnel and the white solid was washed with diethyl ether and dried under vacuum to afford the sulfinic acid adduct **7**.

4.2.1. *N*-{2-(Benzyloxy)-1-[(4-methylphenyl)sulfonyl]-ethyl}-*P*,*P*-diphenylphosphinic amide (7a). The general procedure was followed (specific conditions: 20 h). The crude compound (white powder) was used without purification for the next step. Yield: 97%. Mp 125.0–126.0 °C (dec); R_f 0.45 (100% EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H), 3.80 (dd, J=10.4, 7.5 Hz, 1H), 3.87 (dd, J=10.4, 3.5 Hz, 1H), 4.38 (d, J=11.7 Hz, 1H), 4.44 (d, J=11.8 Hz, 1H), 4 .78 (m, 1H), 6.49 (t, J=11.7 Hz, 1H), 7.11–7.65 (m, 19H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.2, 67.9, 71.6, 72.3, 127.6, 127.7, 128.1 (d, J_{C-P}=13.0 Hz), 128.2 (d, J_{C-P}=13.2 Hz), 128.2, 129.1, 129.5, 131.2 (d, J_{C-P}=10.1 Hz), 131.4 (d, J_{C-P}=10.0 Hz), 131.6 (d, J_{C-P}=10.0 Hz), 131.6 (d, J_{C-P}=10.2 Hz), 132.3 (d, J_{C-P}=77.1 Hz), 134.0, 134.5 (d, J_{C-P}=73.3 Hz), 137.6, 144.4; ^{31}P NMR (121 MHz, DMSO-d_6) δ 25.3; IR (Neat) 3065, 2877, 1595, 1435, 1289, 1191, 1125, 1085, 865, 725, 692, 666, 583 cm^{-1}. LRMS (APCI) *m*/*z* calcd for $C_{21}H_{20}NO_2P$ $[M-SO_2Tol]^+$: 350.1 found: 350.1.

4.2.2. *N*-[1-[(4-Methylphenyl)sulfonyl]-2-(trityloxy)-ethyl]-*P*,*P*-diphenylphosphinic amide (7b). The general procedure was followed, except that reagents and glassware were dried, anhydrous ether was used and the reaction was run under inert atmosphere (specific conditions: 15 h). The crude compound (white powder) was used without purification for the next step. Yield: 70%. Mp 99.5–100.0 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H), 3.41 (dd, J=8.1, 6.8 Hz, 1H), 3.51 (dd, J=9.8, 4.1 Hz, 1H), 4.74–4.78 (m, 1H), 6.61 (dd, J=12.5, 12.3 Hz, 1H), 7.20–7.30 (m, 17H); 7.40–7.43 (m, 4H), 7.47–7.54 (m, 6H); 7.70 (dd, J=11.8, 7.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.2, 63.3, 73.2, 87.9, 128.0, 128.0, 128.9–129.1 (m), 129.2, 130.1 (d, J_{C-P}=8.2 Hz), 132.3 (dd, J_{C-P}=11.8, 11.4 Hz), 132.5 (d, J_{C-P}=9.5 Hz), 135.0, 135.0 (dd, J_{C-P}=125, 59 Hz), 144.0, 145.3; ^{31}P NMR (161 MHz, DMSO-d_6) δ 27.0; IR (Neat) 3058, 2879, 1314, 1299, 1185, 1154, 1125, 1062, 702, 689 cm^{-1}. Elemental analysis calcd for $C_{39}H_{34}NO_4PS$: C, 72.77; H, 5.32; N, 2.18; S, 4.98 found: C, 72.75; H, 5.55; N, 2.24; S, 4.97.

4.2.3. 2-[(Diphenylphosphoryl)amino]-2-[(4-methylphenyl)sulfonyl]ethyl pivalate (7c). The general procedure was followed (specific conditions: 26 h). The crude compound (white powder) was used without purification for the next step. Yield: 54%. Mp 134.0–135.0 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (s, 9H), 2.39 (s, 3H), 4.21 (dd, J=13.0, 7.5 Hz, 1H), 4.52 (dd, J=11.5, 4.3 Hz, 1H), 4.77–4.80 (m, 1H), 6.64 (dd, J=12.0, 11.8 Hz, 1H), 7.33 (d, J=7.9 Hz, 2H), 7.37–7.55 (m, 4H), 7.44–7.55 (m, 4H), 7.66–7.71 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.2, 27.6, 39.1, 62.9, 71.6, 129.2 (dd, J_{C-P}=27.0, 12.5 Hz), 130.4 (d, J_{C-P}=22.0 Hz), 132.1 (dd, J_{C-P}=19.9, 10.3 Hz), 132.6 (d, J_{C-P}=22.0 Hz), 134.4, 134.7 (dd, J_{C-P}=125.7, 42.7 Hz), 145.8, 178.2; ^{31}P NMR (161 MHz, DMSO-d_6) δ 26.7; IR (Neat) 3061, 2976,

2949, 1729, 1438, 1302, 1291, 1279, 1192, 1165, 1135, 1126, 972, 668 cm^{-1}. LRMS (APCI) *m/z* calcd for $C_{19}H_{22}NO_3P$ $[M-SO_2Tol]^+$: 344.1 found: 344.1.

4.2.4. *N*-{2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[(4-methylphenyl)sulfonyl]ethyl}-*P*,*P*-diphenylphosphinic amide (7d). The general procedure was followed, but the product did not precipitate (specific conditions: 15 h). The reaction mixture was evaporated under reduced pressure, and the crude mixture was purified by flash chromatography (70% EtOAC in hexanes). A white foam was obtained (Yield: 38%) and decomposed upon isolation, so it had to be used immediately for the next step. R_f 0.50 (100% EtOAc); ^1H NMR (400 MHz, DMSO-d_6) δ 0.05 (s, 6H), 0.77 (s, 9H), 2.36 (s, 3H), 3.96 (dd, $J=7.5$, 6.6 Hz, 1H), 4.15 (dd, $J=8.4$, 4.6 Hz, 1H), 4.53–4.62 (m, 1H), 6.36 (dd, $J=11.9$, 11.8 Hz, 1H), 7.29 (d, $J=8.0$ Hz, 2H), 7.35–7.45 (m, 4H), 7.48–7.53 (m, 4H), 7.62 (d, $J=8.0$ Hz, 2H), 7.71 (dd, $J=12.1$, 7.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ −4.6, 18.9, 21.9, 26.8, 62.7, 74.8, 125.5, 129.1 (dd, $J_{C-P}=17.2$, 12.7 Hz), 130.2 (d, $J_{C-P}=45.9$ Hz), 132.2–132.6 (m), 132.5, 134.8 (dd, $J_{C-P}=148.0$, 24.3 Hz), 145.3; ^{31}P NMR (161 MHz, DMSO-d_6) δ 26.6.

4.3. General procedure for the asymmetric addition on sulfinic acid adducts 7

A flame-dried round-bottomed flask equipped with a magnetic stirring bar was charged with $Cu(OTf)_2$ (6.5 mg, 0.018 mmol, 4.5 mol%) and (*R*,*R*)-BozPHOS (6.4 mg, 0.02 mmol, 5 mol %) under argon. Anhydrous toluene (1.5 mL) was added to the flask at room temperature via a syringe. The resulting dark green heterogeneous solution was stirred for 1 h at room temperature and neat diethylzinc (102 μL, 1 mmol, 2.5 equiv) was added at room temperature under argon via a gas-tight syringe (*Caution*: pyrophoric). The resulting dark brown suspension was stirred for 20 min at room temperature. The mixture was cooled to the temperature described in Table 2 and stirred 10 min at that temperature. Substrate **7** (0.4 mmol, 1 equiv) in anhydrous toluene (1.5 mL) was added via a teflon cannula (heterogeneous mixture) under argon. The flask was rinsed with 1 mL, and 0.5 mL of toluene. The reaction mixture was allowed to stir 20 h at the temperature mentioned above under argon. Aqueous saturated ammonium chloride (5 mL) was then added dropwise. The mixture was brought to room temperature and poured into a separatory funnel containing aqueous saturated ammonium chloride (20 mL). The biphasic mixture was extracted with dichloromethane (3× 20 mL). The combined extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography with ethyl acetate 100% to afford compound **8**.

4.3.1. *N*-{1-[(Benzyloxy)methyl]propyl}-*P*,*P*-diphenylphosphinic amide (8a). The general procedure was followed, except that the reaction was run 48 h (specific conditions: −60 °C) to afford **8a** as a white solid. Yield 83%, enantiomeric excess (89% ee) was determined by HPLC analysis (Chiralpak AD-H, 80:20 hexanes–*i*-PrOH, 1.0 mL/min: (*S*)-**8a** $t_r=9.52$ min, (*R*)-**8a** $t_r=11.83$ min). $[\alpha]_D^{21}=-32.2$ (*c* 1.30, CH_2Cl_2); mp 89.0–91.0 °C; R_f 0.20 (100% EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J=$ 7.4 Hz, 3H), 1.69 (oc, $J=7.0$ Hz, 2H), 3.05–3.20 (m, 1H), 3.27 (dd, $J=10.4$, 7.0 Hz, 1H), 3.57 (d, $J=3.8$ Hz, 2H), 4.47 (d, $J=12.0$ Hz, 1H), 4.52 (d, $J=12.0$ Hz, 1H), 7.20–7.30 (m, 5H), 7.30–7.50 (m, 6H), 7.84–7.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 15.2, 27.0 (d, $J_{C-P}=$ 6.2 Hz), 52.5, 72.6 (d, $J_{C-P}=4.1$ Hz), 73.1, 127.5, 127.6, 128.2, 128.4, 131.6 (d, $J_{C-P}=2.3$ Hz), 132.0 (d, $J_{C-P}=$ 7.0 Hz), 132.1 (d, $J_{C-P}=7.0$ Hz), 133.7 (d, $J_{C-P}=10.1$ Hz), 138.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 23.5; IR (Neat) 3058, 2841, 1435, 1183, 1108, 1049, 998, 721, 691, 573 cm^{-1}. LRMS (ACPI) *m/z* calcd for $C_{23}H_{26}NO_2P$ $[M+H]^+$: 380.1 found: 380.1. Elemental analysis calcd for $C_{23}H_{26}NO_2P$: C, 72.81; H, 6.91; N, 3.69 found: C, 72.71; H, 7.13; N, 3.72.

4.3.2. *P*,*P*-Diphenyl-*N*-{1-[(trityloxy)methyl]propyl}-phosphinic amide (8b). The general procedure was followed (specific conditions: −60 °C) to afford **8b** as a white solid. Yield 84%, enantiomeric excess (97% ee) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexanes–*i*-PrOH, 1.0 mL/min: (*S*)-**8b** $t_r=10.8$ min, (*R*)-**8b** $t_r=13.6$ min). $[\alpha]_D^{20}=-8.1$ (*c* 1.00, CH_2Cl_2); mp 67.5–68.5 °C; R_f 0.35 (70% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, $J=7.4$ Hz, 3H), 1.86 (dqn, $J=34.5$, 7.4 Hz, 2H), 3.08–3.16 (m, 1H), 3.21–3.33 (m, 2H), 3.28 (dd, $J=3.7$, 3.7 Hz, 1H), 7.25–7.51 (m, 21H), 7.79–7.93 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 28.1, 53.4, 65.7, 86.8, 127.5, 128.3, 128.9 (d, $J_{C-P}=12$, 5 Hz), 129.1, 132.1 (dd, $J_{C-P}=8.8$, 2.5 Hz), 132.6 (dd, $J_{C-P}=33.6$, 9.4 Hz), 133.4 (d, $J_{C-P}=71.9$ Hz), 144.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.5; IR (Neat) 3056, 2928, 1437, 1189, 1089, 1068, 1029, 722, 693 cm^{-1}. Elemental analysis calcd for $C_{35}H_{34}NO_2P$: C, 79.07; H, 6.45; N, 2.63 found: C, 78.90; H, 6.63; N, 2.77.

4.3.3. 2-[(Diphenylphosphoryl)amino]butyl pivalate (8c). The general procedure was followed (specific conditions: 0 °C) to afford **8c** as a white solid. Yield 51%, enantiomeric excess (92% ee) was determined by HPLC analysis (Chiralpak AD-H, 80:20 hexanes–i-PrOH, 1.0 mL/min: (*R*)-**8c** $t_r=6.6$ min, (*S*)-**8c** $t_r=7.8$ min). $[\alpha]_D^{21}=-23.3$ (*c* 0.63, CH_2Cl_2); mp 95.5–96.5 °C; R_f 0.18 (70% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, $J=7.4$ Hz, 3H), 1.19 (s, 9H), 1.61–1.66 (m, 2H), 3.01 (dd, $J=10.9$, 6.4 Hz, 1H), 3.20–3.30 (m, 1H), 4.13 (d, $J=3.0$ Hz, 1H), 4.14 (d, $J=2.6$ Hz, 1H), 7.42–7.48 (m, 6H), 7.88–7.91 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 26.9, 27.0, 38.7, 51.6, 66.5, 128.4 (dd, $J_{C-P}=12.5$, 6.4 Hz), 131.7, 131.9 (dd, $J_{C-P}=9.4$, 2.8 Hz), 133.1 (d, $J_{C-P}=21.1$ Hz), 178.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 23.5; IR (Neat) 2966, 2933, 2873, 1725, 1437, 1282, 1182, 1159, 1121, 1108, 722, 693 cm^{-1}; LRMS (APCI) *m/z* calcd for $C_{21}H_{28}NO_3P$ $[M+H]^+$: 374.2 found: 374.2. Elemental analysis calcd for $C_{21}H_{28}NO_3P$: C, 67.54; H, 7.56; N, 3.75 found: C, 67.24; H, 7.87; N, 3.82.

4.3.4. *N*-[1-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)propyl]-*P*,*P*-diphenylphosphinic amide (8d). The general procedure was followed (specific conditions: −60 °C) to afford **8d** as a colorless oil. Yield 67%, enantiomeric excess (79% ee) was determined by SFC analysis (Chiralpak AD, 10% MeOH, 1.5 mL/min: (*S*)-**8d** $t_r=16.1$ min, (*R*)-**8d** $t_r=$ 18.9 min). $[\alpha]_D^{22}=-20.0$ (*c* 1.40, CH_2Cl_2); R_f 0.42 (100% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (d, $J=7.7$ Hz,

6H), 0.86 (s, 9H), 1.54–1.71 (m, 2H), 2.97–3.07 (m, 1H), 3.20 (dd, $J=10.5$, 7.1 Hz, 1H), 3.67 (d, $J=4.1$ Hz, 2H), 7.42–7.47 (m, 6H), 7.87–7.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, 10.3, 18.1, 25.7, 26.4, 53.7, 65.2, 128.2 (dd, $J_{C-P}=12.5$, 4.7 Hz), 131.5, 131.9 (dd, $J_{C-P}=20.3$, 9.4 Hz), 133.1 (dd, $J_{C-P}=129.1$, 11.2 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.6; IR (Neat) 2954, 2928, 2856, 1438, 1253, 1190, 1106, 835, 723, 697, 630 cm^{-1}; LRMS (APCI) *m/z* calcd for $C_{22}H_{34}NO_2PSi$ $[M+H]^+$: 404.2 found: 404.2.

4.3.5. *N*-[1-(Hydroxymethyl)propyl]-*P*,*P*-diphenylphosphinic amide (9). A flame-dried round-bottomed flask equipped with a magnetic stirring bar was charged with compound **8b** (270 mg, 0.50 mmol, 1 equiv) and $HgCl_2$ (1.37 g, 5.07 mmol, 10 equiv) under argon. Anhydrous MeCN (25 mL, 0.02 M) was added to the flask. The colorless solution was stirred for 30 min at room temperature under argon. Small solid portions of $NaBH_4$ were added to the stirred solution and a dark grey precipitate was formed (gas formation). Additions of $NaBH_4$ were stopped when the precipitate formed 3/4 of the solution and no gas was formed. The mixture was stirred 5 min at room temperature, then was brought to 0 °C. Small portions of H_2O (total of 100 mL) were added (gas formation). The mixture was warmed to room temperature and stirred 25 min. The mixture was extracted with DCM (3×80 mL). The combined extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography with 100% DCM to remove the trityl moiety, then with 5% MeOH in DCM to afford 145 mg of the title compound as a white solid (98% yield). Enantiomeric excess (97% ee) was determined by SFC analysis (Chiralpak AD, 15% MeOH, 1.5 mL/min: (*S*)-**9** $t_r=29.3$ min, (*R*)-**9** $t_r=32.1$ min). $[\alpha]_D^{20}=-39.3$ (*c* 1.00, CH_2Cl_2); mp 139.5–141.0 °C; R_f 0.34 (10% MeOH in DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, $J=7.4$ Hz, 3H), 1.44–1.59 (m, 2H), 2.90–3.10 (m, 2H), 3.46 (dd, $J=11.6$, 6.7 Hz, 1H), 3.65 (d, $J=11.2$ Hz, 1H), 4.55–4.60 (br s, 1H), 7.44–7.54 (m, 6H), 7.54–7.97 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 26.9, 57.5, 67.7, 129.0 (d, $J_{C-P}=12.3$ Hz), 132.0 (dd, $J_{C-P}=130.9$, 118.5 Hz), 132.6 (dd, $J_{C-P}=74.1$, 9.4 Hz), 132.5 (dd, $J_{C-P}=9.7$, 2.7 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.4; IR (Neat) 3253, 2961, 2913, 2871, 1436, 1169, 1142, 1112, 1092, 995, 723, 694 cm^{-1}; LRMS (APCI) *m/z* calcd for $C_{16}H_{20}NO_2P$ $[M+H]^+$: 290.1 found: 290.1.

4.3.6. 2-[(Diphenylphosphoryl)amino]butanoic acid (10). A round-bottomed flask equipped with a magnetic stirring bar was charged with compound **9** (170 mg, 0.5876 mmol, 1 equiv). The amino alcohol was dissolved in a 2:2:3 mixture of MeCN (3.6 mL), CCl_4 (3.6 mL) and H_2O (4.8 mL). Solid $NaIO_4$ (502 mg, 2.35 mmol, 4 equiv), then $RuCl_3\cdot H_2O$ (4 mg, 0.017 mmol, 0.03 equiv) were added in one portion to the reaction mixture. The dark brown mixture was vigorously stirred for 2.5 h at room temperature. The mixture was diluted with DCM (20 mL) and washed with H_2O (20 mL). The aqueous layer was extracted twice with DCM (2×20 mL). The crude product was dissolved in EtOAc (15 mL) and extracted with $NaHCO_3$ sat. (3× 40 mL). Combined basic extracts were acidified (pH 1–2) with HCl 10% v/v and extracted quickly with DCM (3× 80 mL). Combined extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford 106 mg of the title compound as a white solid (60% yield). The crude compound was used without purification for the next step. Analytically pure product can be obtained by flash chromatography with 1% AcOH in EtOAc. Enantiomeric excess (97% ee) was determined by SFC analysis (Chiralpak AD, 20% MeOH, 1.5 mL/min: (*S*)-**10** $t_r=36.9$ min, (*R*)-**10** $t_r=41.3$ min). $[\alpha]_D^{20}=-49.5$ (*c* 1.00, CH_2Cl_2); mp 130.0–131.0 °C; R_f 0.47 (1% AcOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, $J=7.3$ Hz, 3H), 1.77 (qn, $J=7.2$ Hz, 2H), 3.73 (dq, $J=21.5$, 5.0 Hz, 1H), 3.91 (dd, $J=10.7$, 3.9 Hz, 1H), 7.43–7.56 (m, 6H), 7.90–7.97 (m, 4H), 12.57–12.79 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 27.4, 54.3, 130.6 (dd, $J_{C-P}=133.1$, 107.1 Hz), 131.9 (dd, $J_{C-P}=79.1$, 9.8 Hz), 132.1 (dd, $J_{C-P}=3.1$, 3.1 Hz), 174.4; ^{31}P NMR (161 MHz, $CDCl_3$) δ 26.6; IR (Neat) 2877, 2458, 1714, 1438, 1123, 1106, 891, 724, 692 cm^{-1}. Elemental analysis calcd for $C_{16}H_{18}NO_3P$: C, 63.36; H, 5.98; N, 4.62 found: C, 63.50; H, 6.15; N, 4.67.

4.3.7. Methyl 2-[(diphenylphosphoryl)amino]butanoate (12). A flame-dried round-bottomed flask equipped with a magnetic stirring bar was charged with the amino acid **10** (89 mg, 0.2934 mmol, 1 equiv) under argon. Anhydrous DCM (5 mL) was added via a syringe and the colorless solution was cooled to 0 °C. Excess of diazomethane in Et_2O was added at 0 °C under argon until the yellow color persisted. The resulting yellow solution was stirred 5 min under argon at 0 °C and 5 min at room temperature. The solution was evaporated under reduced pressure to afford 93 mg of the title compound as a white solid (99% yield). The crude compound was used without purification for the next step. Analytically pure product can be obtained by flash chromatography with 70–100% EtOAc in hexanes. Enantiomeric excess (97% ee) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexanes–*i*-PrOH, 1.0 mL/min: (*R*)-**12** $t_r=14.3$ min, (*S*)-**12** $t_r=24.5$ min). $[\alpha]_D^{22}=-16.8$ (*c* 1.00, CH_2Cl_2); mp 91.0–92.0 °C; R_f 0.30 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, $J=7.4$ Hz, 3H), 1.77 (sept, $J=1.0$ Hz, 2H), 3.62–2.67 (m, 1H), 3.68 (s, 3H), 3.77–3.86 (m, 1H), 7.41–7.47 (m, 6H), 7.49–7.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 28.1, 52.0, 54.3, 128.3 (dd, $J_{C-P}=12.6$, 5.6 Hz), 131.8, 131.8 (dd, $J_{C-P}=127.6$, 55.6 Hz), 131.9 (dd, $J_{C-P}=20.9$, 9.7 Hz), 173.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 23.4; IR (Neat) 3110, 2936, 2877, 1732, 1436, 1197, 1184, 1106, 903, 721, 691 cm^{-1}. Elemental analysis calcd for $C_{17}H_{20}NO_3P$: C, 64.35; H, 6.35; N, 4.41 found: C, 64.01; H, 6.45; N, 4.39.

4.3.8. Methyl 2-aminobutanoate hydrochloride (13). A round-bottomed flask equipped with a magnetic stirring bar was charged with substrate **12** (67 mg, 0.211 mmol, 1 equiv). A mixture of methanol (1.7 mL) and aqueous concentrated HCl (0.38 mL) was added to the flask. The resulting bright clear yellow solution was allowed to stir at room temperature under closed atmosphere for 24 h. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in aqueous HCl 10% v/v (4 mL). The precipitate (diphenylphosphinic acid) was removed by filtration on a sintered glass funnel. The acidic filtrate was extracted with diethyl ether (3×10 mL), the acidic layer was then evaporated under reduced pressure or

lyophilized to afford 29 mg of the title compound as an off-white solid (90% yield). Analytically pure product can be obtained by triturating in Et_2O, then in EtOAc or by flash chromatography with 10% DCM in MeOH. Enantiomeric excess (97% ee) was determined by GC analysis (Cyclodex β, 30 m, 30 °C, 0 min, 5 °C/min, 220 °C, 5 min: (*R*)-**13** t_r= 12.8 min, (*S*)-**13** t_r=13.0 min). The absolute configuration *S* of **13** was determined by comparison of the optical rotation with that of the literature data. [lit.[25] $[\alpha]_D^{20}=+14.1$ (*c* 1.00, 95% AcOH)]. $[\alpha]_D^{20}=+13.4$ (*c* 0.32, 95% AcOH); R_f 0.42 (20% MeOH in DCM); The physical and spectroscopic properties were in accordance with those described in the literature.[25]

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References and notes

1. (a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561–2576. (b) Ager, D. J.; Prakash, I.; David, R.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.
2. (a) Noren, C. J.; Anthony-Cahill, S. J.; Griffith, M. C.; Schultz, P. G. *Science* **1989**, *244*, 182–188. (b) Dougherty, D. A. *Biopolymers* **2000**, *4*, 645–652. (c) Gallos, J. K.; Sarli, V. C.; Vargogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N. G. *Tetrahedron Lett.* **2003**, *44*, 3905–3909. (d) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650. (e) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: New York, 1989. (f) Williams, R. M. *Chem. Rev.* **1992**, *92*, 889–917. (g) Pojitkov, E. A.; Efremenko, E. N.; Varfolomeev, S. D. *J. Mol. Catal. B* **2000**, *10*, 47–55. (h) Bain, J. D.; Glabe, C. G.; Dix, T. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1989**, *111*, 8013–8014. (i) Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360–366. (j) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854.
3. (a) Cooper, T. A.; Larigo, A. S.; Laurent, P.; Moody, C.; Takle, A. K. *Synlett* **2002**, *10*, 1730–1732. (b) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron Lett.* **2003**, *44*, 9189–9192. (c) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948–9957. (d) Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275–4281. (e) Giri, N.; Petrini, M.; Profeta, R. *J. Org. Chem.* **2004**, *69*, 1290–1297. (f) Schwardt, O.; Veith, U.; Gaspard, C.; Jäger, V. *Synthesis* **1999**, 1473–1490. (g) Ishimaru, K.; Tsuru, K.; Yabuta, K.; Wada, M.; Yamamoto, Y.; Akiba, K. Y. *Tetrahedron* **1996**, *41*, 13137–13144. (h) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946.
4. Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409–10410.
5. Attrill, R.; Tye, H.; Cox, L. R. *Tetrahedron: Asymmetry* **2004**, *15*, 1681–1684.
6. Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970–8972.
7. Katritzky, A. R.; Harris, P. A. *Tetrahedron: Asymmetry* **1992**, *3*, 437–442.
8. Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10–19.
9. Kohn, H.; Sawhney, K. A.; Robertson, D. W.; Leander, J. D. *J. Pharm. Sci.* **1994**, *83*, 689–691.
10. (a) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692–1693. (b) Boezio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260–14261.
11. Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5405–5410.
12. Mirrington, R. B.; Schmalzl, K. L. *J. Org. Chem.* **1972**, *18*, 2877–2881.
13. Kohli, V.; Köster, H. B. *Tetrahedron Lett.* **1980**, *21*, 2683–2686.
14. Jones, G. B.; Chapman, B. J.; Huber, R. S.; Beaty, R. *Tetrahedron: Asymmetry* **1994**, *5*, 1199–1202.
15. Kim, B. M.; Park, J. S.; Cho, J. H. *Tetrahedron Lett.* **2000**, *41*, 10031–10034.
16. Krainer, E.; Naider, F. *Tetrahedron Lett.* **1993**, *34*, 1713–1716.
17. Bergmeier, S. C.; Arason, K. M. *Tetrahedron Lett.* **2000**, *41*, 5799–5802.
18. Maltese, M. *J. Org. Chem.* **2001**, *66*, 7615–7625.
19. Zhao, M.; Li, J.; Mano, E.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564–2566.
20. De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999–5001.
21. Mazitschek, R.; Mülbaeir, M.; Giannis, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4059–4061.
22. Babu, I. R.; Hamill, E. K.; Kumar, K. *J. Org. Chem.* **2004**, *69*, 5468–5470.
23. Carlsen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, B. K. *J. Org. Chem.* **1981**, *46*, 3936–3938.
24. Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513–3516.
25. Ardakani, A. A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4817–4820.

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Preorganization in the Nazarov cyclization: the role of adjacent coordination sites in the highly Lewis acidic catalyst $[IrMe(CO)(dppe)(DIB)](BAr^f_4)_2$

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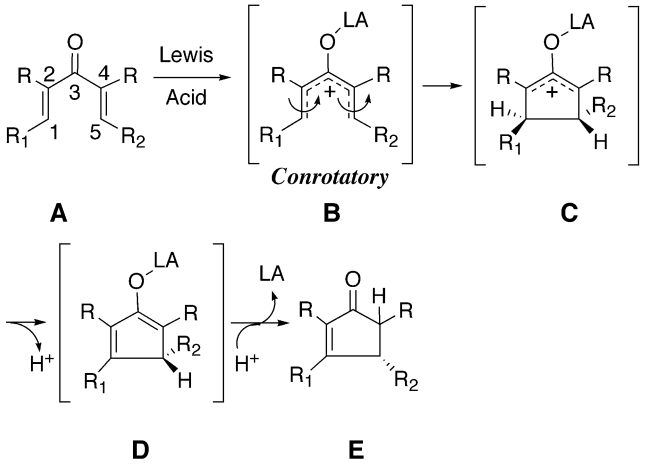
Abstract—The dicationic Ir(III) complex $[IrMe(CO)(dppe)(DIB)](BAr^f_4)_2$ where dppe = bis(diphenylphosphino)ethane and DIB = *o*-diiodobenzene possesses adjacent labile sites and is found to be a very active catalyst for the Nazarov cyclization. ^{31}P NMR spectroscopy provides evidence for substrate–catalyst binding by chelation, and this is found to be the resting state of the system during catalysis. The efficiency of the cyclization is attributed to the electrophilicity of the Ir(III) complex and substrate activation via O,O′-chelation which employs two substrate carbonyl groups or one carbonyl and an ether function, and encourages the s-*trans*/s-*trans* conformation required for cyclization. When two point binding occurs through an oxygen atom and one of the vinyl groups, the s-*trans*/s-*trans* conformation is not achieved, and cyclization is not observed. In one case, monodentate binding of substrate occurs, and the rate of cyclization is significantly slower than when O,O′-chelation is possible. The viability of O,O′-chelation is shown by the crystal structure determination of a model substrate–catalyst complex.

1. Introduction

1.1. Lewis acid catalysis of Nazarov cyclization

Electrocyclic reactions are powerful synthetic transformations with the ability to create new carbon–carbon bonds stereospecifically by simple orbital reorganization. One type of electrocyclic reaction is a 4π-electron process known as the Nazarov cyclization, involving the conversion of divinyl ketones **A** to cyclopentenones **E** by activation with a Lewis acid (see Eq. 1).[1–3] Cyclization of pentadienyl cation **B** must proceed with conservation of orbital symmetry, dictating conrotatory ring closure to give a product with an *anti* relationship between R_1 and R_2 (see **C**, Eq. 1). Since disrotatory closure is electronically forbidden, stereospecificity is ensured for the bond formation.[4] Elimination of a proton gives the enolate **D**, which undergoes reprotonation with release of the Lewis acid to give the product cyclopentenone **E**. Since superstoichiometic amounts of Lewis acid are often required to effect cyclization, it seems that this last protonation step can be inefficient.



(1)

The first example of Lewis-acid catalyzed Nazarov cyclization was reported by Denmark and co-workers in the context of silicon-accelerated cyclization.[5] In this case, substoichiometric $FeCl_3$ (40 mol%) gave a lower yield of the desired product relative to the optimal (1.05 equiv $FeCl_3$) reaction conditions. West later reported several examples of catalysis in interrupted Nazarov processes, using $FeCl_3$, $BF_3 \cdot OEt_2$, and $SnCl_4$.[6–9] A number of new systems have been reported as effective catalysts for the original version of the cyclization (termination by loss of a

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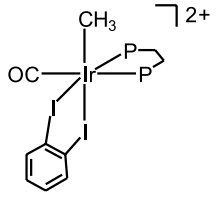
proton) in the last two years. The following catalyst systems were reported in close succession: $Cu(OTf)_2$ (effective at 2 mol%),[10] $PdCl_2(CN)_2$ (effective at 1–10 mol%),[11] $AlCl_3$ (10 mol%),[12] chiral complexes of $Sc(OTf)_3$ (10–20 mol%)[12,13] and $Cu(pyBOX)_2$ (50 mol%).[14] The iridium complex **1** was recently found to be very reactive as a Lewis acidic promoter of Nazarov cyclization, especially relative to $Cu(OTf)_2$.[15]



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These new catalysts allow efficient cyclization under mild conditions, with minimum byproduct formation. Furthermore, the promise of asymmetric catalysis of Nazarov cyclization[16] provides a strong impetus for the development of these and related chiral catalyst systems for this reaction. An excellent understanding of the behavior of oxyallyl intermediate **C** has been gained through the studies of West and co-workers, in which the intermediate has been trapped with a variety of nucleophilic species.[6–9,17–21] While the steps involved in catalysis of Nazarov cyclization can be postulated, the process of collecting experimental evidence describing the details of the catalysis is just beginning. In this context, gaining greater insight into the reaction through the observation of intermediates in the cyclization pathway will undoubtedly aid in the development of improved catalysis of the reaction.

1.2. Iridium (III) complexes as catalysts

Cationic complexes of the platinum group elements that are soluble in nonpolar, aprotic media have represented a fertile source of catalysts for electrophilically driven reactions. Recent developments in the electrophilic chemistry of platinum group metal complexes include catalysis of α-olefin polymerization by cationic Pd(II) systems and C–H bond activation using cationic Pt(II) and Ir(III) complexes.[22–36] In all of these systems, the complexes have one alkyl ligand, one labile binding site occupied by weakly coordinating solvent and a non-coordinating BAr_4^{f-} type anion. (There are two non-coordinating anions that have been labeled as BAr_4^{f-}. One is $B(C_6F_5)_4^-$ and the other is $B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$. In the present study, only the latter has been employed). Stimulated by the electrophilic reactivity of metal complexes for catalysis and bond activation, one of us embarked several years ago on exploring the electrophilic behavior of d^6 Ir(III) with the notion of constructing complexes having either two adjacent labile sites or a single labile site next to an alkyl group. The challenge of keeping the iridium ion in its normally inert 3+ oxidation state while introducing lability into the system was met successfully with the synthesis of the dicationic complex **1** that has 1,2-diiodobenzene (DIB) as a weak and readily dissociable chelating ligand and BAr_4^{f-} as the counterion.[37,38] In earlier studies, it has been shown that this complex exhibits electrophilic behavior leading to polymerization or oligomerization of several, more electron-rich olefins and conjugated dienes.[37–39]

During the past two decades, the use of electrophilic transition metal complexes having chiral ligands as Lewis acids (including in situ generated species) has become critically important in the development of asymmetric catalysts. Successful examples include cationic Cu^{2+} and Sc^{3+} complexes containing different bis(oxazoline) ligands as Lewis acids for enantioselective Diels–Alder, aldol, conjugate addition and amination reactions.[40–45] In these reactions, carbonyl substrates are activated by O coordination and, where feasible, chelation. We reasoned that since complex **1** exhibited high electrophilic behavior and possessed two labile sites for substrate activation, it had great potential for use as a Lewis acid catalyst for different organic transformations. In this context, we have found that complex **1** is an efficient and well defined catalyst for promoting the Nazarov cyclization of aryl vinyl and divinyl ketones and our results have recently been communicated.[15] Further evolution of this catalyst into a chiral form for asymmetric cyclizations remains at this point an ongoing research objective.

Herein, we describe more extensive studies of the Nazarov cyclization catalyzed by complex **1**. The iridium (III) system is unique in its activity as a catalyst for the Nazarov reaction, and provides a window into some of the intermediate species generated in, and important to, the cyclization process.

2. Results and discussion

2.1. Catalytic Nazarov cyclization of divinyl ketones

A number of factors influence the rate of cyclization, including the conformation of the pentadienyl cation, which can be s-*cis*/s-*cis*, s-*cis*/s-*trans* (two possibilities) or s-*trans*/s-*trans* (Fig. 1).[46] The s-*trans*/s-*trans* orientation particularly disposes the system toward cyclization. It was postulated that two-point binding at the adjacent open coordination sites of the Lewis acidic complex **1** would impact the conformational population favoring s-*trans*/s-*trans* and thus promote cyclization. To test the validity of

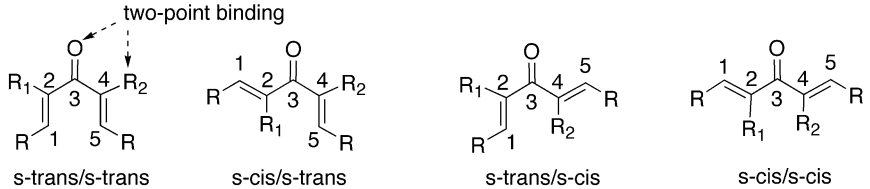
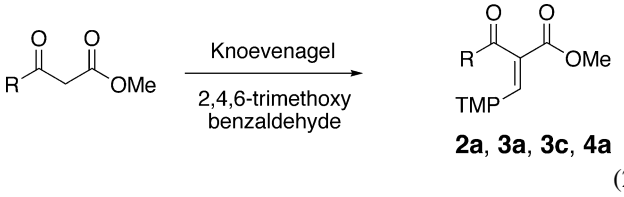


Figure 1. Conformations of divinyl ketones.

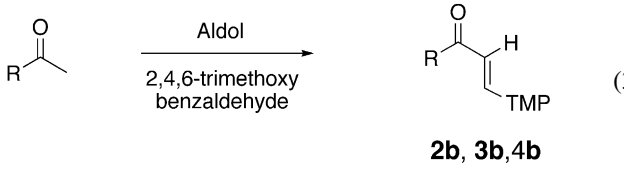
this idea, **1** was allowed to react with substrates having different substitution patterns at positions 2 and 4 of the pentadienyl system (see **A**, Eq. 1). It was hoped that these experiments would help to identify the nature of the binding between **1** and the substrate functional groups.

2.2. Synthesis of Nazarov substrates

Several sets of substrates bearing different substituents at the 4-position of the pentadienyl system (**2**–**4**) were prepared. Knoevenagel condensation[47] of 2,4,6-trimethoxybenzaldehyde with the appropriate β-ketoester yielded substrates **2a**, **3a**, **3c** and **4a**, while aldol condensation on the corresponding methyl ketones gave **2b**, **3b**, and **4b** (Eqs. 2 and 3). Addition of the anion of methyl or ethyl phosphonate to methyl ester **5** gave the desired β-ketophosphonates, and appropriate chlorination at the α-carbon gave the chloro β-ketophosphonate (Scheme 1). These



(2)



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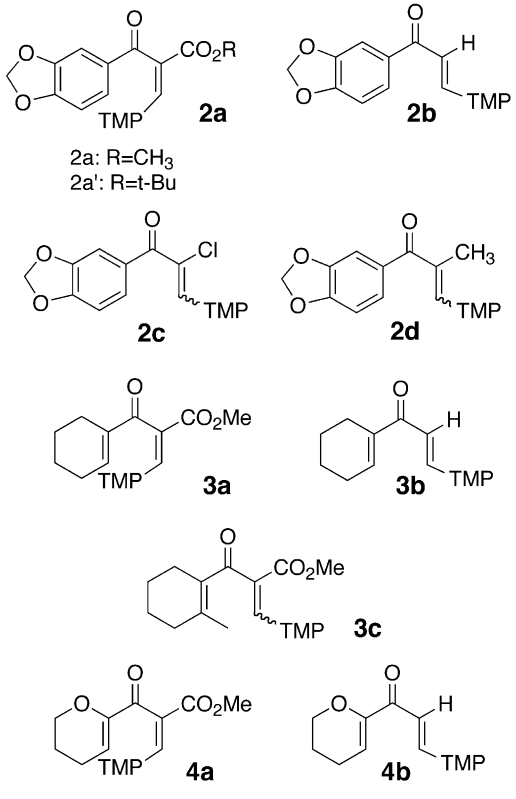
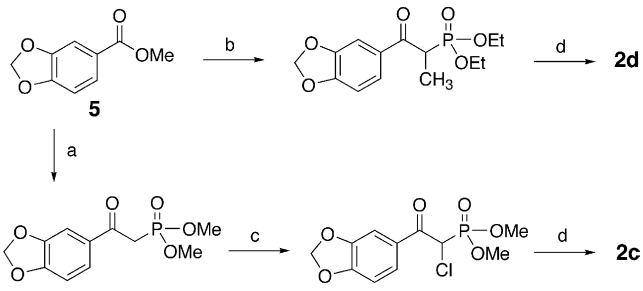




Scheme 1. Synthesis of substrates **2c**–**2d** by Horner–Emmons–Wadsworth condensation. Reaction conditions: (a) ^{n}BuLi, dimethyl methyl phosphonate; (b) ^{n}BuLi, ethylphosphonoacetate; (c) NaH, *N*-chlorosuccinimide, 0 °C; (d) NaH, THF, then TMPCHO, △.

ketophosphonates underwent Horner–Emmons–Wadsworth condensation with 2,4,6-trimethoxybenzaldehyde to provide Nazarov substrates **2c** and **2d**. For some substrates, these synthetic strategies are highly selective for divinyl ketones with E geometry, but for others, a mixture of E and Z isomers is obtained.

2.3. Cyclization experiments with Ir(III) complex 1 and with $Cu(OTf)_2$

The electronic predisposition of the substrate toward cyclization can have a strong influence on cyclization rates and efficiency, as found by us[10] and others[11,12] during studies of substrates with C2-donating groups. Experiments to date also indicate that cyclization rates increase when the substituent at C4 is electron-withdrawing, although the acceleration is less pronounced. Polarizing the divinyl ketone in this way (see Fig. 2) both increases the reactivity of the pentadienyl cation intermediate **B** and leads to regioselective elimination (**C**→**D**, Eq. 1), giving these Nazarov cyclizations a high level of synthetic utility. These original studies employed $Cu(OTf)_2$ as catalyst.

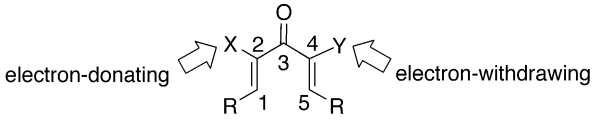
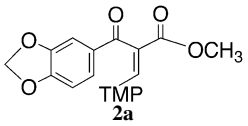
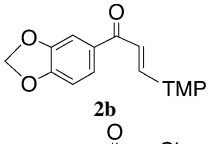
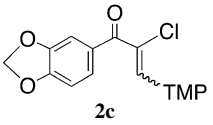
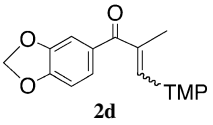
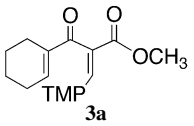
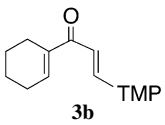
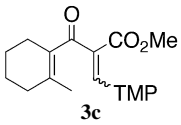
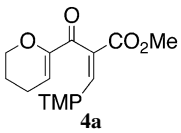
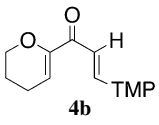


Figure 2. Polarization of divinyl ketone substrates to accelerate Nazarov cyclization.

We soon found that the different substituents affecting the electronic character of the substrate was only one of several factors influencing the cyclization rates of divinyl ketones. The iridium catalyst **1** offered the opportunity to gain a better understanding of these factors, beginning with Nazarov cyclizations of substrates bearing a β-vinyl 2,4,6-trimethoxyphenyl (TMP) group (see Table 1). In the TMP-containing substrates, the rate of *E*/*Z* isomerization was found to be faster than the rate of cyclization,[48] which allowed the direct study of cyclization rates, even when the Nazarov substrate was a mixture of E and Z isomers.

The results of cyclization experiments using both **1** and $Cu(OTf)_2$ are presented in Table 1. For all substrates but one (**3b**), catalyst **1** cyclizes substrates faster and in higher yield than copper triflate. A number of substrates required

Table 1. Cyclization experiments with 2,4,6-trimethoxyphenyl-substituted alkylidene β-ketoesters[a,b,c]

Substrate	Catalyst	Time (min.)	Temperature (°C)	Turnover frequency (h^{-1})	Yield (%)
 **2a**	**1**	8.0	25.7	376	>99
	$Cu(OTf)_2$	30	65.0	—	90
 **2b**	**1**	—	—	—	—
	$Cu(OTf)_2$	—	—	—	—
 **2c**	**1**	41.5	25.4	73	99
	$Cu(OTf)_2$	90	65.0	—	82
 **2d**	**1**	125	25.5	24	96
	$Cu(OTf)_2$	270	65.0	—	71
 **3a**	**1**	3.8	26.0	792	99
	$Cu(OTf)_2$	15	40.0	—	86
 **3b**	**1**	—	—	—	—
	$Cu(OTf)_2$	300	40.0	—	30
 **3c**	**1**	3.8	25.8	792	97
	$Cu(OTf)_2$	240	25–26	—	95
 **4a**	**1**	<1	−5.6	108	99
	$Cu(OTf)_2$	<5	0	—	95
 **4b**	**1**	34	−6.0	88	99
	$Cu(OTf)_2$	18	25–26	—	86

[a] TMP=2,4,6-trimethoxyphenyl.
[b] Reaction conditions for experiments with catalyst **1**: initial substrate concentration=0.063 M in CD_2Cl_2, catalyst loading=2 mol%. Each result is an average of two experiments. Reaction was followed by ^1H NMR spectroscopy.
[c] Reaction conditions for experiments with $Cu(OTf)_2$: substrate (0.2 M in dichloroethane) and catalyst (2 mol%), with stirring at specified temperature. Each result is an average of two experiments. Reaction was monitored closely by thin layer chromatography.

elevated temperatures before cyclization with copper triflate was observed (**2a**, **2c**, **2d**, **3a**), but underwent smooth cyclization at room temperature with catalyst **1**. Two substrates with a disubstituted vinyl group (**2b** and **3b**) did not cyclize effectively with either catalyst, yet cyclization of **4b** having a C2 donating group was successful. All of the substrates with a carbomethoxy substituent at position 4[49] (**2a**) were found to be more reactive than the corresponding substrates with hydrogen (**2b**), chloride (**2c**), or methyl (**2d**) at the C4 position. Similarly **4a** is more reactive than **4b**.

2.4. Binding behavior of 1 with precursor divinyl ketones and product β-ketoesters

In order to probe directly the nature of catalyst–substrate interactions for Nazarov cyclization catalyzed by **1**, we have used variable temperature ^{31}P NMR spectroscopy, which has allowed us to observe the resting state of the system under catalytic conditions for substrates **2**–**4**. The $^{31}P\{^1H\}$ spectrum (Fig. 3a) of a reaction mixture of substrate **2a** and 2 mol% of complex **1** shows two pairs of doublets at δ 30.5 (d, 4.8 Hz) and 15.8 (d, 4.8 Hz) (55%) and at δ 30.0 (d, 4.8 Hz) and 17.3 (d, 4.8 Hz) (45%) upon warming to −10 °C from −60 °C. These are assigned as the regioisomeric complexes **6** and **7** in which the substrate coordinates to Ir(III) by O,O′ chelation. Upon warming to ambient temperature, the cyclization commences, and at 15% conversion, complexes **6** and **7** remain the primary species in solution according to ^{31}P NMR. These data

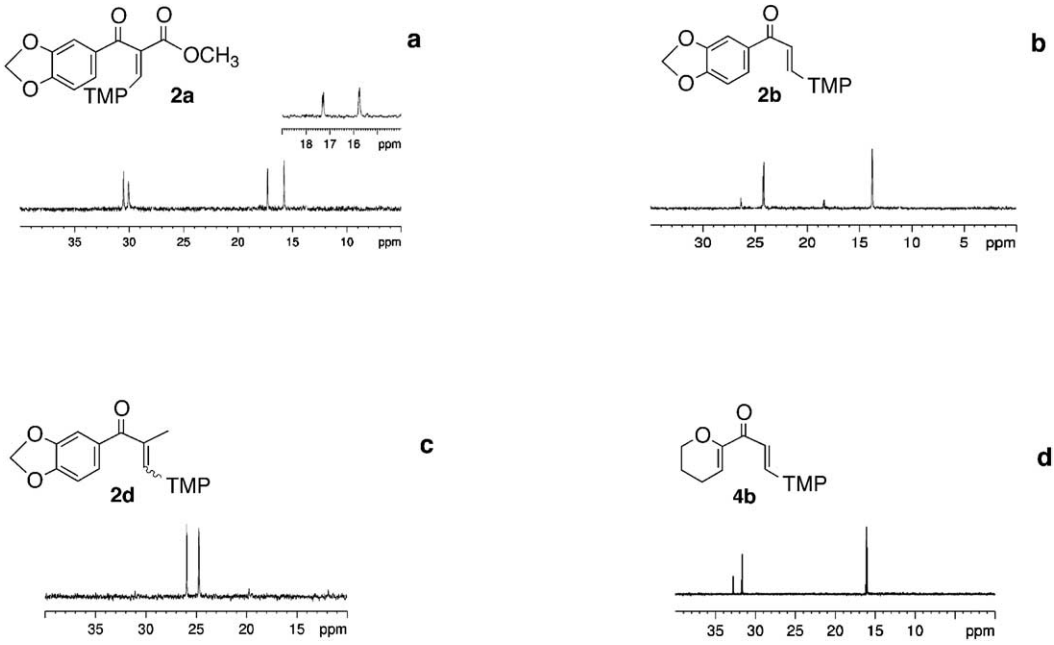


Figure 3. a. $^{31}P\{^{1}H\}$ NMR spectrum of Nazarov substrate **2a** and 2.0 mol% catalyst **1** in CD_2Cl_2 at −10 °C. b. $^{31}P\{^{1}H\}$ NMR spectrum of Nazarov substrate **2b** and 2.0 mol% catalyst **1** in CD_2Cl_2 at −10 °C. c. $^{31}P\{^{1}H\}$ NMR spectrum of Nazarov substrate **2d** and 2.0 mol% catalyst **1** in CD_2Cl_2 at −10 °C. d. $^{31}P\{^{1}H\}$ NMR spectrum of Nazarov substrate **4b** and 2.0 mol% catalyst **1** in CD_2Cl_2 at −20 °C.

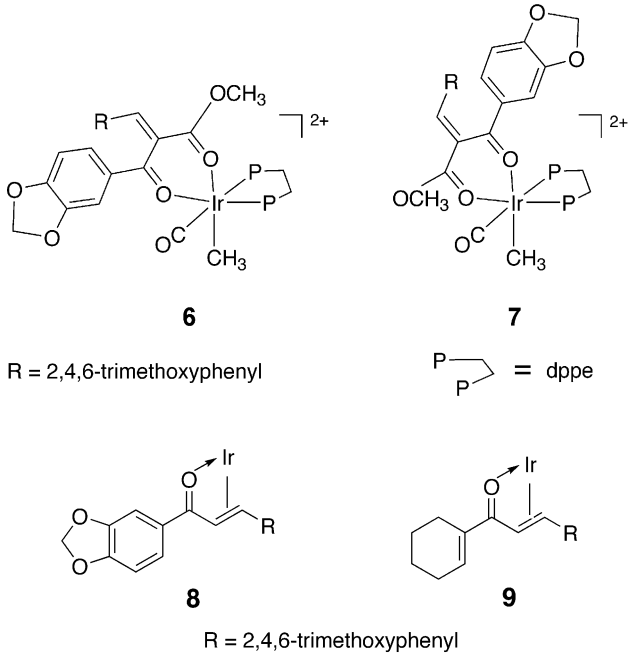
indicate that these substrate–Ir(III) complexes represent the resting state of the catalyst.

In an attempt to increase the regioselectivity of binding, we employed substrate **2a′** having a bulky *t*-butyl ester, but the regioisomeric ratio increased only to 1.6:1. Likewise, substrate **2c** with a chloride substituent at the α-position was found to exhibit two regioisomers in 2.2:1 ratio.

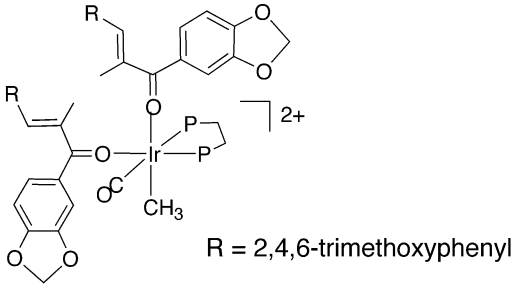
Substrates **2b** and **3b** do not cyclize when treated with **1** even with increased catalyst loading (6 mol%) and longer reaction times (24 h) at high temperature (65 °C). However, ^{1}H NMR spectroscopy of the reaction solutions reveals that both substrates **2b** and **3b** readily displace the DIB chelate of **1**, while the $^{31}P\{^{1}H\}$ NMR spectra of these solutions show two pairs of doublets in 7.1:1 and 6.7:1 ratios, respectively (see Fig. 3b). The observation that **2b** and **3b** bind to **1** but do not cyclize suggests that in the absence of a second carbonyl or an α-substituent, the Ir(III) center may coordinate to an olefinic group of **2b** or **3b** instead, as illustrated for structures **8** and **9**, respectively. Such binding would place the substrate vinyl groups in an untenable orientation for cyclization.

Interestingly, the binding and reactivity profile of substrate **2d** was very different from **2b**, even though the structure differs only by the substitution at C4 (H in **2b** vs CH_3 in **2d**; see Table 1). First, $^{31}P\{^{1}H\}$ spectra suggested that the mode of binding of **2d** and **1** was different from other catalyst-substrate pairs (see Fig. 3). Then, during exchange experiments at −10 °C, it was found that only a single species is formed in solution and that only 60% of the DIB ligand is displaced during reaction between 2 equiv of substrate **2d** and complex **1**. This was also an unexpected result, since stoichiometric (1:1) reaction between chelating ligand *N*-crotonyl-2-oxazolidinone[51] or dimethyl maleate[52] and **1** gives complete displacement of the DIB ligand. Finally, we were surprised to see **2d** cyclize when the reaction was warmed to 25 °C. From these results, it was clear that **1** and **2d** were not interacting in the same manner as **1** and other substrates studied.

Previously, we had observed that methyl acetate (which binds solely through the carbonyl oxygen) displaces the DIB ligand of complex **1** only when it is in excess.[50] Based on the



similarity of the ^{31}P spectra of **1** in the presence of **2d** and methyl acetate and the fact that both ligands displace DIB completely from **1** only when in excess, we propose that **2d** is binding to Ir(III) in a 2:1 complex using simple monodentate coordination as shown in **10**. This model would also account for the observed cyclization of **2d**, since the complex does not involve the detrimental olefin binding observed in **2b**. Thus, while a disubstituted olefin can occupy a coordination site on **1**, the methyl group of the trisubstituted olefin seems to prevent coordination.



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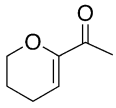

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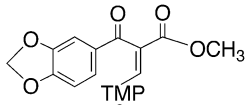
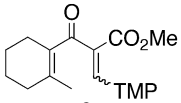
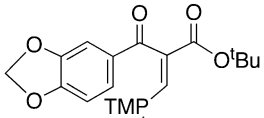
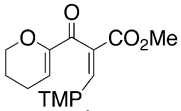
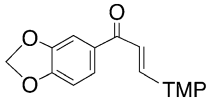
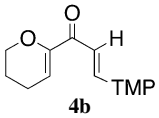
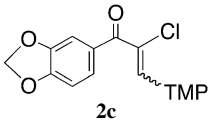
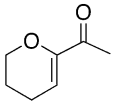
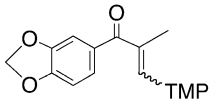
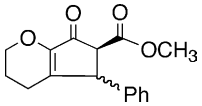
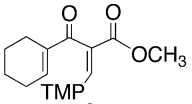
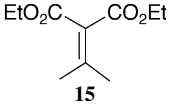
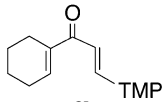
The $^{31}P\{^{1}H\}$ spectrum (Fig. 3d) of dihydropyran substrate **4b** and 2 mol% of **1** recorded at −20 °C shows two pairs of doublets in a 1:2 ratio before cyclization. In this case, binding to the carbonyl and ether oxygen atoms is possible, thus allowing the two vinyl groups to adopt the proper orientation for cyclization. Support for this view is provided by the interaction of **1** with compound **11**. Compound **11** has the equivalent of carbons 1–4 of the pentadienyl system (Eq. 1), but is missing the second vinyl group and is therefore incapable of cyclization. While **11** is also missing the carbomethoxy group of **4a**, it is found to readily displace the DIB ligand of complex **1**. Based on this, we view that dihydropyran substrates without α-ester groups can chelate to Ir(III) using carbonyl and ether oxygens. Consistent with the observations for **4b** and **11**, substrate **4a** and complex **1** generate four regioisomers that result from chelation using either two carbonyls or the carbonyl and ether oxygen atoms (Table 2). Binding studies of β-ketoester alkylidenes **2**–**4** and **1** are summarized in Table 2. Crystallographic evidence to support the notion of O,O′ chelation for substrate binding to the iridium center has also been obtained using diethyl isopropylidenemalonate **15** that cannot undergo cyclization. The X-ray results are discussed below.

In other studies, product binding to the iridium catalyst was examined by reacting **1** with the β-ketoester product mixture

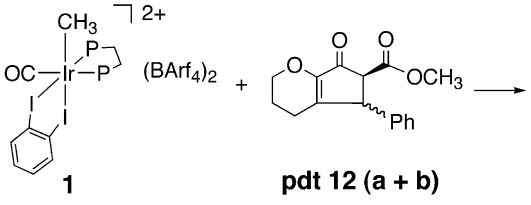
Table 2. Binding of β-ketoester alkylidenes **2**–**4** and **1** from $^{31}P\{^{1}H\}$ NMR data[a,b]

Substrate	Ratio of regioisomers from ^{31}P NMR	Substrate	Ratio of regioisomers from ^{31}P NMR
 **2a**	1:1.2	 **3c**	1:1.9
 **2a′**	1:1.6	 **4a**	1:1.3:1.7:3.4
 **2b**	1:7.1	 **4b**	1:2
 **2c**	1:2.2	 **11**	1:3.4
 **2d**	1	 **12a/b**	1:3:3:4.3
 **3a**	1:2.2	 **15**	1
 **3b**	1:6.7		

[a] TMP = 2,4,6-trimethoxyphenyl.

[b] $^{31}P\{^{1}H\}$ NMR spectra of complex **1** with Nazarov substrates **2**–**3** were obtained in CD_2Cl_2 at −10 °C; corresponding spectra for substrates **4** were recorded in CD_2Cl_2 at −20 °C and for substrates **11**, **12** and **15** at room temperature.

12a/12b (1:6.1 ratio) to give complex **13**, (Eq. 4). Four isomers in the ratio of 1:3:3:4.3 are observed by ^{31}P NMR spectroscopy (Fig. 4). This ratio is consistent with bidentate O,O′-chelation; i.e., coordination of **1** to **12** appears to be analogous to coordination of **1** to **4a** (see Table 2).[53] However, the bound product in **13** is labile, as shown by the ability of **13** to catalyze Nazarov cyclization upon the addition of substrate to the complex solution.



(4)

[IrMe(CO)(dppe)(pdt)](BArf$_4$)$_2$

13

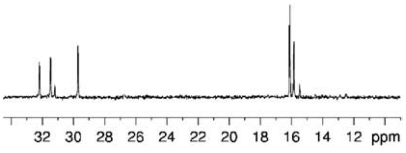
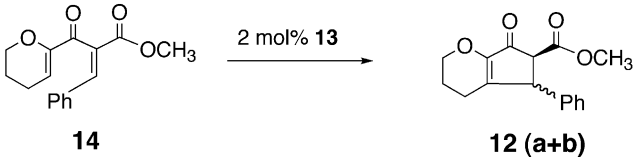


Figure 4. $^{31}P(^1H)$ NMR spectrum of complex **13** in CD_2Cl_2.

Specifically, when a solution of **14** with 2 mol% product-bound complex **13** is warmed from −60 °C to room temperature, complete cyclization (Eq. 5) occurs in less than 20 min. The rate of cyclization is similar to that seen when substrate **14** is treated with the DIB complex **1**.[15] The fact that the product bound iridium complex **13** catalyzes the Nazarov cyclization with a similar rate to that found for **1** indicates lability of the bound product, and suggests that product inhibition is not significant.

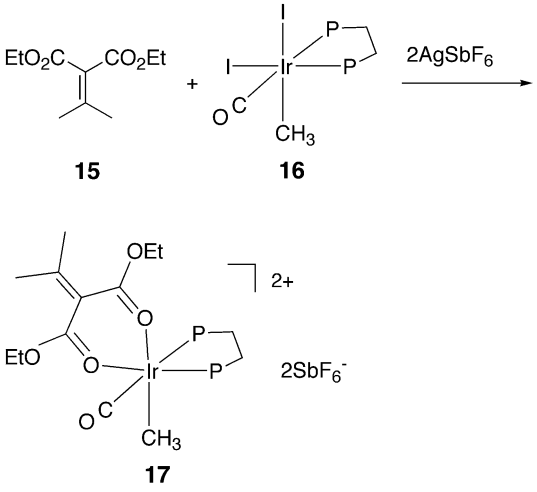


14 **12 (a+b)**

(5)

2.5. Crystallographic characterization of a model substrate–Ir(III) complex

Diethyl isopropylidenemalonate **15** is a compound capable of binding to an Ir(III) center in the same way that a number of the dicarbonyl substrates are thought to do with **1**. Compound **15** has the equivalent of carbons 3–5 of the substrate pentadienyl system (Eq. 1), but lacks a second vinyl group for cyclization. Since **15** is a symmetrical ligand, coordination to the iridium center was expected to give only a single diastereomer. As anticipated, the reaction between diiodide Ir(III) complex **16** with **15** in the presence of 2 equiv of $AgSbF_6$ produces the dicationic complex **17** in good yield (Eq. 6). The complex was characterized by NMR and IR spectroscopies and X-ray crystallography. The $^{31}P\{^1H\}$ spectrum of **15** exhibits a pair of doublets at δ 34.0 ($J_{P-P}=3.7$ Hz) and 18.7 ($J_{P-P}=3.7$ Hz) in CD_2Cl_2 solvent corresponding to the inequivalent *cis*-phosphine donors.



(6)

X-ray quality crystals were grown by slow diffusion of diethyl ether into a methylene chloride solution of complex **17**. An ORTEP representation of **17** is shown in Figure 5a, with crystallographic, data collection, and refinement information summarized in Table 3 and selected bond lengths and angles listed in Table 4.

Complex **17** displays a distorted octahedral geometry around iridium. The diethyl isopropylidenemalonate ligand binds to the iridium center through the two carbonyl oxygens with an O(2)–Ir(1)–O(3) angle of 78.88(13) Å. Different Ir–P bond lengths of 2.3554(13) and 2.2728(13) Å are consistent with the different ligands *trans* to the phosphine donors, the longer distance being *trans* to the terminal CO of the coordination sphere. The Ir–O bond *trans* to the methyl ligand is elongated compared to the Ir–O bond, which is *trans* to phosphine. The methyl-iridium bond length of 2.094(5) Å is similar to the 2.12(2) Å value observed for the related neutral complex $Ir(CH_3)I_2(CO)(dppe)$.[54] In **17** the methyl group is *trans* to one of the carbonyl oxygens of the malonate ligand while in $Ir(CH_3)I_2(CO)(dppe)$ it is *trans* to iodide. The six-membered chelate ring of **17**, Figure 5b, has a boat-like conformation with the alkene and the metal at the apices. The dihedral angle between the O(2)–Ir(1)–O(3) and O(2)–C(5)–C(7)–O(3) planes is 145°, whereas the corresponding dihedral angle between C(5)–C(6)–C(7) and O(2)–C(5)–C(7)–O(3) planes is 33°. This conformational result is similar to that reported for Evan's alkylidene malonate Cu(II) complex [Cu((*S*,*S*)-*t*-Bu-box)-$((CH_3O_2C)_2C{=}CHPh)](SbF_6)_2$.[42]

2.6. Stereochemistry of protonation, in situ isomerization observed by ^1H NMR

Cyclization of the dihydropyran substrate **14** catalyzed by complex **1** is very fast at room temperature. In order to conduct an NMR study of this reaction (see Table 5), cyclization was conducted at −5 °C. In this experiment, peaks corresponding to both product β-ketoesters **12a** and **12b** were observed. The ratio (**12a**:**12b**) at −5 °C was 1.2:1

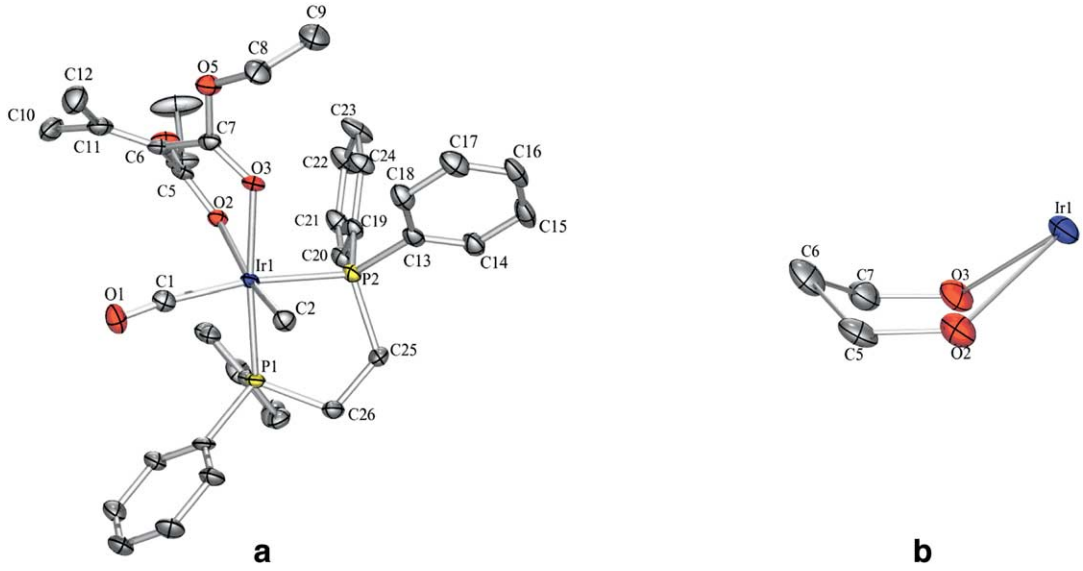


Figure 5. a. An ORTEP32/pov-ray representation of **17** showing 50% probability ellipsoids. For clarity, H atoms and SbF_6^- counterions are not shown. b. Boat conformation of the six-membered chelate.

Table 3. Crystal data and structure refinement for **17**

Empirical formula	C38 H43 F12 Ir O5 P2 Sb2
Formula weight	1305.36
Temperature	273(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, *P*2(1)/*c*
Unit cell dimensions	*a*=18.672(3) Å alpha=90deg.
	b=12.463(2) Å beta=97.130(3)deg.
	c=19.245(3) Å gamma=90deg.
Volume	4443.8(14) $Å^3$
Z, calculated density	4, 1.951 mg/m^3
Absorption coefficient	4.357 mm^{-1}
F(000)	2512
Crystal size	0.38×0.23×0.12 mm
Theta range for data collection	1.95 to 28.42°
Limiting indices	$-24\le h\le 24$, $-16\le k\le 16$, $-25\le l\le 25$
Reflections collected/unique	59001/11122 [*R*(int)=0.0664]
Completeness to theta=28.42	99.6%
Absorption correction	Empirical
Max. and min. transmission	0.593 and 0.312
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	11122/0/546
Goodness-of-fit on F^2	1.038
Final *R* indices [*I*>2*sigma*(*I*)]	*R*1=0.0448, *wR*2=0.1161
R indices (all data)	*R*1=0.0577, *wR*2=0.1260
Largest diff. peak and hole	4.834 and −3.338 $Å^{-3}$

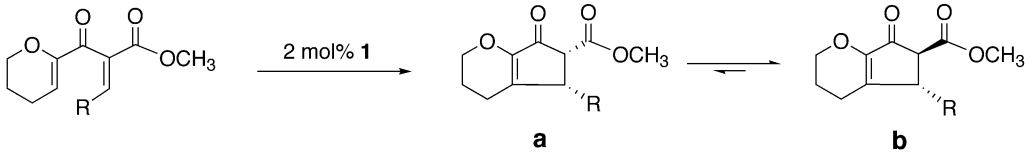
Table 4. Selected bond lengths (Å) and angles (deg) for **17**

Ir(1)–C(1)	1.975(5)	Ir(1)–C(2)	2.094(5)
Ir(1)–O(3)	2.157(3)	Ir(1)–O(2)	2.218(3)
Ir(1)–P(1)	2.2728(13)	Ir(1)–P(2)	2.3554(13)
P(2)–C(13)	1.822(5)	P(2)–C(25)	1.848(5)
C(1)–O(1)	1.110(6)	O(3)–C(7)	1.253(6)
O(5)–C(7)	1.310(6)	O(5)–C(8)	1.462(6)
C(8)–C(9)	1.500(9)	C(6)–C(11)	1.362(8)
C(11)–C(12)	1.517(8)		
C(1)–Ir(1)–C(2)	88.2(2)	C(1)–Ir(1)–O(3)	94.47(18)
C(2)–Ir(1)–O(3)	86.62(17)	C(1)–Ir(1)–O(2)	93.25(17)
C(2)–Ir(1)–O(2)	165.49(17)	O(3)–Ir(1)–O(2)	78.88(13)
C(1)–Ir(1)–P(1)	89.82(15)	C(2)–Ir(1)–P(1)	90.39(15)
O(3)–Ir(1)–P(1)	174.68(10)	O(2)–Ir(1)–P(1)	104.04(9)
C(1)–Ir(1)–P(2)	171.59(15)	C(2)–Ir(1)–P(2)	88.41(15)
O(3)–Ir(1)–P(2)	93.01(10)	O(2)–Ir(1)–P(2)	91.96(10)
P(1)–Ir(1)–P(2)	82.51(5)	O(3)–C(7)–C(6)	124.9(4)
C(7)–O(3)–Ir(1)	123.2(3)	C(7)–C(6)–C(5)	112.5(4)

in favor of the *cis* isomer **12a**, which is the product expected from kinetic protonation of the intermediate enolate, with H^+ approach *anti* to the aryl group. However, as the solution temperature was allowed to increase, the ratio of **12a**:**12b** changed, indicating thermal epimerization at C4. At 10 °C, the ratio was 1:2.3, and at 25 °C, it rose to 1:6.1 (Table 5). The ratio at 25 °C is consistent with the product distribution obtained from the copper triflate catalyzed cyclization that was conducted at room temperature.

In accord with the observations for substrate **14**, substrates **18** and **19** upon cyclization in the presence of catalyst **1** at −5 °C yielded product ratios of 1.2:1 and 1.3:1, respectively, in favor of the *cis* isomer. Upon warming to 25 °C, the product ratios observed were 1:6.4 and 1:12.8, respectively (Table 5).

Table 5. Ratio of *cis* and *trans* products observed during thermal equilibration



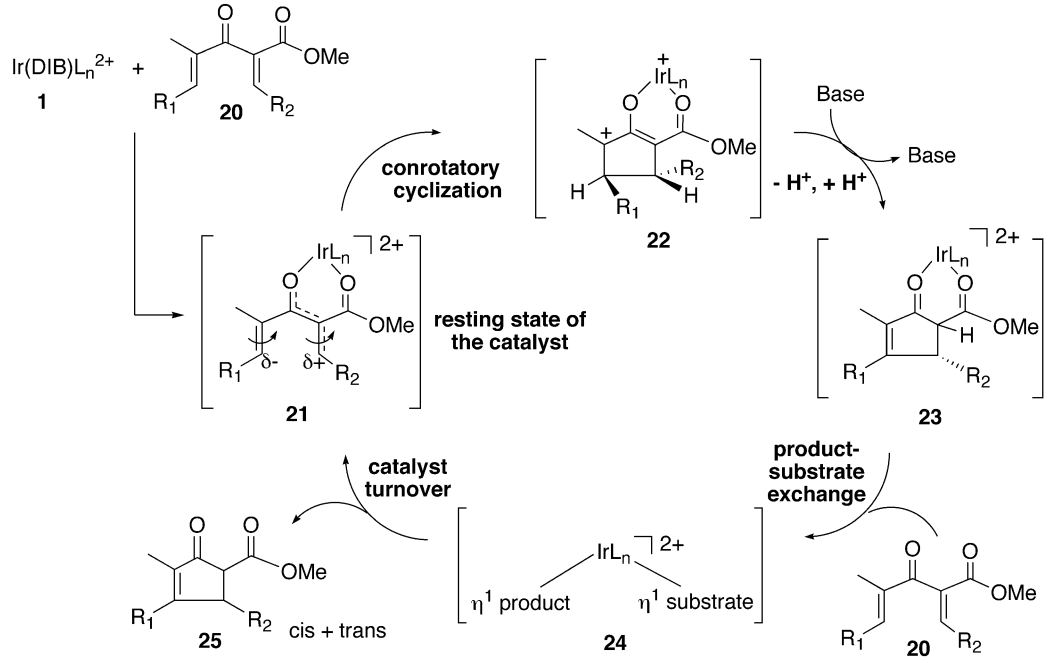
Substrate	R	Ratio **a**:**b**	
		at −5 °C	at 25 °C
14	Phenyl	1.2:1	1:6.1
18	4-Methoxyphenyl	1.2:1	1:6.4
19	2,4,6-Trimethoxyphenyl	1.3:1	1:12.8

These results suggest that protonation at low temperature is at least partially kinetically controlled with epimerization of the relatively acidic C4 proton occurring at elevated temperature.

3. Mechanistic considerations

The fact that binding of substrate to the Ir(III) center can be seen using ^{31}P NMR spectroscopy makes possible a more in-depth analysis of the reaction mechanism of Nazarov cyclization than has been achieved with the $Cu(OTf)_2$ catalyst system or other recently described metal-based systems.[10,12–14] Chelation of the substrate to the Ir(III) center determined by ^{31}P NMR spectroscopy is reinforced by crystallographic characterization of the model catalyst–substrate complex **17**. The O,O′-chelation of substrate to Ir(III) employs two substrate carbonyl groups or one carbonyl and an ether function that helps favor adoption of the s-*trans*/s-*trans* conformation required for cyclization (see Fig. 1). Because the adjacent binding sites of **1** after displacement of DIB are inequivalent, pairs of regioisomers are seen in ratios that indicate relatively little preference for one isomer over the other. On the other hand, when chelation or two-point binding involves one of the vinyl groups, the ratio of regioisomers shows greater differentiation, but because the s-*trans*/s-*trans* conformation is not achieved, cyclization is not catalyzed. For one case in which only monodentate binding is seen (substrate **2d**), cyclization catalysis does occur but at a distinctly slower rate than when O,O′-chelation of substrate is achieved.

From all of the observations obtained to date, a mechanism for Nazarov cyclization catalyzed by **1** can be formulated as shown in Scheme 2. After DIB displacement, O,O′-chelation employing substrate carbonyl groups substantially increases the electrophilicity of one of the vinyl groups for ring closure and C–C bond formation. The rapid isomerization of *E* and *Z* isomers having a TMP group[48] gives additional support for the notion of electrophilic activation of this vinyl group. From the s-*trans*/s-*trans* conformation of the O,O′-chelated substrate, cyclization by a conrotatory mechanism follows, as has been described previously.[1]



Scheme 2. Proposed reaction mechanism of Nazarov cyclization catalyzed by **1**.

Subsequent steps of proton loss and reprotonation take place with the latter appearing to proceed at least in part under kinetic control with H^+ addition *anti* to the aromatic group R_2. When the substrate possesses an ester functionality attached to C4 carbon, epimerization at this position occurs to give a different ratio of products at thermodynamic equilibrium.

Exchange of bound product for new substrate completes the catalytic cycle. A detailed study of the kinetics for Nazarov cyclization catalyzed by **1** has been conducted using both **2a** and **14** as substrates. This study, the details of which will be reported elsewhere,[55] reveals that the reaction is first order in both catalyst and substrate concentrations (saturation is not observed.) Since the resting state of the system under catalytic conditions is the catalyst-substrate complex, this observation indicates that conrotatory cyclization cannot be the turnover limiting step of the catalysis. A process with turnover-limiting cyclization would not have a simple first-order dependence on substrate: saturation would be observed.

Instead, the turnover limiting step, or one of the steps preceding it beginning with the resting state of the system, must involve substrate in addition to that found in the catalyst-substrate resting state. There are two possible steps in which substrate could play a role. The first is as a general base in the deprotonation/reprotonation sequence, and the second is as a ligand that displaces the cyclized product in the turnover step. In light of prior observations of exchange reactions of **1** in which η^1-DIB intermediates are seen and the second dissociation is rate limiting,[38] we favor the idea that the turnover limiting step in the catalytic cycle is an associatively driven substitution involving substrate, as shown in Scheme 2. Such a substitution is totally consistent with the kinetics of the reaction.

4. Conclusion

Iridium (III) catalyst **1** is a strong Lewis acid capable of catalyzing Nazarov cyclization with great efficiency. The complex cyclizes nearly every substrate studied faster and in higher yield than copper triflate. Observations of intermediate complexes have been obtained by examining ^{31}P NMR spectra of the reaction system thereby providing detailed information about catalyst-substrate interactions during the catalytic reaction. Dissociation of labile diodobenzene from complex **1** readily occurs, providing two adjacent coordination sites that are occupied by two functional groups of one substrate in nearly all of the divinyl ketones studied. Thus, substrate chelation to Ir(III) occurs prior to cyclization whenever possible. Two regioisomeric binding modes for unsymmetrical substrates are possible, and both isomers are observed in all binding studies.

Chelation using carbonyl oxygen atoms preorganizes the substrate toward reaction by encouraging adoption of the s-*trans*/s-*trans* conformation necessary for cyclization. When binding prevents the s-*trans*/s-*trans* divinyl ketone conformation, as in cases when only a single oxygen atom is available for coordination, allowing olefin binding to complete the chelation (**4b**), catalysis of cyclization does not occur. In one case when only single point or monodentate binding of substrate is seen (**2d**), cyclization occurs, but at a significantly slower rate.

An interesting observation made during the reaction by ^1H NMR spectroscopy shows that at low temperature, significant protonation of the enolate happens *trans* to the β-substitutent, to give product with alkyl groups *cis* to one another. However, epimerization at this center occurs at higher temperatures to give predominantly product in which the alkyl groups are in the thermodynamically more stable *trans* configuration, corresponding to protonation *cis* to the β-substituent.

A highly selective catalytic system for asymmetric Nazarov cyclization is missing from current synthetic methodology.[16] In this electrocyclization reaction, it is not clear that blocking one face of the substrate will result in enantioselective conrotatory cyclization, since the reaction involves intramolecular bond formation via an unusual twisted intermediate. Furthermore, the site of bond formation and the points of chelation for the catalyst are separated by a number of atoms, raising questions about the ability of ligands to influence the reaction over such a distance. However, judicious choice of chiral phosphine substituents may allow us to achieve enantioselective cyclization, which represents a key current research objective.

5. Experimental

5.1. General procedures and materials

Chloroform-d and dichloromethane-d_2 were purchased from Cambridge Isotope. [IrMe(CO)(dppe)(DIB)]$(BAr^f_4)_2$,[37,38] $NaBAr^f_4$,[56] and *N*-crotonyl-2-oxazolidinone[57] were synthesized according to published procedures. Known Nazarov substrates and cyclized products were prepared and characterized as reported before.[10] Column chromatography was performed on Silica Gel (40–140 mesh). TLC visualization was accomplished using UV light or with $KMnO_4$ solution. Dichloromethane, diethyl ether, hexanes, pentane, and tetrahydrofuran were purified using a solvent purification system as described by Grubbs.[58] All NMR spectra were recorded on either a Bruker AMX or Avance 400 MHz spectrometer. ^1H and ^{13}C chemical shifts (δ in ppm) are relative to tetramethylsilane and referenced using chemical shifts of residual solvent resonances. ^{31}P chemical shifts (δ in ppm) are relative to an external 85% solution of phosphoric acid in the appropriate solvent. Unless otherwise stated, all reactions and manipulations were performed in dry glassware under a nitrogen atmosphere using either standard Schlenk techniques or an inert-atmosphere glovebox.

5.2. Synthesis of Nazarov substrates

5.2.1. Synthesis of Nazarov substrate 2c. To a stirred solution of α-chloro-β-keto methylphosphonic acid dimethyl ester[59] (630 mg, 2.05 mmol) in dry THF (6.0 mL) at 0 °C was added NaH (60% dispersed in mineral

oil, 86.2 mg, 2.15 mmol) in small portions. After the suspension had warmed to room temperature, 2,4,6-trimethoxybenzaldehyde (421 mg, 2.15 mmol) was added all at once. The reaction was then heated to reflux for 24 h before it was quenched with water. The organic phase was separated and the aqueous phase was extracted with EtOAc (3×25 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (loaded with 10% MeOH/EtOAc, eluting with 30% EtOAc/hexanes) to afford 120 mg (16%) of **2c** as a yellow powder (3.3:1) ratio of *E*/*Z* isomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (*E*/*Z*, m, 1.3H), 7.38 (*E*/*Z*, d, J=4 Hz, 1.3H), 7.34 (*E*, s, 1H), 7.17 (*Z*, s, 0.3H), 6.86 (*E*, d, J=8.2 Hz, 1H), 6.72 (*Z*, d, J=8.2 Hz, 0.3H), 6.16 (*E*, s, 2H), 6.05 (*E*, s, 2H), 6.01 (*Z*, s, 0.6H), 5.93 (*Z*, s, 0.6H), 3.86 (m, 11.7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.5, 188.4, 162.6, 161.8, 158.6, 157.9, 151.4, 147.7, 134.2, 132.9, 131.3, 129.9, 126.4, 125.2, 110.0, 108.9, 107.7, 107.5, 105.3, 104.3, 101.8, 101.6, 90.4, 90.1, 55.6, 55.4, 55.2, 54.8; IR (NaCl plate, cm^{-1}): 1035, 1107, 1128, 1157, 1205, 1226, 1257, 1280, 1415, 1440, 1454, 1487, 1583, 1602, 1656, 2852, 2921, 2952; HRMS calculated for $C_{19}H_{17}ClO_6$ $(M+H)^+$ 377.0791. Found: 377.07901.

5.2.2. Synthesis of Nazarov substrate 2d. A solution of the α-methyl-β-keto methylphosphonic acid diethyl ester[60] (197 mg, 0.69 mmol) in THF (5.0 mL) was cooled to 0 °C and NaH (60% dispersed in mineral oil, 30.0 mg, 0.72 mmol) was added in small portions. After the suspension had warmed to room temperature, 2,4,6-trimethoxybenzaldehyde (142 mg, 0.72 mmol) was added all at once and the reaction was stirred at room temperature overnight before it was quenched with water. The organic phase was separated and the aqueous phase was extracted by EtOAc (3×25 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography eluting with 30% EtOAc/hexanes to afford 117 mg (46%) of **2d** as a white crystalline powder (5:1 ratio of *E*/*Z* isomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (*E*, d-d, J_1=8.0 Hz, J_2=1.3 Hz, 1H), 7.39 (*E*, d, J=1.3 Hz, 1H), 7.32 (*Z*, d, J=8.0 Hz, 0.2H), 7.29 (*Z*, s, 0.2H), 6.96 (*E*, s, 1H), 6.85 (*E*, d, J=8.0 Hz, 1H), 6.70 (*Z*, s, 0.2H), 6.58 (*Z*, d, J=8.0 Hz, 0.2H), 6.17 (*E*, s, 2H), 6.04 (*E*, s, 2H), 5.94 (*Z*, s, 0.4H), 5.89 (*Z*, s, 0.4H), 3.86 (*E*, s, 3H), 3.82 (*E*, s, 6H), 3.77 (*Z*, s, 0.6H), 3.64 (*Z*, s, 1.2H), 2.19 (*Z*, s, 0.6H), 1.88 (*E*, s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.7, 196.9, 161.7, 160.8, 158.3, 157.9, 150.6, 150.6, 147.4, 147.4, 137.9, 134.8, 134.3, 133.1, 131.4, 125.9, 125.5, 123.8, 110.1, 108.5, 107.6, 107.4, 107.1, 106.5, 101.5, 101.4, 90.3, 89.9, 55.5, 55.3, 55.2, 54.9, 22.6, 15.4; IR (NaCl plate, cm^{-1}): 811, 933, 1016, 1037, 1058, 1093, 1118, 1130, 1155, 1205, 1226, 1255, 1328, 1255, 1415, 1438, 1454, 1487, 1583, 1604, 1633, 2916, 2939, 2958; HRMS calculated for $C_{20}H_{20}O_6$ $(M+H)^+$ 357.1335. Found: 357.13364.

5.3. Nazarov cyclization using $Cu(OTf)_2$

5.3.1. Nazarov cyclization of substrate 2c. To a vial containing $Cu(OTf)_2$ (0.70 mg, 0.002 mmol) under argon was added a solution of divinyl ketone **2c** (38 mg, 0.1 mmol) in 1,2-dichloroethane (DCE) (0.8 mL) at room temperature. The reaction was stirred for 1.5 h at 65 °C. The crude mixture was concentrated under reduced pressure and purified by pipette column chromatography (eluting with 35% EtOAc/hexanes) to give 31.2 mg product (a mixture of *cis*:*trans* (5:4) diastereomers, 0.082 mmol, 82%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (*cis*/*trans*, s, 1.8H), 6,64 (*cis*, s, 1H), 6.48 (*trans*, s, 0.8H), 6.23 (*trans*, s, 0.8H), 6.20 (*cis*, d, J=2.2 Hz, 1H), 6.04 (*cis*, s, 2H), 6.03 (*trans*, s, 0.8H), 6.00 (*trans*, s, 1.6H), 5.97 (*cis*, d, J=2.2 Hz, 1H), 5.40 (*cis*, d, J=6.2 Hz, 1H), 5.06 (*trans*, d, J=3.5 Hz, 0.8H), 4.92 (*cis*, d, J=6.2 Hz, 1H), 4.83 (*trans*, d, J=3.5 Hz, 0.8H), 3.90 (*cis*/*trans*, s, 5.4H), 3.79 (*trans*, s, 2.4H), 3.70 (*cis*, s, 3H), 3.46 (*trans*, s, 2.4H), 3.40 (*cis*, s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.4, 160.8, 160.7, 159.9, 159.0, 158.7, 154.8, 154.1, 153.4, 151.1, 148.1, 148.0, 128.6, 127.8, 107.8, 106.7, 105.4, 104.3, 102.3, 102.1, 102.0, 102.0, 91.2, 90.9, 90.8, 90.6, 62.2, 61.8, 56.2, 55.9, 55.2, 55.1, 55.1, 54.7; IR (NaCl plate, cm^{-1}):703, 734, 817, 875, 939, 1035, 1058, 1074, 1118, 1147, 1203, 1251, 1296, 1330, 1419, 1438, 1460, 1469, 1498, 1593, 1608, 1712, 2910, 2939, 2962; HRMS calculated for $C_{19}H_{17}ClO_6$ $(M+Na)^+$ 399.0606. Found: 399.05991.

5.3.2. Nazarov cyclization of substrate 2d. To a vial containing $Cu(OTf)_2$ (1.4 mg, 0.004 mmol) under argon was added a solution of the divinyl ketone **2d** (71.2 mg, 0.2 mmol) in DCE (1.6 mL) at room temperature. The reaction was heated to 65 °C and checked with TLC. Upon complete consumption of the starting material, the crude mixture was concentrated under reduced pressure and purified by pipette column chromatography (eluting with 30% EtOAc/hexanes) to give 50.6 mg product (a mixture of *cis*:*trans* (1:5) diastereomers, 0.14 mmol, 71%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (*cis*, s, 0.2H), 7.10 (*trans*, s, 1H), 6.59 (*cis*, s, 0.2H), 6.49 (*trans*, s, 1H), 6.05 (*trans*, s, 1H), 6.04 (*cis*, s, 0.2H), 6.01 (*trans*, s, 1H), 5.99 (*cis*/*trans*, m, 2.4H), 5.98 (*cis*, s, 0.2H), 5.12 (*cis*, d, J=8.0 Hz, 0.2H), 4.53 (*trans*, d, J=7.4 Hz, 1H), 3.88 (*cis*, s, 0.6H), 3.87 (*trans*, s, 3H), 3.81 (*trans*, s, 3H), 3.79 (*cis*, s, 0.6H), 3.42 (*trans*, s, 3H), 3.29 (*cis*, s, 0.6H), 2.91 (*cis*/*trans*, m, 1.2H), 1.26 (*trans*, d, J=7.4 Hz, 3H), 0.94 (*cis*, d, J=8.0 Hz, 0.6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.5, 160.1, 160.1, 159.6, 159.4, 159.0, 159.0, 155.6, 154.3, 153.7, 153.1, 147.4, 147.3, 131.3, 130.0, 110.0, 108.5, 105.0, 104.2, 101.7, 101.6, 101.4, 91.3, 90.9, 90.6, 90.5, 55.9, 55.9, 55.2, 55.2, 55.1, 54.5, 49.4, 46.2, 42.2, 38.2, 15.3, 11.2; IR (NaCl plate, cm^{-1}): 734, 813, 941, 954, 1035, 1056, 1099, 1120, 1149, 1203, 1218, 1251, 1267, 1298, 1328, 1419, 1456, 1467, 1496, 1593, 1606, 1697, 2935, 2962; HRMS calculated for $C_{20}H_{20}O_6$ $(M+H)^+$ 357.1333. Found: 357.13425.

5.3.3. Synthesis of [IrMe(CO)(dppe)(Me_2C=C(CO_2-Et)$_2$)](SbF_6)$_2$ (17). In a glovebox, a 100 mL round bottom flask equipped with a stir-bar was charged with IrMe(CO)(dppe)I_2 (200.0 mg, 0.25 mmol), Me_2C=C(CO_2-Et)$_2$ (**15**, 53 μL, 0.27 mmol) and 10.0 mL of CH_2Cl_2. $AgSbF_6$ (155 mg, 0.50 mmol) was then added in the dark to the rapidly stirred solution followed by an additional 5.0 mL of CH_2Cl_2. After 5 min, the solid AgI was removed by filtration and the solution was concentrated in vacuo to ca. 5 mL at which point 20 mL of diethyl ether was added. The white solid was filtered inside a glovebox and washed with

diethyl ether several times to remove any residual diethyl isopropylidenemalonate. Isolated 230.0 mg (80%). X-ray quality crystals were grown from diethyl ether/CH_2Cl_2. ^1H NMR (CD_2Cl_2) at 25 °C: δ 7.06–7.85 (overlapping m, 20H, phenyl), 4.84 (m, 1H, $Me_2C{=}C(CO_2CH_2CH_3)_2$), 4.66 (m, 1H, $Me_2C{=}C(CO_2CH_2CH_3)_2$), 4.34 (m, 1H, $Me_2C{=}C(CO_2CH_2CH_3)_2$), 3.92 (m, 1H, $Me_2C{=}C(CO_2CH_2CH_3)_2$), 2.89–3.28 (m, 4H, PCH_2CH_2P), 2.33 (s, 3H, $(CH_3)_2C{=}C(CO_2Et)_2$), 2.02 (s, 3H, $(CH_3)_2C{=}C(CO_2Et)_2$), 1.55 (t, $J_{H-H}=7.2$ Hz, 3H, $Me_2C{=}C(CO_2CH_2CH_3)_2$), 1.35 (t, $J_{H-H}=7.2$ Hz, 3H, $Me_2C{=}C(CO_2CH_2CH_3)_2$), 0.84 (dd, $J_{P-H}=6.0$, 2.0 Hz, 3H, Ir–CH_3). $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at 25 °C: δ 34.0 (d, $J_{P-P}=3.7$ Hz, 1P, *trans* to CO), 18.7 (d, $J_{P-P}=3.7$ Hz, 1P, *cis* to CO). IR (KBr pellet): 2108 cm^{-1} (CO).

5.4. Binding studies of Nazarov substrates with $[IrMe(CO)(dppe)(DIB)](BAr^f_4)_2$ (1)

5.4.1. Binding study of the Nazarov substrate 2a with 1. In a glovebox, an NMR tube was charged with **1** (6.5 mg, 0.0024 mmol), 0.20 mL of CD_2Cl_2 and sealed with a septum. The tube was cooled to −60 °C in the NMR spectrometer. Pre-cooled (−78 °C) substrate **2a** (50.0 mg, 0.12 mmol) in 0.40 mL of CD_2Cl_2 was quickly added to the tube and transferred back to the spectrometer. A $^{31}P\{^1H\}$ NMR spectrum recorded at −60 °C shows the DIB bound complex **1**. On warming the sample to −10 °C, the $^{31}P\{^1H\}$ NMR spectrum was recorded again. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C for the major isomer (55%): δ 30.5 (d, $J_{P-P}=4.8$ Hz, 1P, *trans* to CO), 15.8 (d, $J_{P-P}=4.8$ Hz, 1P, *cis* to CO). For the minor isomer (45%): δ 30.0 (d, $J_{P-P}=4.8$ Hz, 1P, *trans* to CO), 17.3 (d, $J_{P-P}=4.8$ Hz, 1P, *cis* to CO).

5.4.2. Binding study of the Nazarov substrate 2a′ with 1. The same procedure was followed as described above for **2a** with 40.0 mg (0.085 mmol) of **2a**, 9.3 mg (0.0034 mmol) of **1** and 0.60 mL of CD_2Cl_2. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C for the major isomer (62%): δ 25.5 (d, $J_{P-P}=4.6$ Hz, 1P, *trans* to CO), 14.0 (d, $J_{P-P}=4.6$ Hz, 1P, *cis* to CO). For the minor isomer (38%): δ 30.5 (d, $J_{P-P}=4.6$ Hz, 1P, *trans* to CO), 16.4 (d, $J_{P-P}=4.6$ Hz, 1P, *cis* to CO).

5.4.3. Binding study of the Nazarov substrate 2b with 1. The same procedure was followed as described above for **2a** with 36.0 mg (0.11 mmol) of **2b**, 11.9 mg (0.0044 mmol) of **1** and 0.60 mL of CD_2Cl_2. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C for the major isomer (88%): δ 23.6 (d, $J_{P-P}=7.0$ Hz, 1P, *trans* to CO), 12.9 (d, $J_{P-P}=7.0$ Hz, 1P, *cis* to CO). For the minor isomer (12%): δ 25.3 (d, $J_{P-P}=7.0$ Hz, 1P, *trans* to CO), 15.1 (d, $J_{P-P}=7.0$ Hz, 1P, *cis* to CO).

5.4.4. Binding study of the Nazarov substrate 2c with 1. The same procedure was followed as described above for **2a** with 32.0 mg (0.084 mmol) of **2c**, 9.2 mg (0.0034 mmol) of **1** and 0.60 mL of CD_2Cl_2. $^1P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C for the major isomer (69%): δ 29.3 (d, $J_{P-P}=5.6$ Hz, 1P, *trans* to CO), 17.7 (d, $J_{P-P}=5.6$ Hz, 1P, *cis* to CO). For the minor isomer (31%): δ 34.9 (d, $J_{P-P}=5.6$ Hz, 1P, *trans* to CO), 18.1 (d, $J_{P-P}=5.6$ Hz, 1P, *cis* to CO).

5.4.5. Binding study of the Nazarov substrate 2d with 1. The same procedure was followed as described above for **2a** with 40.0 mg (0.084 mmol) of **2d**, 12.0 mg (0.0045 mmol) of **1** and 0.60 mL of CD_2Cl_2. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C: δ 26.5 (d, $J_{P-P}=5.9$ Hz, 1P, *trans* to CO), 24.5 (d, $J_{P-P}=5.9$ Hz, 1P, *cis* to CO).

5.4.6. Binding study of the Nazarov substrate 3a with 1. The same procedure was followed as described above for **2a** with 25.0 mg (0.069 mmol) of **3a**, 7.5 mg (0.0028 mmol) of **1** and 0.60 mL of CD_2Cl_2. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C for the major isomer (69%): δ 31.9 (d, $J_{P-P}=5.5$ Hz, 1P, *trans* to CO), 16.3 (d, $J_{P-P}=5.5$ Hz, 1P, *cis* to CO). For the minor isomer (31%): δ 29.9 (d, $J_{P-P}=5.5$ Hz, 1P, *trans* to CO), 16.8 (d, $J_{P-P}=5.5$ Hz, 1P, *cis* to CO).

5.4.7. Binding study of the Nazarov substrate 3b with 1. The same procedure was followed as described above for **2a** with 36.0 mg (0.12 mmol) of **3b**, 6.5 mg (0.0024 mmol) of **1** and 0.60 mL of CD_2Cl_2. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C for the major isomer (87%): δ 24.1 (d, $J_{P-P}=6.0$ Hz, 1P, *trans* to CO), 13.8 (d, $J_{P-P}=6.0$ Hz, 1P, *cis* to CO). For the minor isomer (13%): δ 26.3 (d, $J_{P-P}=6.0$ Hz, 1P, *trans* to CO), 18.4 (d, $J_{P-P}=6.0$ Hz, 1P, *cis* to CO).

5.4.8. Binding study of the Nazarov substrate 3c with 1. The same procedure was followed as described above for **2a** with 35.0 mg (0.095 mmol) of **3c**, 10.0 mg (0.0037 mmol) of **1** and 0.60 mL of CD_2Cl_2. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C for the major isomer (66%): δ 31.7 (d, $J_{P-P}=5.8$ Hz, 1P, *trans* to CO), 16.0 (d, $J_{P-P}=5.8$ Hz, 1P, *cis* to CO). For the minor isomer (34%): δ 32.8 (d, $J_{P-P}=5.8$ Hz, 1P, *trans* to CO), 16.0 (d, $J_{P-P}=5.8$ Hz, 1P, *cis* to CO).

5.4.9. Binding study of the Nazarov substrate 4a with 1. The same procedure was followed as described above for **2a** with 20.0 mg (0.073 mmol) of **4a**, 8.0 mg (0.003 mmol) of **1** and 0.60 mL of CD_2Cl_2. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −20 °C for the major isomer (46%): δ 23.2 (d, $J_{P-P}=5.8$ Hz, 1P, *trans* to CO), 17.6 (d, $J_{P-P}=5.8$ Hz, 1P, *cis* to CO). For the first minor isomer (23%): δ 25.4 (d, $J_{P-P}=6.0$ Hz, 1P, *trans* to CO), 11.0 (d, $J_{P-P}=6.0$ Hz, 1P, *cis* to CO). For the second minor isomer (17.5%): δ 24.9 (d, $J_{P-P}=5.8$ Hz, 1P, *trans* to CO), 13.9 (d, $J_{P-P}=5.8$ Hz, 1P, *cis* to CO). For the third minor isomer (13.5%): δ 28.1 (d, $J_{P-P}=5.5$ Hz, 1P, *trans* to CO), 14.6 (d, $J_{P-P}=5.5$ Hz, 1P, *cis* to CO).

5.4.10. Binding study of the Nazarov substrate 4b with 1. The same procedure was followed as described above for **2a** with 37.0 mg (0.12 mmol) of **4b**, 6.5 mg (0.0024 mmol) of **1** and 0.60 mL of CD_2Cl_2. The ^{31}P NMR spectrum (CD_2Cl_2) was recorded at −20 °C. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −20 °C for the major isomer (67%): δ 31.7 (d, $J_{P-P}=4.8$ Hz, 1P, *trans* to CO), 16.0 (d, $J_{P-P}=4.8$ Hz, 1P, *cis* to CO). For the minor isomer (33%): δ 32.8 (d, $J_{P-P}=5.1$ Hz, 1P, *trans* to CO), 16.0 (d, $J_{P-P}=5.1$ Hz, 1P, *cis* to CO).

5.4.11. Binding study of 11 and 1. The same procedure was followed as described above for **2a** with 1.1 mg (0.006 mmol) of **11**, 15.0 mg (0.006 mmol) of **1** and 0.60 mL of CD_2Cl_2. The ^{31}P NMR spectrum (CD_2Cl_2) was recorded at 25 °C. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C for the major isomer (78%): δ 27.1 (d, $J_{P-P}=5.4$ Hz, 1P,

trans to CO), 18.5 (d, $J_{P-P}=5.4$ Hz, 1P, *cis* to CO). For the minor isomer (22%): δ 29.5 (d, $J_{P-P}=5.4$ Hz, 1P, *trans* to CO), 14.2 (d, $J_{P-P}=5.4$ Hz, 1P, *cis* to CO).

5.4.12. Binding study of the Nazarov cyclization product 12 with 1. The same procedure was followed as described above for **2a** with 2.0 mg (0.0073 mmol) of **12**, 20.0 mg (0.0073 mmol) of **1** and 0.60 mL of CD_2Cl_2. $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at 0 °C for the major isomer (38%): δ 29.7 (d, $J_{P-P}=5.7$ Hz, 1P, *trans* to CO), 15.8 (d, $J_{P-P}=5.7$ Hz, 1P, *cis* to CO). For the first minor isomer (26.5%): δ 32.2 (d, $J_{P-P}=5.8$ Hz, 1P, *trans* to CO), 16.1 (d, $J_{P-P}=5.8$ Hz, 1P, *cis* to CO). For the second minor isomer (26.5%): δ 31.5 (d, $J_{P-P}=6.2$ Hz, 1P, *trans* to CO), 16.1 (d, $J_{P-P}=6.2$ Hz, 1P, *cis* to CO). For the third minor isomer (9%): δ 31.2 (d, $J_{P-P}=5.5$ Hz, 1P, *trans* to CO), 15.4 (d, $J_{P-P}=5.5$ Hz, 1P, *cis* to CO).

5.5. Binding study of chelating non-cyclizing substrates with [IrMe(CO)(dppe)(DIB)](BAr$^f_4$)$_2$ (1)

5.5.1. Binding study of *N*-crotonyl-2-oxazolidinone and 1. In a glovebox, an NMR tube was charged with *N*-crotonyl-2-oxazolidinone (1.0 mg, 0.0063 mmol), **1** (17.0 mg, 0.0063 mmol) and 0.60 mL of CD_2Cl_2 and sealed with septum. NMR spectral analysis at 25 °C demonstrated conversion to the new product and free 1,2-diiodobenzene. Spectral information for the major isomer (66%): ^1H NMR (CD_2Cl_2) at 25 °C: δ 6.86–8.0 (overlapping, phenyl, BAr$^f_4$, olefinic), 6.04 (dt, $J_{H-H}=14.5$, 1.6 Hz, 1H, olefinic), 2.50–5.00 (overlapping, PCH_2CH_2P, oxazolidinone), 2.21 (dd, $J_{H-H}=7.3$, 1.4 Hz, 3H, CH_3CHCHCO), 0.97 (dd, $J_{P-H}=5.7$, 2.0 Hz, 3H, Ir–CH_3). $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at 25 °C: δ 32.7 (d, $J_{P-P}=4.7$ Hz, $J_{P-C}=130$ Hz, 1P, *trans* to CO), 15.1 (d, $J_{P-P}=4.7$ Hz, 1P, *cis* to CO). Spectral information for the minor isomer (34%): ^1H NMR (CD_2Cl_2) at 25 °C: δ 6.86–8.0 (overlapping, phenyl, BAr$^f_4$, olefinic), 5.76 (dq, $J_{H-H}=14.5$, 1.8 Hz, 1H, olefinic), 2.50–5.00 (overlapping, PCH_2CH_2P, oxazolidinone), 2.01 (dd, $J_{H-H}=7.3$, 1.4 Hz, 3H, CH_3CHCHCO), 0.92 (dd, $J_{P-H}=6.1$, 1.8 Hz, 3H, Ir–CH_3). $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at 25 °C: δ 31.9 (d, $J_{P-P}=4.7$ Hz, $J_{P-C}=123$ Hz, 1P, *trans* to CO), 15.9 (d, $J_{P-P}=4.7$ Hz, 1P, *cis* to CO).

5.5.2. Binding study of dimethyl maleate and 1. The same procedure was followed as described above for binding study of N-crotonyl-2-oxazolidinone and **1**. Dimethyl maleate (0.79 μL, 0.0063 mmol), **1** (17.0 mg, 0.0063 mmol), and 0.60 mL CD_2Cl_2 were used. ^1H NMR (CD_2Cl_2) at 25 °C: δ 6.86–7.82 (overlapping, 46H, phenyl, BAr$^f_4$, olefinic), 4.12 (s, 3H, COOCH_3), 3.74 (s, 3H, COOCH_3), 3.0–3.50 (overlapping m, 4H, PCH_2CH_2P), 0.92 (dd, $J_{P-H}=5.7$, 2.0 Hz, 3H, Ir–CH_3). $^1P\{^1H\}$ NMR (CD_2Cl_2) at 25 °C: δ 33.6 (d, $J_{P-P}=4.7$ Hz, 1P, *trans* to CO), 17.2 (d, $J_{P-P}=4.7$ Hz, 1P, *cis* to CO).

5.6. General procedure for Nazarov cyclization catalyzed by 1

Stock solutions of catalyst **1** and the appropriate substrate were prepared in CD_2Cl_2 inside a glovebox. Calculated amount of the catalyst solution was transferred to NMR tube using Hamilton syringe and sealed with septum. The NMR tube was evacuated and backfilled three times with N_2 at −78 °C on a Schlenk-line. The required amount of pre-cooled (−78 °C) substrate was added and quickly transferred to pre-cooled NMR spectrometer. The ^1H NMR spectrum was recorded at −60 °C to insure that no reaction has started. It was then brought to the desired temperature and the ensuing reaction was monitored by ^1H NMR spectroscopy. Each experiment was repeated two times. The reaction was purified by column chromatography on silica gel eluting with 50% EtOAc/hexanes.

5.7. X-ray structural determination of 17

A crystal of complex **17** was mounted under paratone-8277 oil on a glass fiber and immediately placed in a cold nitrogen stream at −173 °C on the X-ray diffractometer. The X-ray intensity data were collected on a standard Bruker APEX II CCD area detector system equipped with a fine focus molybdenum-target X-ray tube operated at 1.5 kW (50 kV, 30 mA). Data (1.3 hemispheres) were collected using a narrow frame method with scan widths of 0.3° in ω and exposure times of 5 s/frame using a detector-to-crystal distance of 5.09 cm (maximum 2θ angle of 56.8°). The total data collection time was approximately 8 h. Frames were integrated to a maximum 2θ angle with the Siemens SAINT program and corrected for absorption with the program SADABS. The structure was solved by direct methods and refined employing full-matrix least-squares on F^2. All non-H atoms of the complex were refined with anisotropic thermal parameters. The hydrogen atoms were included in idealized positions. Crystallographic data (excluding structure factors) for **17** has been deposited with the Cambridge Crystallographic Data Center, under reference number CCDC 257337.

Acknowledgements

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References and notes

1. Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1–158.
2. Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429–442.
3. Denmark, S. E.; Habermas, G. A. *Helv. Chim. Acta* **1988**, *71*, 168–194.
4. Woodward, R. B.; Hoffmann, R. *The conservation of orbital symmetry*; Verlag Chemie: Weinheim, 1970.
5. Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377–2396.
6. Giese, S.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 8393–8396.
7. Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221–10228.
8. Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876–877.

9. Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750.
10. He, W.; Sun, X.; Frontier Alison, J. *J. Am. Chem. Soc.* **2003**, *125*, 14278–14279.
11. Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927–4930.
12. Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931–4934.
13. Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544–9545.
14. Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075–5078.
15. Janka, M.; He, W.; Frontier Alison, J.; Eisenberg, R. *J. Am. Chem. Soc.* **2004**, 6864–6865.
16. Some progress has been made toward catalytic asymmetric Nazarov cyclization: see: Kim, S. H.; Cha, J. K. *Synthesis* **2000**, 2113–2116 and references 12–14; but each method has serious limitations.
17. Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430–2431.
18. Browder, C. C.; West, F. G. *Synlett* **1999**, *9*, 1363–1366.
19. Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443–7444.
20. Browder, C. C.; Marmsater, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033–3035.
21. Yungai, A.; West, F. G. *Tetrahedron Lett.* **2004**, *45*, 5445–5448.
22. Ittel, D. F.; Johnson, L. K. *Chem. Rev.* **2000**, *100*, 1169–1203.
23. Johnson, L. K.; Killian, C. M.; Brookhart, M. *J. Am. Chem. Soc.* **1995**, *117*, 6414–6415.
24. Gibson, V. C.; Spitzmesser, S. K. *Chem. Rev.* **2003**, *103*, 283–315.
25. Drent, E.; Budzelaar, P. H. M. *Chem. Rev.* **1996**, *96*, 663–681.
26. Rix, F. C.; Brookhart, M.; White, P. S. *J. Am. Chem. Soc.* **1996**, *118*, 4746–4764.
27. Arndtsen, B. A.; Bergman, R. G. *Science* **1995**, *270*, 1970–1973.
28. Tellers, D. M.; Bergman, R. G. *J. Am. Chem. Soc.* **2000**, *122*, 954–955.
29. Tellers, D. M.; Bergman, R. G. *Organometallics* **2001**, *20*, 4819–4832.
30. Golden, J. T.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 5837–5838.
31. Tellers, D. M.; Yung, C. M.; Arndtsen, B. A.; Adamson, D. R.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 1400–1410.
32. Holtcamp, M. W.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1997**, *119*, 848–849.
33. Johansson, L.; Tilset, M.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 10846–10855.
34. Johansson, L.; Ryan, O. B.; Tilset, M. *J. Am. Chem. Soc.* **1999**, *121*, 1974–1975.
35. Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514.
36. Wik, B. J.; Lersch, M.; Tilset, M. *J. Am. Chem. Soc.* **2002**, *124*, 12116–12117.
37. Albietz, P. J.; Cleary, B. P.; Paw, W.; Eisenberg, R. *J. Am. Chem. Soc.* **2001**, *123*, 12091–12092.
38. Albietz, P. J.; Cleary, B. P.; Paw, W.; Eisenberg, R. *Inorg. Chem.* **2002**, *41*, 2095–2108.
39. Janka, M.; Eisenberg, R. Unpublished results.
40. Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. G.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.
41. Evans, D. A.; Tregay, S. W.; Berugey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936–7943.
42. Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134–9142.
43. Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.
44. Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595–598.
45. Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375–3378.
46. Smith, D. A.; Ulmer, C. W. *Tetrahedron Lett.* **1991**, *32*, 725–728.
47. Desimoni, G.; Faita, G.; Ricci, M.; Righetti, P. *Tetrahedron* **1998**, *54*, 9581–9602.
48. He, W.; Atesin, T. A.; Caruana, P. A.; Frontier, A. J. Unpublished results.
49. See Figure 3 'position 4'.
50. Albietz, P. J. Ph.D. Thesis, University of Rochester, NY, 2001. $^{1}P\{^{1}H\}$ NMR (CD_2Cl_2) at 25 °C: δ 21.2 (d, $J_{P-P}=4.8$ Hz, 1P, *trans* to CO), 16.5 (d, $J_{P-P}=4.8$ Hz, 1P, *cis* to CO).
51. $^{31}P\{^{1}H\}$ NMR (CD_2Cl_2) at 25 °C for the major isomer (66%): δ 32.7 (d, $J_{P-P}=4.7$ Hz, $J_{P-C}=130$ Hz, ^{1}P, *trans* to CO), 15.1 (d, $J_{P-P}=4.7$ Hz, 1P, *cis* to CO). For the minor isomer (34%): δ 31.9 (d, $J_{P-P}=4.7$ Hz, $J_{P-C}=123$ Hz, 1P, *trans* to CO), 15.9 (d, $J_{P-P}=4.7$ Hz, $J_{P-C}=123$ Hz, 1P, *cis* to CO).
52. $^{1}P\{^{1}H\}$ NMR (CD_2Cl_2) at 25 °C: δ 33.6 (d, $J_{P-P}=4.7$ Hz, 1P, *trans* to CO), 17.2 (d, $J_{P-P}=4.7$ Hz, 1P, *cis* to CO).
53. Consistent with this observation, binding of **1** with **19b/19a** (in a 12.8:1 ratio) also indicated four isomers in the ratio of 1:2:2.8:5 as observed by ^{31}P NMR spectroscopy.
54. Cleary, B. P. Ph.D. Thesis, University of Rochester, NY, 1995.
55. Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R. Manuscript in preparation.
56. Brookhart, M.; Grant, B.; Volpe, A. F. *Organometallics* **1992**, *11*, 3920–3922.
57. Jaquith, J. B.; Levy, C. J.; Bondar, G. V.; Wang, S.; Collins, S. *Organometallics* **1998**, *17*, 914–925.
58. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
59. α-Chloro-β-keto methylphosphonic acid dimethyl ester was prepared from piperonylic acid methyl ester **5** (Anderson, K.; Kuruvilla, A.; Uretsky, N.; Miller, D. *J. Med. Chem.* **1981**, *24*, 683–687) in three steps. Treatment of **5** with ^{n}BuLi and methylphosphonic acid dimethyl ester gave β-keto methylphosphonic ester (Tomiyama, T.; Wakabayashi, Y. *J. Med. Chem.* **1989**, *32*, 1988–1996) which was then chlorinated using NaH and NCS in DME.
60. The phosphonate was prepared in a similar manner through condensation of the piperonylic acid methyl ester with dimethylethylphosphonate. See Ref. 59.

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Imidazo[1,5-*a*]pyridine-3-ylidenes—pyridine derived N-heterocyclic carbene ligands

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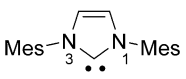
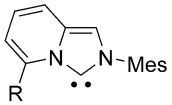
Abstract—The ready synthesis of differently substituted 2*H*-imidazo[1,5-*a*]pyridin-4-ium bromides is reported. These salts are precursors for a new class of N-heterocyclic carbene ligands. As a consequence of their bicyclic geometry, these ligands are capable of influencing the coordination sphere of a carbene bound metal. The usefulness of these ligands was demonstrated in the palladium-catalyzed Suzuki–Miyaura cross-coupling of sterically hindered aryl chlorides.

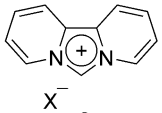
In the last 10 years, N-heterocyclic carbenes (NHCs) have become indispensable ligands for many areas of transition metal catalysis.[1] Many favorable characteristics render NHC to be attractive ligands for catalysis. They are electron rich donor ligands and generally form intriguingly stable complexes with many metals. Moreover, the geometry of NHC is different from other ligands, allowing the design of new ligand geometries. Therefore, it is rather surprising that most NHC ligands used in catalysis are 1,3-disubstituted imidazolylidenes like IMes, IiPr or their saturated analogues.[2] These ligands influence the metal's coordination sphere only to some extent. Ligand **1**, a hybrid between IMes and the NHC derived from **2**,[3] is different. As a result of its bicyclic structure the R substituent is placed in close proximity to a carbene bound metal, thus allowing significant shielding of the metal or, alternatively, stable or hemilabile coordination to the metal. Here we report on the flexible synthesis of pyridine derived imidazolium salts of type **1** and their first application in catalysis.



IMes



1



2

1. Results and discussion

The synthesis of a range of differently substituted pyridine derived NHC ligands started with pyridine carboxaldehydes **3** which are commercially available or easily prepared following literature methods. Reaction of **3** with 2,4,6-trimethyl aniline resulted in the smooth formation of pyridine imines **4** in good yields (Table 1). The imidazolium salt formation of **2** from bispyridine relied on the use of the elaborated arsonium salt **6** as an alkylating agent, severely reducing the attractivity of this ligand class.[3] This might be the reason why no successive reports on the use of this particular carbene have appeared. On the other hand the successful usage of a commercially available or easily prepared alkylating agent would allow easy access to pyridine-derived carbenes. Therefore, we were pleased to find that a reagent formed from equal amounts of AgOTf and chloromethyl pivalate[4] resulted in the formation of the desired imidazolium triflates, isolated as the corresponding bromide **5** after anion exchange (Scheme 1). These bromide salts crystallize more readily, significantly facilitating the purification process. Overall, this route is efficient and flexible and allows the formation of differently substituted 2*H*-imidazo[1,5-*a*]pyridin-4-ium salts **5** (R=H, Me, Ph, OMe, Br).

Table 1. Yields for the synthesis of **5**

Ligand	R	Yield of **4** (%)	Yield of **5** (%)
a	H	90	53
b	Me	90	52
c	Ph	99	47
d	OMe	89	22
e	Br	88	54

Keywords: Ligand design; N-heterocyclic carbene; Suzuki–Miyaura cross-coupling.
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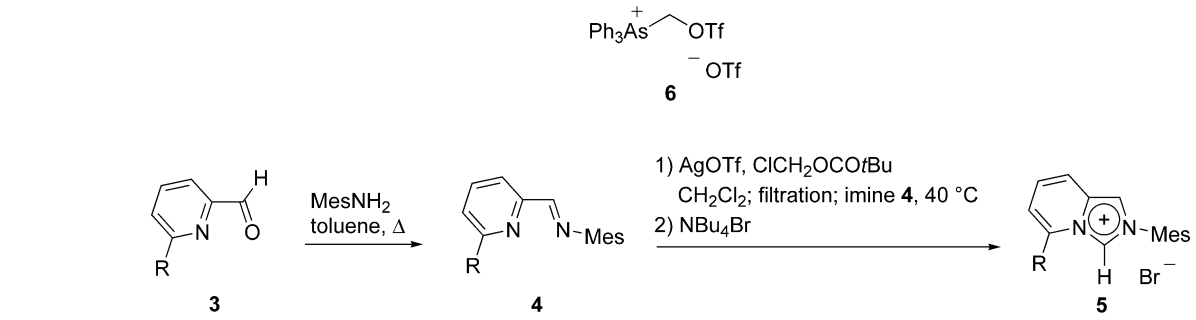


Scheme 1.

The structural identity of these compounds was unequivocally determined by X-ray structure analysis of **5a** and **5b** (Figs. 1 and 2).[5,6] These two compounds have similar bond lengths and angles. Most interestingly, on closer inspection of the bond lengths in **5a** and **5b** both molecules show the expected bond length alteration in the six-membered ring as expected from the canonical forms shown in Scheme 2. The two formal double bonds are approximately 0.08 Å shorter than the single bond in between. These three bonds and the bridging bond are identical within one σ in **5a** and **5b**.

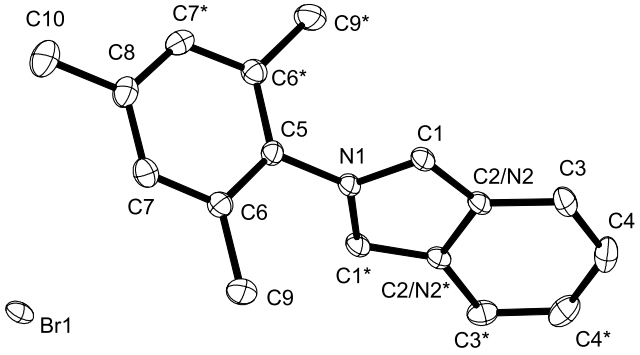


Figure 1. Molecular structure of **5a** which is situated on a crystallographic 2-fold axis. Atoms C2 and N2 share one position. Anisotropic displacement parameter ellipsoids are drawn at the 50% level. Selected bond lengths (Å) and angles (°): C1–N1 1.356(2), C1–C2 1.357(2), C2–N2^{i} 1.403(3), C2–C3 1.412(2), C3–C4 1.351(3), C4–C4^{i} 1.435(5), C5–N1 1.453(3), symmetry code (i) $-x+1/4$, $-y+5/4$, z.

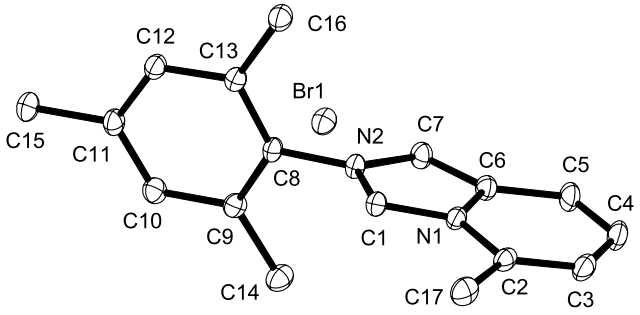
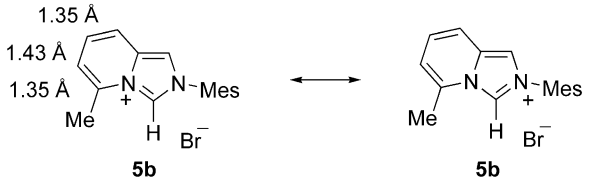


Figure 2. Molecular structure of **5b**. Anisotropic displacement parameter ellipsoids are drawn at the 50% level. Selected bond lengths (Å) and angles (°): N1–C1 1.3484(17), N1–C2 1.4044(18), N1–C6 1.4061(18), C1–N2 1.3359(17), N2–C7 1.3761(17), N2–C8 1.4475(18), C2–C3 1.355(2), C3–C4 1.433(2), C4–C5 1.354(2), C5–C6 1.4222(19), C6–C7 1.3703(19).



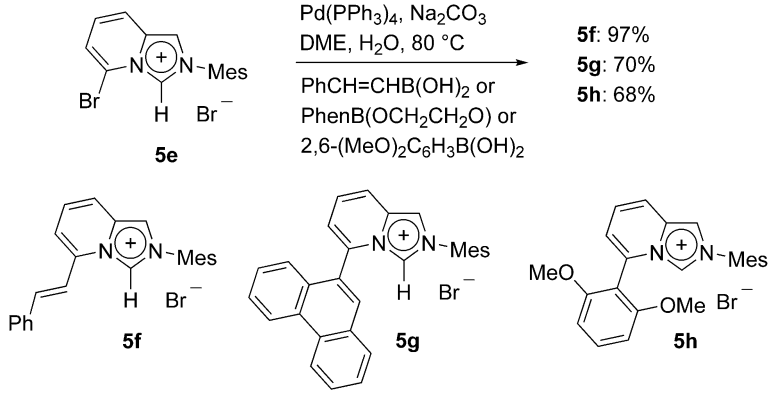
Scheme 2. Most important canonical forms of the imidazolium salts **5b**.

Interestingly, in **5c** the ^{1}H NMR signal of H–C(1) is shifted upfield compared to the other imidazolium salts **5a** and **5b** by more than 1 ppm This indicates that H–C(1) lies in the anisotropic cone of the phenyl ring. A similar interaction is envisioned to occur with a carbene bound metal.

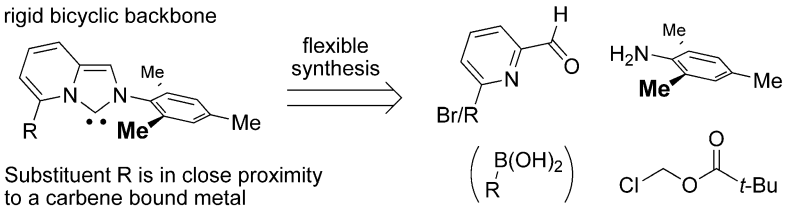
Ligand precursors **5a–e** can readily be synthesized. However, in order to introduce a new substituent R the whole sequence has to be repeated. A common synthetic precursor that could be manipulated to yield differently substituted products in one step would be highly desirable. In general, organic halides enable a plethora of synthetic transformations.[7] Therefore, we investigated the derivatization of bromide **5e**. Transition metal catalyzed coupling reactions seemed tempting, however, palladium catalyzed transformations of aryl halides in the presence of 2-unsubstituted imidazolium salts can provide potential pitfalls. Namely, deprotonation of the imidazolium salts might occur, providing sensitive NHCs or the corresponding palladium NHC complexes. Gratefully, after some optimization Suzuki cross-coupling of **5e** with different boronic acids or boronic acid esters provided the desired substituted imidazolium salts **5f**, **5g** and **5h** in good yields. This strategy allows the synthesis of a variety of differently substituted NHC-precursors in one step from **5e** (Schemes 3 and 4).

Compounds **5f** and **5g** can exist as atropisomers. Whereas the two *ortho*-methyl groups of the mesitylene moiety of **5f** give only one signal in ^{1}H and ^{13}C NMR, in compound **5g** they result in two individual signals. This implies that rotation of the 1-styryl moiety in **5f** is fast relative to the NMR time scale, whereas rotation of the phenanthrene unit in **5g** is slow. As a further indication for a relatively long life time, capillary electrophoresis of **5g** also results in two discrete base line separated peaks with diffusion times of 15.8 and 16.2 min. However, separation of the two atropisomers of **5g** by HPLC on a chiral phase was not successful.

Complexes of the NHCs derived from the ligand precursor **5** with R=H, Ph and C≡C–Ph have also been characterized by single crystal structure analysis in order to investigate their coordinational behavior. The differently substituted



Scheme 3. Suzuki–Miyaura cross-coupling of **5e**.



Scheme 4. Retrosynthetic analysis and ligand features.

ligands behave differently and the stability of the complexes formed depends strongly on the steric demand of the ligand.

Taking the unsubstituted **5a**, the stable $(NHC)_2PdI_2$ complex **7** smoothly forms in 52% yield under standard conditions (**5a**, $Pd(OAc)_2$, NaI, KO*t*Bu, THF).[8] In the distorted square planar complex **7** two carbene ligands (R = H) are *trans*-coordinated to the palladium (Fig. 3).[5] Both aza-indolizinyl ligands are rotated almost perpendicular to the coordination plane. The mesityl rings are oriented perpendicular to the heterocycles and adopt a proximal arrangement. The shortest non-bonding C···C distance is 3.537 Å, formed between C12 and C30. The bond lengths of the carbene ligand are all within three to four σ to those in **5b**, with the exception of the two carbene carbon–nitrogen atom bonds. These are, after averaging over both ligands in **7**, 1.357(3) and 1.367(3) Å long compared to 1.3359(19) and 1.3484(17) Å in the aza-indolizinium salt.

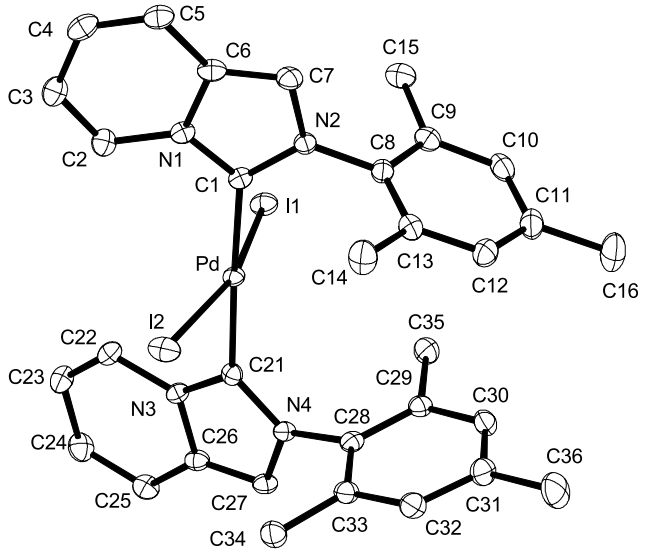
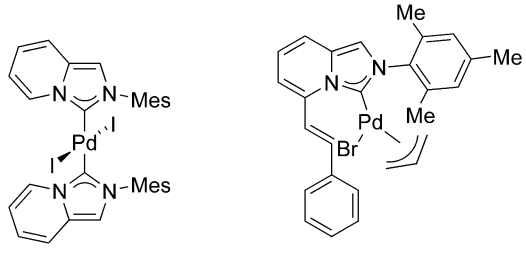
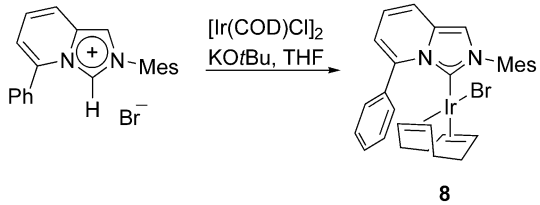


Figure 3. Molecular structure of **7**. Anisotropic displacement parameter ellipsoids are drawn at the 50% level. Selected bond lengths (Å) and angles (°): Pd–C21 2.015(2), Pd–C1 2.033(2), Pd–I2 2.6062(2), Pd–I1 2.6289(2), N1–C1 1.369(3), N1–C2 1.391(3), N1–C6 1.411(3), N2–C1 1.358(3), N2–C7 1.381(3), N2–C8 1.446(3), N3–C21 1.364(3), N3–C22 1.393(3), N3–C26 1.407(3), N4–C21 1.356(3), N4–C27 1.388(3), N4–C28 1.458(3), C2–C3 1.345(4), C3–C4 1.436(4), C4–C5 1.347(4), C5–C6 1.428(3), C6–C7 1.357(4), C22–C23 1.350(4), C23–C24 1.436(4), C24–C25 1.351(4), C25–C26 1.427(3), C26–C27 1.359(3), C21–Pd–C1 177.68(9), C21–Pd–I2 88.45(6), C1–Pd–I2 92.45(7), C21–Pd–I1 87.41(6), C1–Pd–I1 92.30(6), I2–Pd–I1 163.418(10).



The isolation of the corresponding $(NHC)_2PdI_2$ complex of the sterically more demanding **5c** failed under standard conditions. However, sterically demanding **5c** (R = Ph) can also form complexes. Stirring $[Ir(COD)Cl]_2$ with



Scheme 5. Synthesis of complex **8**.

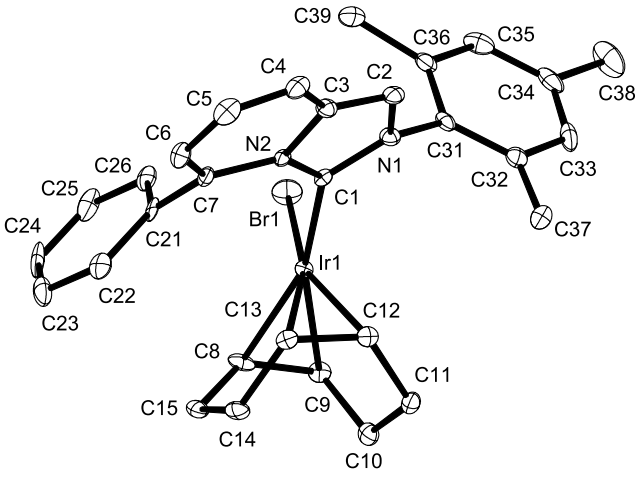


Figure 4. Molecular structure of **8**. Anisotropic displacement parameter ellipsoids are drawn at the 50% level. Selected bond lengths (Å) and angles (°): C1–N1 1.366(7), C1–N2 1.382(6), C1–Ir1 2.046(4), C2–C3 1.362(7), C2–N1 1.370(7), C3–C4 1.407(7), C3–N2 1.438(6), C4–C5 1.343(8), C5–C6 1.438(7), C6–C7 1.360(6), C7–N2 1.414(6), C8–Ir1 2.163(5), C9–Ir1 2.190(4), C12–Ir1 2.099(5), C13–Ir1 2.106(5), C31–N1 1.470(6), Br1–Ir1 2.4975(5), C1–Ir1–C12 87.43(19), C1–Ir1–C13 89.11(18), C1–Ir1–C8 158.17(18), C12–Ir1–C8 97.2(2), C13–Ir1–C8 81.15(19), C1–Ir1–C9 163.04(18), C12–Ir1–C9 80.9(2), C13–Ir1–C9 89.83(18), C1–Ir1–Br1 96.58(12), C12–Ir1–Br1 153.83(16), C13–Ir1–Br1 164.88(13), C8–Ir1–Br1 88.62(15), C9–Ir1–Br1 88.73(13).

imidazolium salt **5c** and KO*t*Bu in THF results in the formation of Ir(COD)**5c**Br (**8**) (Scheme 5).[9] X-ray structural analysis reveals interesting features of this complex (Fig. 4, 5).[5] The iridium center is coordinated in a distorted pseudo-square planar arrangement. The carbene ligand and the bromine are *cis* to each other and the two remaining places of the co-ordination sphere are occupied by the midpoints of the two carbon–carbon double bonds of the cycloocta-1,4-diene. As expected, the phenyl-substituent of the ligand shields one of the two faces of the coordination plane of iridium. Most notable, there is an additional intramolecular interaction between two of the phenyl carbon atoms and the metal, resulting in a slight pyramidalization of C21 (Fig. 5). The distances to the iridium atom are 3.183 and 3.322 Å for C26 and C21, respectively.

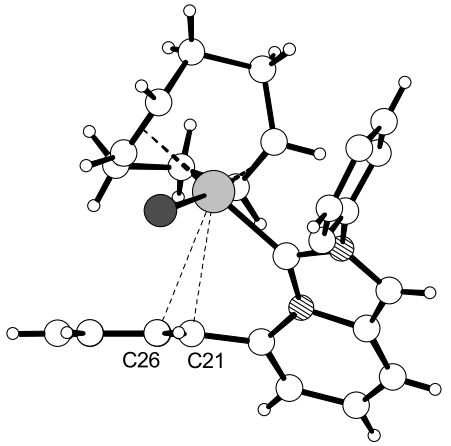


Figure 5. Molecular structure of **8**. Intramolecular contact between the iridium metal and carbon atom C21 (3.322 Å) and C26 (3.183 Å) shown as thin dashed lines. Carbon atom C21 is slightly pyramidalized, the sum of all bond angles for this atom is 359.59. The methyl groups of the mesityl ring have been omitted for clarity.

Secondary interactions, as observed in complex **8** between the phenyl group and the metal, arguably play an important role in catalysis.[10] This might result in a stabilization or activation of a catalytically active complex. This renders ligands **5c**, **5d**, **5f**, **5g** and **5h** especially valuable. It is obvious that the electronic and steric character of the R group can be fine tuned and also varied over a wide range.

We prepared palladium allyl complex **9** by stirring of the NHC derived from **5f** with palladium allyl chloride dimer.[9] It is important to note that the bromo and not the chloro complex is formed. The molecular structure is also distorted pseudo-square planar (Fig. 6).[5] The carbene ligand adopts a conformation similar to the one in **8** and the bond lengths follow the same trend as previously observed. The carbene carbon–nitrogen bonds are even more elongated than in **7**. In addition, a short contact is observed between the metal center and carbon atom C11 of the styrene substituent. With 3.081 Å, the distance is shorter than the sum of the van der Waals radii. A possible pyramidalisation of this carbon is not detectable from the X-ray crystal structure, due to the uncertainty of the hydrogen atom position. However, the torsion angle C5–C11–C12–C13 deviates by 4° from the ideal 180°, also indicating a weak interaction between palladium and C11.

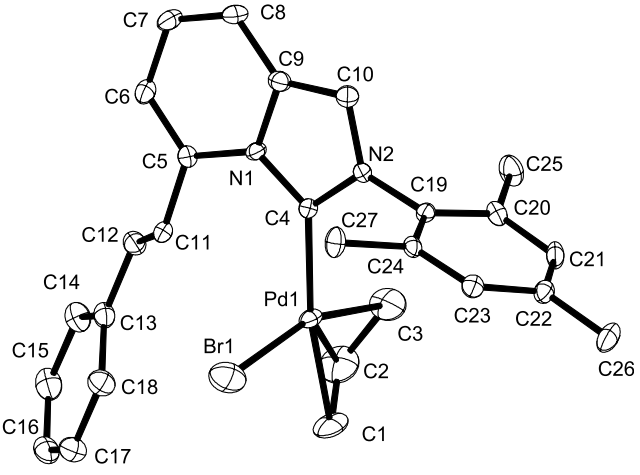
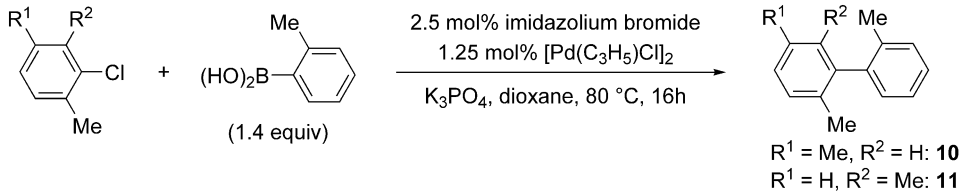


Figure 6. Molecular structure of **9**. Anisotropic displacement parameter ellipsoids are drawn at the 50% level. Selected bond lengths (Å) and angles (°): C1–C2 1.359(9), C1–Pd1 2.186(5), C2–C3 1.385(9), C2–Pd1 2.133(6), C3–Pd1 2.123(6), C4–N2 1.360(5), C4–N1 1.377(5), C4–Pd1 2.059(4), C5–C6 1.361(6), C5–N1 1.405(5), C6–C7 1.429(6), C7–C8 1.353(7), C8–C9 1.420(6), C9–C10 1.369(6), C9–N1 1.412(5), C10–N2 1.375(6), C19–N2 1.448(5), C4–Pd1–C3 99.86(19), C4–Pd1–C2 132.2(2), C4–Pd1–C1 167.6(2), C3–Pd1–C1 67.7(2), C4–Pd1–Br1 98.08(11), C3–Pd1–Br1 161.81(16), C2–Pd1–Br1 126.6(2), C1–Pd1–Br1 94.31(16).

A more cationic metal with free coordination sites should result in much stronger interactions. Treatment of a CH_2Cl_2 solution of complex **9** with $AgSbF_6$ results in characteristic changes in the ^1H NMR spectrum, indicating a cationic palladium complex stabilized by double bond complexation. However, this complex decomposes on standing and no crystals suitable for X-ray structural analysis could be obtained.



Scheme 6.

2. Suzuki–Miyaura cross-coupling

The Suzuki–Miyaura cross-coupling is one of the most important method for the formation of unsymmetrical biaryls, substructures of many important compounds.[11] In general, aryl bromides and aryl iodides are used as coupling partner. However, the use of the cheaper but less reactive aryl chlorides under mild conditions is of great academic and practical interest and many research programs are devoted to this.[12] As a first test for the usefulness of this new ligand system we chose the Suzuki–Miyaura cross-coupling of sterically demanding aryl chlorides with aryl boronic acids to give di- and tri-orthosubstituted biaryls (Scheme 6, Table 2). Distinctive differences were found for the different ligands. Employing 2.5 mol% catalyst, most ligand/palladium combinations produced only low amounts of the desired product. In contrast, ligands **5g** and **5h** lead to the formation of di- and tri-orthosubstituted biaryls in respectable yields of up to 86% isolated yield.

Table 2. Suzuki–Miyaura cross-coupling of sterically hindered aryl chlorides resulting in di- and triortho-substituted biaryls[a]

Entry	Ligand	Product	Yield[a]
1	**5a**	**10**	(<10)
2	**5b**	**10**	(38)
3	**5c**	**10**	(39)
4	**5d**	**10**	(34)
5	**5f**	**10**	(22)
6	**5g**	**10**	86
7	**5h**	**10**	(67)
8	**5a**	**11**	<10
9	**5b**	**11**	30 (28)
10	**5c**	**11**	(27)
11	**5d**	**11**	(<10)
12	**5f**	**11**	(<10)
13	**5g**	**11**	78
14	**5h**	**11**	67 (69)

[a] Yield of isolated product; GC yield in brackets.

For Suzuki–Miyaura cross-couplings it is believed that a monoligated Pd-species is the active catalyst.[13] In order to increase the life time of this species steric shielding or hemilabile binding might be beneficial. Ligands derived from **5g** (R=phenanthryl) and **5h** (R=2,6-dimethoxyphenyl)[14] are suitable for this kind of interaction. The substituents R on the ligand shield the metal and in addition they can bind to the metal possibly resulting in a stabilization or activation of the catalytically active complex.

In conclusion we have reported a facile synthetic route to a new class of pyridine derived NHC ligands and transition metal complexes thereof. The first investigation of their catalytic activity has been reported, demonstrating the usefulness of this exciting ligand class.

3. Experimental

3.1. General remarks

All reactions were conducted in dried glassware under an atmosphere of argon. The solvents used were purified by distillation over the drying agents indicated and were transferred and stored under argon: tetrahydrofuran (THF) (Na), CH_2Cl_2 (P_4O_{10}), toluene (Na/K). For flash chromatography, Merck silica gel 60 (230–400 mesh) was used. NMR spectra were recorded on a DPX 300 or AV 400 spectrometer (Bruker) in the solvents indicated; chemical shifts (δ) are given in parts per million relative to tetramethylsilane, and coupling constants (J) are given in Hertz. For IR, a Nicolet FT-7199 spectrometer or Perkin–Elmer Fourier transform-IR Diamant Spectrum One (ATR) was used; wavenumbers (ν) are given in cm^{-1}. For MS (electron ionization (EI)), a FinniganMAT 8200 (70 eV) was used, and for high-resolution MS (HRMS), a Finnigan MAT 95 was used. All commercially available compounds were used as received. K_3PO_4 was ground with a mortar and flame dried.

3.1.1. 2-Bromo-6-methoxypyridine. To a stirred solution of 2,6-dibromopyridine (4.74 g, 20 mmol) in anhydrous MeOH (20 ml) was added NaOMe (2.16 g, 40 mmol) in anhydrous MeOH (8 ml) and the solution was refluxed for 24 h. The reaction mixture was poured into a cold aqueous 5% $NaHCO_3$ solution (40 ml), and extracted with ether (5× 10 ml). The organic layer was washed with brine (15 ml) and dried over Na_2SO_4. After evaporation of the solvent the remaining residue was purified by Kugelrohr distillation (2×10^{-2} mbar, 70 °C) to give the title compound (2.56 g, 68%) as a colorless liquid.

R_f=0.38 (hexane/EtOAc 9:1); IR (film) 2952, 1595, 1581, 1556, 1469, 1411, 1297, 1150, 1122, 1021, 855, 786; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.37 (m, 1H), 7.03 (d, J= 7.5 Hz, 1H), 6.66 (d, J=8.2 Hz, 1H), 3.92 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 163.7, 140.3, 138.6, 120.1, 109.3, 54.0; MS (EI) m/z (%) 189 (64), 188 (100), 187 (66), 186 (95), 160 (24), 159 (39), 158 (29), 157 (39), 108 (12), 93 (59), 78 (50), 76 (15), 65 (22), 64 (22), 53 (11), 76 (15), 65 (22), 64 (22), 53 (11), 51 (10), 50 (14), 39 (48), 38 (32), 37 (11); HRMS (ESI) calcd for $C_{27}H_{27}N_2$:186.9633, found 186.9631.

3.1.2. 6-Methoxypyridine-2-carbaldehyde (3d). To a solution of 2-bromo-6-methoxypyridine (2.56 g,

13.7 mmol) in anhydrous THF (50 ml) was added *n*-butyl lithium (1.6 M in THF, 8.9 ml, 14.2 mmol) at −78 °C and the solution was stirred for 1 h. DMF (1.18 ml, 15.2 mmol) was added dropwise, and the solution was stirred for 30 min at −78 °C. The cold solution was poured into an aqueous solution of 5% $NaHCO_3$ (130 ml) and extracted with ether (3×50 ml). The organic layer was dried over Na_2SO_4. After evaporation of the solvent the remaining residue was purified by column chromatography (3×12 cm, hexane/EtOAc 9:1) to give **3d** (1.0 g, 54%) as a colorless liquid.

R_f=0.68 (hexane/EtOAc 9:1); IR (film) 2986, 2954, 2828, 1720, 1702, 1599, 1473, 1331, 1274, 1219, 1028, 806, 779; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (m, 1H), 7.73–7.68 (m, 1H), 7.55–7.53 (m, 1H), 6.97–6.94 (m, 1H), 4.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 164.4, 150.4, 139.0, 116.2, 115.4, 53.5; MS (EI) *m/z* (%) 137 (100), 136 (58), 108 (25), 107 (21), 94 (12), 93 (27), 80 (10), 79 (45), 78 (10), 66 (10), 65 (13), 52 (16), 51 (10), 39 (28), 38 (14); HRMS (EI) calcd for $C_7H_7NO_2$: 137.0478, found 137.0477.

3.1.3. 2-Bromo-6-formylpyridine (3e). A solution of *n*-butyl lithium (1.6 M in THF, 24.1 ml, 38.5 mmol) in toluene (30 ml) was cooled to −10 °C and *n*-butyl magnesiumbromide (2 M in THF, 10.95 ml, 21.9 mmol) was added dropwise. To this mixture was added a solution of 2,6-dibromopyridine (13 g, 55 mmol) in THF (40 ml). After stirring for 4 h at −10 °C the reaction mixture was poured into a solution of citric acid (21 g, 110 mmol) in water (45 ml), and extracted with MTBE (4×25 ml). The organic layer was dried over Na_2SO_4, and the solvent removed in vacuo. The remaining residue was purified by column chromatography (5×12 cm, hexane/EtOAc 10:1) followed by crystallization from MTBE/hexane to give **3e** (6.05 g, 60%) as colorless crystals.

R_f=0.45 (hexane/EtOAc 10:1); IR (KBr) 3040, 2872, 1732, 1574, 1436, 1413, 1291, 1213, 1120, 986, 856, 796; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99–9.98 (m, 1H), 7.92–7.90 (m, 1H), 7.76–7.70 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 191.6, 153.5, 142.6, 139.3, 132.6, 120.3; MS (EI) *m/z* (%) 187 (43), 185 (43), 159 (96), 158 (22), 157 (98), 156 (17), 78 (100), 77 (20), 76 (40), 75 (12), 52 (14), 51 (44), 50 (40), 29 (11); HRMS (ESI) calcd for C_6H_4BrO: 184.9476, found: 184.9474.

3.1.4. (*E*)-2,4,6-Trimethyl-*N*-((pyridin-2-yl)methylene)-benzenamine (4a). 2-Pyridinecarboxaldehyde (3.57 ml, 37.3 mmol) and 2,4,6-trimethylaniline (5.2 ml, 37.3 mmol) were dissolved in EtOH (50 ml) and heated to 90 °C for 30 min. Evaporation of the solvent in vacuo, followed by Kugelrohr distillation (2×10^{-2} mbar, 100–150 °C) of the remaining residue resulted in **4a** as a yellowish solid (7.5 g, 90%).

R_f=0.60 (EtOAc); IR (KBr) 3051, 2974, 2946, 2911, 2854, 1640, 1585, 1566, 1482, 1468, 1435, 1202, 1143, 876, 862, 770, 739; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (m, 1H), 8.35 (s, 1H), 8.29 (dt, *J*=1.0, 7.9 Hz, 1H), 7.84 (tdd, *J*=0.6, 1.7, 7.6 Hz, 1H), 7.41 (ddd, *J*=1.2, 4.9, 7.5 Hz, 1H), 6.91 (s, 2H), 2.31 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 154.6, 149.6, 147.8, 136.7, 133.4, 128.8, 126.8, 125.2, 121.2, 20.7, 18.2; MS (EI), *m/z* (%) 224 (69), 209 (100), 196 (9), 181 (6), 157 (20), 146 (36), 131 (17), 115 (6), 104 (8), 91 (18), 79 (20), 65 (8); HRMS (EI) calcd for $C_{15}H_{16}N_2$: 224.1313, found 224.1312.

3.1.5. (*E*)-2,4,6-Trimethyl-*N*-((6-methylpyridin-2-yl)-methylene)benzenamine (4b). Aldehyde **3b** (3.0 g, 24.8 mmol) and 2,4,6-trimethylaniline (3.5 ml, 24.8 mmol) were dissolved in EtOH (40 ml) and heated to 90 °C for 2 h. Evaporation of the solvent in vacuo, followed by Kugelrohr distillation (2×10^{-2} mbar, 100–140 °C) of the remaining residue resulted in **4b** as a yellow solid (5.3 g, 90%).

R_f=0.58 (EtOAc); IR (KBr) 3063, 2967, 2912, 2855, 1640, 1590, 1572, 1480, 1458, 1380, 1208, 1144, 987, 856, 837, 807, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.10 (d, *J*=7.8 Hz, 1H), 7.72 (t, *J*=7.8 Hz, 1H), 7.26 (d, *J*=6.7 Hz, 1H), 6.90 (s, 2H), 2.65 (s, 3H), 2.31 (s, 3H), 2.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 158.3, 154.0, 147.9, 136.8, 133.2, 128.7, 126.8, 124.8, 118.2, 24.3, 20.7, 18.2; MS (EI), *m/z* (%) 238 (100), 223 (45), 196 (7), 157 (14), 146 (35), 131 (15), 119 (12), 103 (7), 93 (41), 77 (13), 65 (11); HRMS (ESIpos, CH_3OH and CH_2Cl_2) calcd for $C_{16}H_{19}N_2+H$: 239.1548, found 239.1550.

3.1.6. (*E*)-2,4,6-Trimethyl-*N*-((6-phenylpyridin-2-yl)-methylene)benzenamine (4c). 2-(6-Phenylpyridine)carboxaldehyde (2.9 g, 16.0 mmol) and 2,4,6-trimethylaniline (3.5 ml, 24.8 mmol) were dissolved in EtOH (25 ml) and heated to 90 °C for 1 h. Evaporation of the solvent in vacuo, followed by evaporation of the impurities by Kugelrohr distillation (2×10^{-2} mbar, up to 80 °C) resulted in **4c** as a yellow solid (4.8 g, 99%).

R_f=0.64 (EtOAc/hexane 1:1); IR (KBr) 3064, 3010, 2971, 2940, 2916, 2857, 1635, 1587, 1578, 1566, 1476, 1460, 1448, 1207, 1143, 850, 760, 685, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J*=0.3 Hz, 1H), 8.27 (dd, *J*=1.1, 7.6 Hz, 1H), 8.10–8.08 (m, 2H), 7.91 (td, *J*=0.6, 7.8 Hz, 1H), 7.84 (dd, *J*=1.2, 7.8 Hz, 1H), 7.54–7.44 (m, 3H), 6.93 (s, 2H), 2.32 (s, 3H), 2.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 157.3, 154.5, 148.0, 138.9, 137.3, 133.3, 129.2, 128.8, 128.8, 127.0, 126.8, 121.9, 119.2, 20.7, 18.2; MS (EI), *m/z* (%) 300 (100), 285 (34), 155 (30), 144 (5), 131 (10), 91 (9), 77 (9); HRMS (EI) calcd for $C_{21}H_{20}N_2$: 300.1626, found 300.1629.

3.1.7. (*E*)-*N*-((6-Methoxypyridin-2-yl)methylene)-2,4,6-trimethylbenzenamine (4d). A solution of 2-methoxy-6-formylpyridine (**3d**) (831 mg, 6.0 mmol) and 2,4,6-trimethyl aniline (847 µl, 6.0 mol) in EtOH (13 ml) were refluxed for 4 h. The solvent was removed in vacuo and the residue purified by Kugelrohr distillation, yielding **4d** as yellow solid (1.59 g, 89%).

R_f=0.89 (hexane/EtOAc 9:1+1% NEt_3); IR (film) 3062, 3007, 2976, 2949, 2915, 2857, 1641, 1590, 1573, 1468, 1440, 1332, 1321, 1267, 1206, 1142, 1033, 987, 856, 841, 805, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22–8.17 (m, 1H), 7.86–7.84 (m, 1H), 7.73–7.68 (m, 1H), 6.89 (s, 2H), 6.86–6.83 (m, 1H), 3.99 (s, 3H), 2.29 (s, 3H), 2.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 163.6, 152.1, 148.1, 138.8, 133.2, 128.7, 126.8, 114.0, 112.5, 53.4, 20.7, 18.1; MS (EI) *m/z* (%) 255 (17), 254 (100), 253 (38), 238 (48),

196 (20), 195 (29), 146 (55), 145 (14),131 (18), 130 (11), 110 (18), 109 (25), 91 (16), 77 (12); HRMS (EI) calcd for $C_{16}H_{18}N_2O$: 254.1419, found 254.1421.

3.1.8. *N*-((6-Bromopyridin-2-yl)methylene)-2,4,6-trimethylbenzenamine (4e). A solution of 2-bromo-6-formylpyridine (2.96 g, 15.9 mmol) and 2,4,6-trimethyl aniline (2.24 ml, 15.9 mmol) in EtOH (30 ml) was refluxed for 4 h. The solvent was removed in vacuo and the residue purified by Kugelrohr distillation (2×10^{-2} mbar, 70–90 °C), yielding **4e** as yellow oil which solidifies upon standing (6.97 g, 88%).

R_f=0.82 (hexane/EtOAc 9:1); IR (KBr) 3065, 2912, 2854, 1645, 1550, 1478, 1440, 1334, 1206, 1123, 985, 853, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.25 (dd, J= 7.7, 0.8 Hz, 1H), 7.68 (dd, J=7.8, 7.7 Hz, 1H), 7.59 (dd, J=7.8, 0.8 Hz, 1H), 6.90 (s, 2H), 2.29 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 155.7, 147.3, 141.7, 138.8, 133.7, 129.5, 128.8, 126.7, 119.6, 20.7, 18.1; MS (EI) *m/z* (%) 304 (30), 303 (16), 302 (30), 301 (12), 286 (3), 224 (18), 223 (100), 146 (66), 145 (14), 131 (20), 130 (11), 103 (9), 91 (13), 77 (11); HRMS (EI) calcd for $C_{15}H_{15}BrN_2$: 302.0419, found 302.0420.

3.1.9. Imidazolium bromide 5a. To a suspension of AgOTf (4.8 g, 18.7 mmol) in CH_2Cl_2 (50 mL) was added chloromethyl pivalate (2.78 mL, 18.7 mmol) and the resulting suspension was stirred for 45 min. After filtration the filtrate was added to pyridine imine **4a** (3.0 g, 13.4 mmol) and the solution was stirred in a sealed tube in the dark at 40 °C for 19 h. After the solution was cooled to rt MeOH (20 mL) was added, the solvent was removed in vacuo and the resulting oil was chromatographed on silica gel (2.5×10 cm, CH_2Cl_2/MeOH 50:1 to 10:1). The resulting foam was dissolved in CH_2Cl_2 (30 mL), NBu_4Br (6 g, 18.6 mmol) was added and the solution was stirred. After 2 h MTBE (100 mL) was added and the crystals were collected by filtration. Subsequent crystallisation from EtOH 2.75 g (53%, 7.1 mmol) of imidazolium triflate **5a** as colorless crystals.

R_f (of **5a**-OTf)=0.51 (CH_2Cl_2/MeOH 10:1); IR (KBr) 3070, 3045, 2992, 2917, 1649, 1607, 1537, 1497, 1449, 1212, 1158, 828, 763, 675; ^{1}H NMR (400 MHz, D_6-DMSO) δ 10.01 (d, J=1.0 Hz, 1H), 8.62 (dd, J=0.6, 7.1 Hz, 1H), 8.39 (s, 1H), 7.93 (d, J=9.2 Hz, 1H), 7.38 (dd, J=6.5, 8.8 Hz, 1H), 7.28 (td, J=0.9, 7.1 Hz, 1H), 7.18 (s, 2H), 2.35 (s, 3H), 2.01 (s, 6H); ^{13}C NMR (100 MHz, D_6-DMSO) δ 140.7, 134.3, 131.7, 129.9, 129.4, 127.8, 125.4, 124.8, 118.5, 118.1, 114.8, 20.8, 17.0; MS (EI), *m/z* (%) 236 (59), 221 (16), 206 (7), 158 (100), 144 (14), 115 (7), 103 (5), 91 (6), 80 (9); HRMS (ESIpos, CH_3OH and CH_2Cl_2) calcd for $C_{16}H_{17}N_2$ (cation): 237.1391, found 237.1389.

3.1.10. Imidazolium bromide 5b. To a suspension of AgOTf (6.0 g, 23.5 mmol) in CH_2Cl_2 (60 mL) was added chloromethyl pivalate (3.5 mL, 23.5 mmol) and the resulting suspension was stirred for 45 min. After filtration the filtrate was added to pyridine imine **4b** (4.0 g, 16.8 mmol) and the solution was stirred in a sealed tube in the dark at 40 °C for 24 h. After the solution was cooled to rt EtOH (20 mL) was added, the solvent was removed in vacuo and the resulting oil was chromatographed on silica gel (3× 10 cm, EtOAc/MeOH 10:1 to 5:1). The resulting oil was dissolved in CH_2Cl_2 (90 mL), NBu_4Br (10.8 g, 33.6 mmol) was added and the solution was stirred. After 2 h the solvent was removed in vacuo. Subsequent crystallisation from EtOH/MTBE (1:4, 100 mL) gave 2.91 g (52%, 8.8 mmol) of imidazolium triflate **5b** as yellow/brown crystals.

R_f (of **5b**-OTf)=0.57 (CH_2Cl_2/MeOH 10:1); IR (KBr) 3131, 3115, 3064, 2986, 2969, 2914, 1659, 1561, 1505, 1482, 1455, 1317, 1224, 1200, 1157, 1084, 1039, 860, 811, 772, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (m, 1H), 7.89 (d, J=1.7 Hz, 1H), 7.84 (d, J=9.3 Hz, 1H), 7.23 (m, 1H), 6.98 (s, 2H), 6.93 (t, J=0.9 Hz, 1H), 3.00 (s, 3H), 2.31 (s, 3H), 1.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 134.4, 134.0, 131.2, 130.9, 129.7, 126.5, 125.9, 117.0, 116.1, 114.5, 21.0, 19.9, 17.7; MS (ESIpos, CH_2Cl_2), *m/z* (%) 251 (100); HRMS (ESIpos, CH_3OH and CH_2Cl_2) calcd for $C_{17}H_{19}N_2$ (cation): 251.1548, found 251.1550. Anal. calcd For $C_{17}H_{20}BrN_2$: C, 61.64; H, 5.78; N, 8.46. Found C, 61.52; H, 5.72; N, 8.41.

3.1.11. Imidazolium bromide 5c. To a suspension of AgOTf (3.0 g, 11.7 mmol) in CH_2Cl_2 (30 mL) was added chloromethyl pivalate (1.75 mL, 11.7 mmol) and the resulting suspension was stirred for 45 min. After filtration the filtrate was added to pyridine imine **4c** (2.5 g, 8.3 mmol) and the solution was stirred in a sealed tube in the dark at 40 °C for 14 h. After the solution was cooled to rt EtOH (20 mL) was added, the solvent was removed in vacuo and the resulting oil was chromatographed on silica gel (3.5× 10 cm, CH_2Cl_2 to CH_2Cl_2/MeOH 10:1). The resulting oil was dissolved in CH_2Cl_2 (35 mL), NBu_4Br (5.0 g, 15.5 mmol) was added and the solution was stirred. After 12 h, the solvent was removed in vacuo and the resulting oil was chromatographed on silica gel (4×15 cm, EtOAc/MeOH 10:1 to 4:1). Subsequent crystallisation from CH_2Cl_2/MTBE (1:4, 100 mL) gave 1.52 g (47%, 3.9 mmol) of imidazolium triflate **5c** as colorless crystals.

R_f (of **5c**-OTf)=0.68 (CH_2Cl_2/MeOH 10:1); IR (KBr) 3065, 3029, 2998, 2916, 1651, 1608, 1549, 1491, 1448, 1154, 851, 806, 763, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J=1.1 Hz, 1H), 8.78 (d, J=1.8 Hz, 1H), 8.48 (d, J=9.3 Hz, 1H), 7.73–7.70 (m, 2H), 7.61–7.57 (m, 3H), 7.43 (dd, J=7.0, 9.3 Hz, 1H), 7.15 (dd, J=0.9, 7.0 Hz, 1H), 6.99 (s, 2H), 2.31 (s, 3H), 2.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 135.2, 133.9, 132.2, 131.3, 131.0, 130.6, 130.2, 129.7, 128.4, 125.8, 122.3, 119.6, 119.3, 117.6, 21.0, 17.7; MS (ESIpos, CH_2Cl_2), *m/z* (%) 313 (100); HRMS (ESIpos, CH_3OH and CH_2Cl_2) calcd for $C_{22}H_{21}N_2$ (cation): 313.1704, found 313.1699.

3.1.12. Imidazolium bromide 5d. To a suspension of AgOTf (2.06 g, 8 mmol) in CH_2Cl_2 (27 ml), chloromethyl pivalate (1.24 g, 8 mmol) was added and stirred in the dark for 45 min at rt. After filtration the filtrate was added to imine **4d** (1.46 g, 5.7 mmol) and stirred in the dark for 20 h at 45 °C. The solution was cooled to room temperature and quenched with EtOH (10 ml). The solvent was removed in vacuo and the resulting residue was purified by column chromatography (SiO_2, 2.5×12 cm, EtOAc/MeOH 9:1). Ion exchange with tetrabutylammonium bromide in CH_2Cl_2

and recrystallization from CH_2Cl_2/THF yielded **5d** (419 mg, 22%) as a greenish powder.

R_f=0.32 (EtOAc/MeOH 9:1); IR (KBr) 3058, 3031, 1656, 1555, 1374, 1281, 1200, 964, 854, 810, 772; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.65 (s, 1H), 8.17–8.07 (m, 1H), 7.69 (d, J=9.3 Hz, 1H), 7.43 (dd, J=7.6, 9.3 Hz, 1H), 7.10 (s, 2H), 6.59 (d, J=7.6 Hz, 1H), 4.28 (s, 3H), 2.38 (s, 3H), 2.06 (s, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 147.1, 141.7, 132.1, 131.2, 134.1, 127.9, 122.3, 115.0, 110.5, 93.2, 129.7, 58.1, 20.9, 17.3; MS (ESI) *m/z* 267; HRMS (ESI) calcd for $C_{17}H_{19}N_2O$: 267.1497, found 267.1489.

3.1.13. Imidazolium bromide 5e. To a suspension of AgOTf (7.23 g, 28.14 mmol) in CH_2Cl_2 (100 ml) was added chloromethyl pivalate (4.24 g, 28.14 mmol), and the suspension was stirred in the dark for 45 min at rt. After filtration, the filtrate was added to imine **4e** (6.1 g, 20.1 mmol) and the solution was stirred in the dark for 17 h at 45 °C. The solution was cooled to room temperature and quenched with EtOH (40 ml). The solvent was removed in vacuo and the resulting residue was purified by column chromatography (SiO_2, 4.5×12 cm, CH_2Cl_2/MeOH 10:1). Ion exchange with tetrabutylammonium bromide in CH_2Cl_2 and recrystallization from CH_2Cl_2/diethyl ether yielded **5e** (4.3 g, 54%) as brownish crystals.

R_f=0.35 (CH_2Cl_2/MeOH 10:1); IR (KBr) 3053, 2974, 2914, 1646, 1523, 1307, 1297, 1184, 1154, 1037, 857, 812, 748, 648, 586; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94–9.91 (m, 1H), 8.76 (d, J=1.8 Hz, 1H), 8.48 (d, J=9.3 Hz, 1H), 7.47–7.45 (m, 1H), 7.24 (dd, J=9.2 Hz, 9.3 Hz, 1H, with $CHCl_3$), 6.99 (s, 2H), 2.31 (s, 3H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ?141.5, 133.8, 132.2, 130.8, 129.7, 126.1, 125.6, 123.1, 119.5, 118.4, 112.4, 21.0, 17.6; MS (ESI) *m/z* 315; HRMS (ESI) calcd for $C_{16}H_{16}N_2$: 315.0497, found 315.0499.

3.1.14. Imidazolium bromide 5f. A solution of imidazolium salt **5e** (793 mg, 2 mmol) and $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) in 1,2-dimethoxyethane (8 ml) was degassed and stirred at room temperature for 30 min. To this suspension was added a solution of Na_2CO_3 (222.6 mg, 2.1 mmol) in degassed H_2O (2 ml) and 2-phenylvinylboronic acid (310 mg, 2.1 mmol). After 2.5 h, the reaction mixture was cooled to room temperature and water (10 ml) was added. The mixture was extracted with CH_2Cl_2 (5× 15 ml), and the organic layer was dried over Na_2SO_4. The solvent was removed in vacuo and the resulting residue was purified by column chromatography (SiO_2, 2.5×12 cm, CH_2Cl_2/MeOH 20:1) to give **5f** as a yellow solid (818 mg, 97%).

R_f=0.39 (CH_2Cl_2/MeOH); IR (KBr) 3400, 3030, 2919, 1647, 1623, 1535, 1497, 1449, 1198, 1155, 966, 852, 797, 753, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 8.40 (d, J=15.8 Hz, 1H), 7.99–7.97 (m, 2H), 7.84–7.79 (m, 2H), 7.40–7.36 (m, 2H), 7.31–7.24 (m, 3H), 7.24–7.20 (m, 1H), 6.92 (s, 2H), 2.26 (s, 3H), 2.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 138.3, 135.7, 135.0, 133.9, 131.1, 129.6, 129.5, 128.8, 128.6, 127.2, 125.9, 117.3, 116.2, 114.1, 113.1, 131.2, 21.0, 17.7; MS (ESI) *m/z* 339; HRMS (ESI) calcd for $C_{24}H_{23}N_2$: 339.1861, found 339.1865.

3.1.15. 2-(Phenanthren-10-yl)-1,3,2-dioxaborolane. Magnesium turnings (1.94 g, 80 mmol) and a few crystals of iodine were heated with a heatgun. After cooling, a solution of 9-bromophenanthrene (12.8 g, 40 mmol) and ethyliodide (6.24 g, 40 mmol) in THF (40 ml) was added dropwise. After 1 h at room temperature this suspension was added dropwise to a solution of trimethylborate (8.31 g, 80 mmol) in THF (40 ml) at −78 °C. The reaction mixture was warmed to room temperature and the solvent removed in vacuo. To the resulting solid was added ethylene glycol (6.7 ml, 120 mmol) and toluene (120 ml). After refluxing overnight, toluene was removed in vacuo and the remaining solid recrystalized from CH_2Cl_2/MTBE, yielding the title compound as white crystals (7.01 g, 70%).

R_f=0.95 (CH_2Cl_2/MeOH) IR (KBr) 3053, 2982, 2905, 1444, 1402, 1384, 1328, 1267, 1212, 1028, 770, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86–8.80 (m, 1H), 8.75–8.67 (m, 2H), 8,46 (s, 1H), 7.95 (d, J=7.8 Hz, 1H), 7.75–7.57 (m, 4H), 4.51 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 134.0, 131.7, 130.6, 129.6, 129.1, 128.6, 127.6, 126.4, 126.2, 125.9, 122.3, 122.2, 65.7; ^{11}B NMR (128 MHz, $CDCl_3$) δ ?33.2; MS (EI), *m/z* (%) 248 (100), 247 (25), 218 (4), 217 (8), 204 (16), 203 (7), 191 (10), 178 (5), 177 (6), 176 (9), 151 (4), 124 (4); HRMS (EI) calcd for $C_{16}H_{13}O_2B$: 248.1009, found 248.1011.

3.1.16. Imidazolium bromide 5g. A solution of imidazolium salt **5e** (300 mg, 0.756 mmol) and $Pd(PPh_3)_4$ (87.4 mg, 0.0756 mmol) in 1,2-dimethoxyethane (6 ml) was degassed and stirred at room temperature for 30 min. To this suspension was added a solution of Na_2CO_3 (84.2 mg, 0.794 mmol) in degassed H_2O (1.5 ml) and 2-(phenanthren-9-yl)-1,3,2-dioxaborolane (197 mg, 0.794 mmol). After 4 h at 80 °C the reaction mixture was cooled to room temperature and water (6 ml) was added. The mixture was extracted with CH_2Cl_2 (4×10 ml), and the organic layer was dried over Na_2SO_4. The solvent was removed in vacuo and the resulting residue was purified by column chromatography (SiO_2, 2.5×12 cm, CH_2Cl_2/MeOH 20:1) to give **5g** as a brownish solid foam (288 mg, 77%).

R_f=0.38 (DCM/MeOH 10:1) IR (KBr) 3382, 3145, 3056, 2955, 1653, 1553, 1450, 1311, 1187, 1153, 1039, 856, 809, 759, 729; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.96 (d, J=9.3 Hz, 1H), 8.82 (d, J=8.3 Hz, 1H), 8.74 (d, J= 8.3 Hz, 1H), 8.16 (s, 1H), 8.03–7.99 (m, 1H), 7.85–7.68 (m, 4H), 7.60–7.50 (m, 2H), 4.45–4.43 (m, 1H), 7.22 (d, J= 8.1 Hz, 1H), 6.90 (s, 2H), 2.25 (s, 3H), 1.96 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 141,8; 134,1; 134,0; 133,9; 132,1; 131,5; 131,4; 131,1; 131,0; 130,8; 129,7; 129,6; 129,6; 129,1; 128,1; 128,0; 127,9; 126,4; 126,0; 124,2; 124,2; 123,3; 122,9; 122,6; 120,9; 120,2; 118,0; 20,8; 17,3; 17,1; MS (ESI) *m/z* 413; HRMS (ESI) calcd for $C_{30}H_{25}N_2$: 413.2018, found 413.2019.

3.1.17. Imidazolium bromide 5h. A solution of imidazolium salt **5e** (595 mg, 1.5 mmol) and $Pd(PPh_3)_4$ (260 mg, 0.225 mmol) in 1,2-dimethoxyethane (12 ml) was degassed and stirred at room temperature for 30 min. To this suspension was added a solution of Na_2CO_3 (954 mg, 9 mmol) in degassed H_2O (3 ml) and 2,6-dimethoxyphenylboronic acid (819 mg, 4.5 mmol). After 18 h at

80 °C, more $Pd(PPh_3)_4$ (120 mg, 0.1 mmol), 2,6-dimethoxyphenylboronic acid (546 mg, 3 mmol) and Na_2CO_3 (636 mg, 6 mmol) were added to the reaction mixture. After heating for another 6 h at 80 °C, the reaction mixture was cooled to room temperature and water (10 ml) was added. The mixture was extracted with CH_2Cl_2 (5×15 ml), and the organic layer was dried over Na_2SO_4. The solvent was removed in vacuo and the resulting residue was purified by column chromatography (SiO_2, 2.5×12 cm, CH_2Cl_2/MeOH 10:1) to give **5h** as a brownish solid foam (462 mg, 68%).

R_f=0.25 (CH_2Cl_2/MeOH); IR (KBr) 3387, 3008, 2942, 2838, 1654, 1598, 1584, 1476, 1433, 1254, 1108, 783, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (m, 1H), 8.50 (d, J=9.3 Hz, 1H), 8.36 (m, 1H), 7.51 (t, J=8.5 Hz, 1H), 7.39 (dd, J=9.3, 9.3 Hz, 1H), 7.12–7.10 (m, 1H), 7.00 (s, 2H), 6.7 (d, J=8.5 Hz, 2H), 3.77 (s, 6H), 2.33 (s, 3H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 141.4, 133.9, 133.5, 131.9, 131.1, 129.7, 128.7, 125.3, 123.0, 121.6, 119.4, 116.9, 107.1, 104.5, 56.0, 21.0, 17.3; MS (ESI) *m*/*z* 373; HRMS (ESI) calcd for $C_{24}H_{25}N_2O_2$: 373.1916, found 373.1920.

3.1.18. Synthesis of complex 7. A mixture of imidazolium triflate **5a** (100 mg, 0.26 mmol), $Pd(OAc)_2$ (23.2 mg, 0.10 mmol), NaI (62.2 mg, 0.41 mmol) and KO*t*Bu (31.4 mg, 0.28 mmol) in THF (7 ml) was stirred for 16 h at room temperature. The solvent was evaporated in vacuo and the remaining solid was purified by column chromatography (SiO_2, 1.5×15 cm, hexane/EtOAc 3:1) to give **7** (45 mg, 52%) as a yellow solid.

R_f=0.62 (EtOAc/hexane 1:1); IR (KBr) 3137, 3111, 3006, 2957, 2916, 2854, 1752, 1736, 1651, 1608, 1525, 1484, 1464, 1366, 1333, 1241, 1196, 1034, 855, 847, 744, 681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (m, 2H), 7.26–7.21 (m, 2H), 7.11 (s, 2H), 6.87 (s, 4H), 6.87–6.84 (m, 2H), 6.72–6.68 (m, 2H), 2.50 (s, 6H), 1.98 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 137.9, 135.5, 135.3, 131.3, 130.3, 129.1, 122.9, 116.8, 114.4, 111.8, 21.3, 20.8; MS (EI), *m*/*z* (%) 837 (1), 836 (2), 835 (1), 834 (3), 833 (2), 832 (4), 831 (3), 830 (1), 705 (32), 577 (9), 237 (100); HRMS (EI) calcd for $C_{32}H_{32}I_1N_4$: 705.0705, found 705.0704.

3.1.19. Synthesis of complex 8. $[Ir(COD)Cl]_2$ (60 mg, 0.09 mmol) and KO*t*Bu (25.3 mg, 0.23 mmol) were stirred for 10 min in THF (6 ml). Imidazolium bromide **5c** (73.9 mg, 0.19 mmol) was added and the reaction mixture was stirred for 1.5 h at room temperature. The solvent was removed in vacuo and the remaining solid was purified by column chromatography (SiO_2, 1×12 cm, hexane/EtOAc 3:1) to give **8** (96 mg, 77%) as a yellow solid. This material might contain a small amount of the corresponding chloro complex.

R_f=0.71 (EtOAc/hexane 1:3); IR (KBr) 3107, 3050, 2913, 2876, 2829, 1648, 1488, 1445, 1358, 1328, 1196, 1157, 1035, 780, 757, 710, 694.

3.1.20. Palladium complex 9. A solution of imidazolium salt **5f** (350 mg, 0.834 mmol) in THF (10 ml) was stirred with potassium *tert*-butoxide (86 mg, 0.77 mmol) for 1 h at room temperature. After addition of palladium allyl chloride dimer (134 mg, 0.348 mmol) and LiBr (183 mg, 2.1 mmol) the suspension was stirred for 3 h at room temperature. After evaporation of the solvent the remaining solid was purified by column chromatography (SiO_2, 2.5×10 cm, CH_2Cl_2/MeOH 95:5) to give **9** (326 mg, 83%) as a yellow solid.

R_f=0.95 (CH_2Cl_2/MeOH 10:1); IR (KBr) 3135, 3000, 2917, 1647, 1493, 1448, 1369, 1196, 1155, 956, 853, 782, 752, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, J=15.7 Hz, 1H), 9.26 (d, J=15.3 Hz, 1H), 7.74–7.65 (m, 4H), 7.41–7.24 (m, 10H), 7.08–6.71 (m, 10H), 4.80–4.66 (m, 1H), 4.66–4.52 (m, 1H), 4.04–3.91 (m, 2H), 3.52–3.38 (m, 2H), 2.88–2.79 (m, 1H), 2.70–2.60 (m, 1H), 2.38 (s, 3H), 2.33 (s, 6H), 2.24 (s, 3H), 2.17–2.11 (m, 1H), 2.03–1.96 (m, 1H), 1.85 (s, 6H); MS (ESI) *m*/*z* 485; HRMS (ESI) calcd for $C_{27}H_{27}N_2Pd$: 485.1208, found 485.1208.

3.1.21. Synthesis of a cationic complex from 9. A solution of complex **9** (40 mg, 0.0767 mmol) in CH_2Cl_2 (1 ml) was stirred with $AgSbF_6$ (27.7 mg, 0.081 mmol) in the dark for 1 h. The resulting suspension was filtered and the filtrate evaporated to dryness (40 mg, 73%).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.68–7.61 (m, 3H), 7.48–7.35 (m, 5H), 7.12–7.03 (m, 4H), 6.85–6.84 (m, 1H), 5.34–5.38 (m, 1H), 3.49–3.15 (m, 2H), 3.07–2.78 (m, 1H), 2.56–2.53 (m, 1H), 2.36 (s, 3H), 1.95 (s, 3H), 1.90 (s, 3H); MS(ESI) *m*/*z* 485.

3.2. General procedure for Suzuki–Miyaura cross-coupling

Preparation of the catalyst solution: in a glove box **5g** (24.7 mg, 0.025 mmol) and KO*t*Bu (5.6 mg, 0.025 mmol) were suspended in THF (0.6 ml) and stirred for 20 min. $[Pd(allyl)Cl]_2$ (9.7 mg, 0.0125 mmol) was added and the mixture was stirred for another 20 min at room temperature to give the catalyst solution.

To a vial containing the 2-methyl benzene boronic acid (0.7 mmol) and K_3PO_4 (1.5 mmol) in degassed dioxane (1.6 ml) was added the corresponding aryl halide (0.5 mmol), followed by addition of one half of the catalyst solution. After 16 h at 80 °C the solvent was removed in vacuo and the residue chromatographed on silica with hexane to give the biaryl product.

Note added in proof

In parallel to this work, the investigation of imidazo[1,5-*a*]pyridine derived NHCs has been reported by Lassaletta and co-workers: Alcarazo, M.; Roseblade, S. L.; Cowley, A. R.; Fernandez, R.; Brown, J. M.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3290.

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Supplementary data

Capillary electrophoresis plot for **5g** together with UV–vis spectra of the two atropisomers (peaks).

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.115

References and notes

1. For excellent reviews on the use of NHC ligands in catalysis, see: (a) Herrmann, W. A. *Angew. Chem. Int., Ed.* **2002**, *41*, 1290. (b) Herrmann, W. A.; Köcher, C. *Angew. Chem. Int., Ed.* **1997**, *36*, 2162. See also, (c) Arduengo, A. J., III; Krafczyk, R. *Chem. Unserer Zeit* **1998**, *32*, 6. (d) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (e) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69–82.
2. For some applications of sterically demanding NHC ligands, see: (a) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem. Int., Ed.* **2002**, *41*, 1363. (b) Eckhardt, M.; Fu, G. *J. Am. Chem. Soc.* **2003**, *125*, 13642. (c) Ma, Y.; Song, C.; Jiang, W.; Wu, Q.; Wang, Y.; Liu, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 3317. (d) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem. Int., Ed.* **2003**, *42*, 3690. (e) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195.
3. Weiss, R.; Reichel, S.; Handke, M.; Hampel, F. *Angew. Chem. Int., Ed.* **1998**, *37*, 344.
4. Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704.
5. Suitable crystals were obtained by recrystallization from methylenchloride/hexane (**5a**, **7** and **9**), ethanol/MTBE (**5b**) and MTBE/hexane (**8**). Data were recorded using an Enraf–Nonius KappaCCD diffractometer with graphite-monochromated Mo K_α-radiation ($\lambda=0.71073$ Å) and a rotating anode (FR 591) from the same manufacturer. The crystal was mounted on the tip of a glass fibre using viscous perfluoropolyether (Lancaster) and cooled in a stream of cold nitrogen gas. The structures were solved by direct methods (SHELXS-97; G.M. Sheldrick, Program for the determination of crystal structures, University of Göttingen, Germany, 1997) and refined by full-matrix least-squares techniques against F^2 (SHELXL-97; G.M. Sheldrick, Program for least-squares refinement of crystal structures, University of Göttingen, Germany, 1997). Hydrogen atoms were inserted from geometry consideration using the HFIX option of the program. Crystallographic data for **5a**: $C_{16}H_{17}BrN_2$, $M_r=317.23$ g mol^{-1}, colorless, crystal size $0.10\times0.09\times0.08$ mm, orthorhombic, *Fddd* [No. 70], $a=9.2195(2)$, $b=15.2969(4)$, $c=42.5886(11)$ Å, $V=6006.3(3)$ Å^3, $Z=16$, $D_{calc}=1.403$ mg m^{-3}, $\mu=2.726$ mm^{-1}, $T=100$ K, 26,654 reflections collected, 1546 independent reflections, 1499 reflections with $I>2\sigma(I)$, $\theta_{max}=26.43$(, Gaussian absorption correction (T_{min} 0.79/T_{max} 0.84), 91 refined parameters, $R=0.019$, $R_w=0.086$, $S=1.415$, largest diff. peak and hole$=0.4/-0.6$ e Å^{-3}. Crystallographic data for **5b**: $C_{17}H_{19}BrN_2$, $M_r=331.25$ g mol^{-1}, colorless, crystal size $0.21\times0.19\times0.05$ mm, monoclinic, $P2_1/n$ [No. 14], $a=9.49180(10)$, $b=12.3577(2)$, $c=13.2973(2)$ Å, $\beta=94.8220(10)°$, $V=1554.21(4)$ Å^3, $Z=4$, $D_{calc}=1.416$ mg m^{-3}, $\mu=2.637$ mm^{-1}, $T=100$ K, 43,271 reflections collected, 5929 independent reflections, 5048 reflections with $I>2\sigma(I)$, $\theta_{max}=33.2°$, Gaussian absorption correction (T_{min} 0.61/T_{max} 0.88), 185 refined parameters, $R=0.031$, $R_w=0.095$, $S=0.967$, largest diff. peak and hole$=0.5/-0.5$ e Å^{-3}. Crystallographic data for **7**: $C_{32}H_{32}I_2N_4Pd$, $M_r=832.82$ g mol^{-1}, yellow, crystal size $0.30\times0.09\times0.05$ mm, orthorhombic, *Pbca* [No. 61], $a=15.40640(10)$, $b=14.49290(10)$, $c=27.6507(2)$ Å, $V=6173.94(7)$ Å^3, $Z=8$, $D_{calc}=1.792$ mg m^{-3}, $\mu=2.629$ mm^{-1}, $T=100$ K, 72,369 reflections collected, 7659 independent reflections, 6531 reflections with $I>2\sigma(I)$, $\theta_{max}=28.30°$, Gaussian absorption correction (T_{min} 0.51/T_{max} 0.88), 358 refined parameters, $R=0.024$, $R_w=0.056$, $S=1.003$, largest diff. peak and hole$=0.7/-0.6$ e Å^{-3}. Crystallographic data for **8**: $C_{30}H_{32}BrIrN_2$, $M_r=692.69$ g mol^{-1}, orange, crystal size $0.16\times0.14\times0.14$ mm, orthorhombic, *Pbca* [No. 61], $a=12.78330(10)$, $b=17.9798(2)$, $c=21.8389(2)$ Å, $V=5019.48(8)$ Å^3, $Z=8$, $D_{calc}=1.833$ mg m^{-3}, $\mu=6.934$ mm^{-1}, $T=100$ K, 50,356 reflections collected, 5765 independent reflections, 4604 reflections with $I>2\sigma(I)$, $\theta_{max}=27.50°$, Gaussian absorption correction (T_{min} 0.46/T_{max} 0.53), 307 refined parameters, $R=0.032$, $R_w=0.149$, $S=1.139$, largest diff. peak and hole$=1.4/-1.7$ e Å^{-3}. Crystallographic data for **9**: $C_{27}H_{27}BrN_2Pd$, $M_r=565.82$ g mol^{-1}, yellow, crystal size $0.13\times0.09\times0.06$ mm, monoclinic, $P2_1/n$ [No. 14], $a=7.76490(10)$, $b=19.3896(2)$, $c=15.7751(2)$ Å, $\beta=93.0000(10)°$, $V=2371.82(5)$ Å^3, $Z=4$, $D_{calc}=1.585$ mg m^{-3}, $\mu=2.484$ mm^{-1}, $T=100$ K, 54,264 reflections collected, 5442 independent reflections, 5119 reflections with $I>2\sigma(I)$, $\theta_{max}=27.50°$, Gaussian absorption correction (T_{min} 0.88/T_{max} 0.95), 280 refined parameters, $R=0.052$, $R_w=0.175$, $S=1.147$, largest diff. peak and hole$=2.2/-3.5$ e Å^{-3}. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 256664 (**7**), CCDC 256665 (**5b**), CCDC 256666 (**8**), CCDC 256667 (**5a**), CCDC 256668 (**9**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 144-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
6. Worth mentioning is the strict crystallographic two-fold symmetry of **5a**, while the molecule itself possesses only C_s symmetry resulting in the mutual disorder of the bridging carbon and nitrogen atom. This disorder was taken into account in the structure refinement, by equivalencing the shared C/N position and displacement parameter with a 1:1 site occupation.
7. *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., de Meijere, A., Eds.; Wiley: New York, 2004.
8. (a) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem. Int., Ed. Engl.* **1995**, *34*, 2371.

(b) Enders, D.; Gielen, H. *J. Organomet. Chem.* **2001**, *70*, 617–618. The triflate salt of **5a** was employed for this reaction.
9. Because of their sensitivity and lability, the iridium complex **8** and the palladium complex **9** were not fully characterized. In the case of **8**, the formation of a small amount of the corresponding chloro complex can not be excluded.
10. (a) Glorius, F. *Angew. Chem. Int., Ed.* **2004**, *43*, 3364. (b) Slone, C. S.; Weinberger, D. A.; Mirkin, C. A. *Prog. Inorg. Chem.* **1999**, *48*, 233.
11. (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (e) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11.
12. For a review on Pd-catalyzed cross-coupling reactions of aryl chlorides, see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem. Int., Ed.* **2002**, *41*, 4176. See also: (b) Miura, M. *Angew. Chem. Int., Ed.* **2004**, *43*, 2201.
13. The importance of monoligated Pd(0) complexes as catalytically active species in Suzuki–Miyaura cross-coupling has been proposed. See, for example: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (b) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem. Int., Ed.* **2002**, *41*, 4746. (c) Hu, Q.-S.; Lu, Y.; Tang, Z.-Y.; Yu, H.-B. *J. Am. Chem. Soc.* **2003**, *125*, 2856.
14. The 2,6-dimethoxyphenyl group was also used in an exceptionally practical and general catalyst system for the Suzuki–Miyaura cross-coupling: Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int., Ed.* **2004**, *43*, 1871.

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Synthesis of cyclic sulfamoyl carbamates and ureas via ring-closing metathesis

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Abstract—Synthetic routes to a diverse set of cyclic sulfamoyl carbamates and ureas are reported. These routes utilize 3-component coupling, Mitsunobu alkylation, and ring-closing metathesis using the second-generation Grubbs catalyst to achieve the synthesis of the target *S*-heterocyclic compounds. Cyclic *S*-heterocycles ranging from 9- to 11-membered rings have been obtained.

1. Introduction

The recent growth of high-throughput screening for biologically active agents has increased the demand for diverse libraries of synthetic compounds.[1] A growing area in combinatorial chemistry[2] is the generation of novel structural scaffolds that are inherently advantageous from both a chemical and a biological standpoint.[3] The ability of the sulfonamide moiety, and related analogs, to serve as non-hydrolyzable amide surrogates has opened the door for their use as key functional groups in the development of new scaffolds. A number of compounds based on this premise have been developed including, biologically active sulfonamides,[4] sulfamides,[5] sulfamoyl carbamates,[6] sulfahydantoins,[7] and sulfamoyl ureas.[8] Recently, novel libraries based on sulfonamide,[9] sulfamoyl urea,[10] sulfahydantoin,[11] and sulfamide[12] scaffolds have been reported. Our interest in the development of new routes to both phosphorus and sulfur-containing heterocycles (*P*- and *S*-heterocycles)[13] leads us to herein report a ring-closing metathesis (RCM) route[13,14] to a diverse set of cyclic sulfamoyl carbamates (**4**) and sulfamoyl ureas (**5**). These compounds represent novel scaffolds possessing multiple points of diversity from which to produce combinatorial libraries.

Sulfamoyl carbamates of structure **2** (Fig. 1) have been primarily used as important synthetic intermediates in the generation of unsymmetric sulfamides[13a,15] and sulfahydantoins.[16] Their popularity originates from their ease

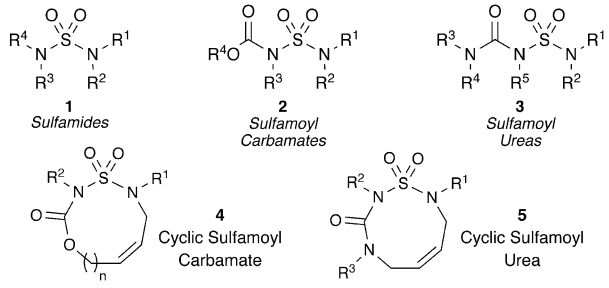

Figure 1.

of synthesis utilizing the 3-component coupling with chlorosulfonyl isocyanate (CSI), and facile derivatization by standard alkylation and Mitsunobu alkylation.[17] The result has been the production of linear sulfamoyl carbamates,[18,19] sulfahydantoins,[16] and linear[16,20] and cyclic sulfamides.[13a,15] Sulfamoyl carbamates have been studied as acyl-CoA:cholesterol *O*-acyl-transferase (ACAT) inhibitors[21] in conjunction with sulfamoyl ureas, vide infra. While examples of acyclic sulfamoyl carbamates are prevalent in the literature, reports of cyclic sulfamoyl carbamates are limited, with only two cases reported to date (compounds **6** and **7**, Fig. 2).[22] Furthermore, no examples of

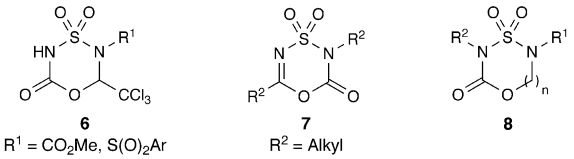

Figure 2.

Keywords: Cyclic sulfamoyl carbamate; Cyclic sulfamoyl urea; Sulfur heterocycles; RCM; Metathesis.
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cyclic sulfamoyl carbamates of general structure **8** have been reported.

Sulfamoyl ureas have been shown to be active as hypoglycemic agents,[23] ACAT inhibitors,[21] and herbicides.[24] Large libraries of linear sulfamoyl ureas have been synthesized from the 3-component coupling of two amine nucleophiles and CSI. The chemical features of the sulfamoyl urea group are different from that of a sulfamoyl carbamate. The higher pK_a of the urea N–H, compared to the carbamate N–H, has hindered efforts to alkylate the urea N–H using the Mitsunobu reaction. Thus, derivatization of these compounds has previously fallen solely to base alkylation. Cyclic sulfamoyl ureas have been largely unexplored. To date, a single report has appeared detailing the synthesis of cyclic sulfamoyl ureas **9** and **10** (Fig. 3).[25]

The emergence of ring-closing olefin metathesis (RCM)[26,27] over the last decade has fundamentally changed the method of generating both carbocyclic and heterocyclic targets.[27] Specifically, RCM has become a routine transformation for the facile construction of small-, medium-, and large ring-containing systems.[27,28] When coupled with the versatile nature of both titled compounds, several factors provided impetus for this investigation, including: (i) the ease of synthesis and analog generation in both sulfamoyl carbamate and urea classes, (ii) the convenience of using RCM to generate cyclic structures, (iii) the ability of both sulfamoyl carbamate and urea moieties to serve as surrogates for sulfamide or urea groups present in known biologically active systems, and (iv) the correlation to the known biological activities of linear sulfamoyl carbamates and ureas.

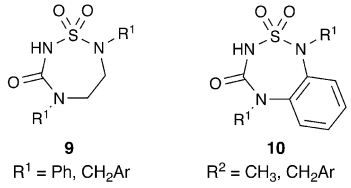


Figure 3.

2. Results and discussion

Previously, we have utilized sulfamoyl carbamate building blocks as synthetically valuable starting materials to generate a variety of unsymmetic cyclic sulfamides related to the potent HIV protease inhibitors DMP-323 and DMP-450.[15] Our new route utilizes this functional group as the central 'linchpin' in an RCM methodology. The strength of this approach lies in the wide variety of 9–11-membered cyclic sulfamoyl carbamates (**4**) (Fig. 4) and sulfamoyl ureas (**5**) (Fig. 5) that can be accessed from the corresponding dienes of general structure **11** and **12**, respectively. The focal points of this method include the ability to: (i) use 3-component coupling of CSI, allylic alcohols and allylic amines to synthesize sulfamoyl carbamates and sulfamoyl ureas with asymmetry in peripheral areas of the molecules; (ii) functionalize the sulfamoyl carbamate nitrogen via a Mitsunobu reaction; (iii) utilize base-promoted alkylation or the Mitsunobu reaction to functionalize the sulfamoyl urea

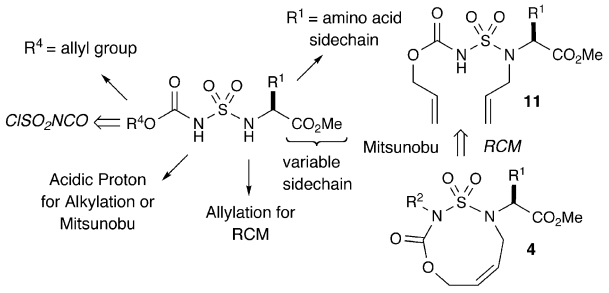


Figure 4.

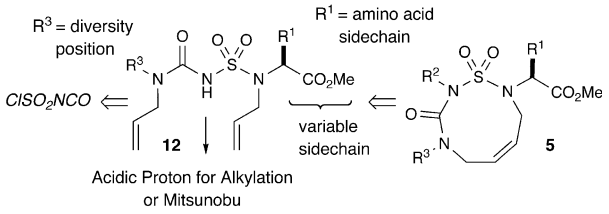
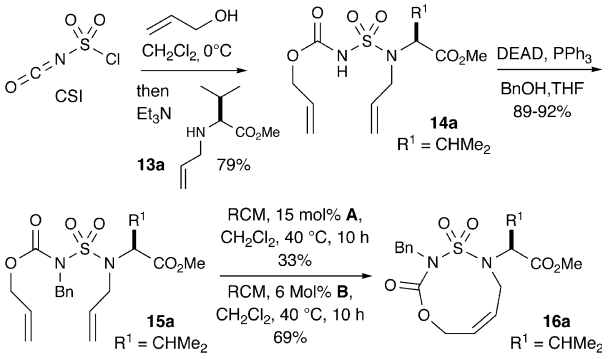


Figure 5.

nitrogen; and (iv) generate novel cyclic sulfamoyl carbamates and sulfamoyl ureas utilizing RCM.

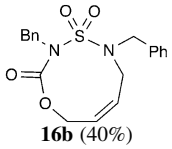
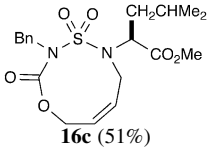
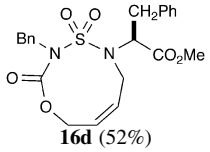
Our initial efforts began with the 3-component coupling of allyl alcohol, CSI, and *N*-allyl (L)-valine methyl ester (**13a**) to produce the corresponding sulfamoyl carbamate **14a** (Scheme 1). Optimization of the reaction conditions led to the use of 1.2 equiv of Et_3N to efficiently facilitate the formation of sulfamoyl carbamate **14a** in 79% yield. Sulfahydantoin formation via intramolecular cyclization between the carbamate nitrogen and the ester group was thwarted under these conditions. Next, it was synthetically desirable to functionalize the carbamate nitrogen in **14a**. Though alkylation of sulfamoyl carbamates with K_2CO_3 was a viable option, the Mitsunobu reaction was employed because of its versatility and to reduce possible hydantoin formation. Subjection of **14a** to Mitsunobu conditions gave sulfamoyl carbamate **15a** in excellent yield (89–92%).



Scheme 1.

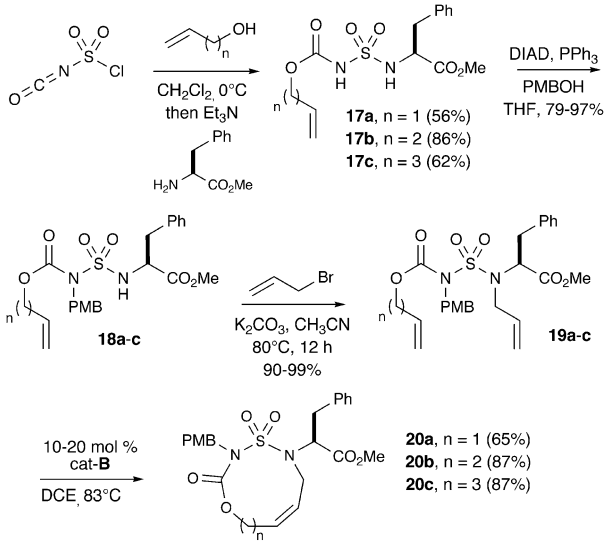
The initial attempts to cyclize diene **15a** using $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (cat-**A**)[29] resulted in formation of 9-membered cyclic sulfamoyl carbamate **16a** in only 33% yield, with a major byproduct tentatively assigned as the dimer arising from cross-metathesis (X-MET).[30] RCM using the more active $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ catalyst (cat-**B**)[31] resulted in the formation of desired 9-membered

Table 1

Entry	3-Component coupling yield	Mitsunobu yield	Product RCM yield
1	**14b** (90%)	**15b** (92%)	 **16b** (40%)
2	**14c** (85%)	**15c** (87%)	 **16c** (51%)
3	**14d** (86%)	**15d** (81%)	 **16d** (52%)

cyclic sulfamoyl carbamate **16a** in 69% overall yield, with no observable dimer formation via X-MET. This newly formed sulfamoyl carbamate represents the first example of RCM on this class of compounds and highlights the potential for library production utilizing more elaborate alcohols at the stage of both initial coupling and Mitsunobu alkylation steps.

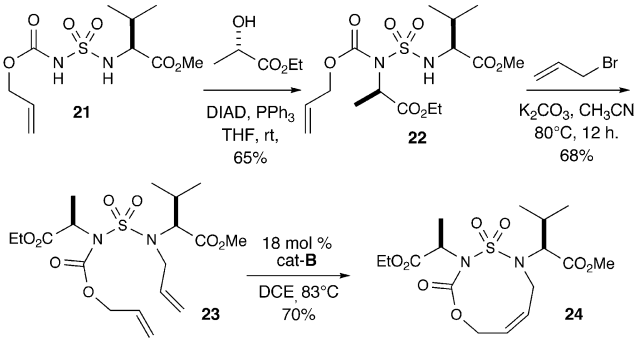
With a general route to cyclic sulfamoyl carbamates in hand, analogous cyclic sulfamoyl carbamates were synthesized using benzylamine and other (L)-amino esters as represented in Table 1. Coupling with CSI and allyl alcohol afforded sulfamoyl carbamates **14b–d** in good yields (85–90%). Benzylation via the Mitsunobu reaction afforded metathesis precursors **15b–d** in 81–92% yields. RCM with 6 mol% of cat-**B** gave cyclic sulfamoyl carbamates **16b–d** in modest yields of 40–52%. The Georg RCM purification procedure,[32] employing DMSO, was utilized to purify compounds throughout this study. Surprisingly, although these yields were marginal, no X-MET dimer was observed, prompting us to further optimize the RCM reaction.



Scheme 2.

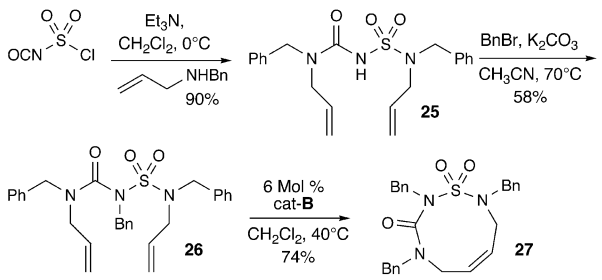
In the second route shown in Scheme 2, 3-component coupling was carried out with various olefinic alcohols, CSI, and (L)-phenylalanine methyl ester to produce corresponding sulfamoyl carbamates **17a–c** in good yields (56–86%). The Mitsunobu reaction was employed to regioselectively install the PMB moiety at the carbamate position (N–R^2 position) in sulfamoyl carbamates **18a–c** (79–97%). Allylation under standard conditions produced RCM precursors **19a–c** (90–99%). Subjection to RCM conditions using cat-**B** in refluxing DCE gave corresponding 9-, 10-, and 11-membered cyclic sulfamoyl carbamates **20a–c** in good yields (65–87%).

The initial examples outlined in Schemes 1 and 2 utilized simple Mitsunobu benzylation to install diversity at the sulfamoyl carbamate N–R^2 position. Installation of side chains bearing stereogenic centers, as previously shown in the synthesis of unsymmetric sulfamides,[15] were next pursued as outlined in Scheme 3. Thus, alkylation of **21** with naturally occurring (*S*)-ethyl lactate under Mitsunobu conditions, generated **22** in 65% yield. Simple allylation, followed by RCM in DCE afforded cyclic sulfamoyl carbamate **24** in good yield (70%) containing both valine and alanine side chains at the periphery.



Scheme 3.

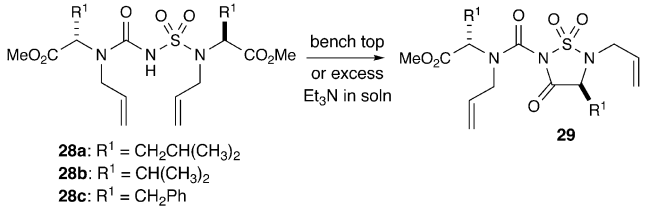
Subsequent efforts were focused toward the exploration of a similar three-step protocol to generate 9-membered cyclic sulfamoyl ureas (Scheme 4). Benzylamine was chosen as the initial test substrate, due to potential problems with sulfahydantoin formation from the use of amino esters, vide infra. Coupling of 2 equiv of benzylamine with CSI gave **25** in 90% yield (Scheme 4). As with the sulfamoyl carbamates, functionalization of the urea nitrogen with a benzyl group was desirable. Unfortunately, sulfamoyl ureas were unable to undergo Mitsunobu benzylations under standard DEAD



Scheme 4.

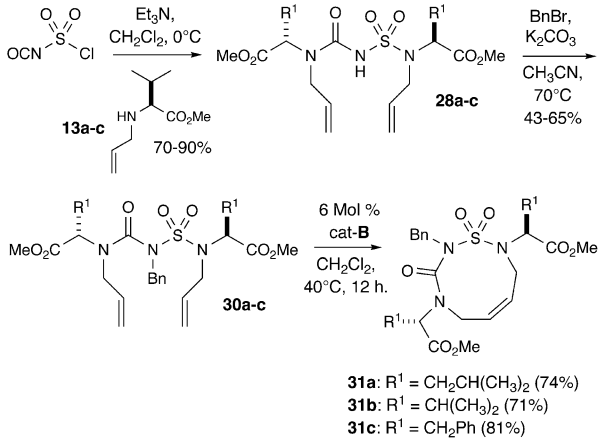
or DIAD conditions. Initial attempts at benzylation using DBU and NaH were found to be surprisingly ineffective despite literature precedent,[21] yielding no noticeable benzylated product. Utilizing our previous method to alkylate sulfamides (K_2CO_3, BnBr) resulted in the formation of benzylated sulfamoyl carbamate **26**, albeit in a modest 58% yield. RCM of **26** proved to be efficient as 6 mol% cat-**B** afforded 9-membered cyclic sulfamoyl urea **27** in 74% yield. Importantly, no product from X-MET was observed. This result represents the first known example of RCM on a sulfamoyl urea template, and opens opportunities to diversification strategies.

With a method for the generation of cyclic sulfamoyl ureas in hand, the synthesis of sulfamoyl ureas utilizing allylated aminoesters was explored. Sulfahydantoin formation, arising from attack of the sulfamoyl urea nitrogen into the sulfamide amino ester forming hydantoin **29**, was of major concern (Scheme 5). Thus, our initial use of excess base in the 3-component coupling reaction generated sulfahydantoins as a significant byproduct. In addition, the sulfamoyl ureas were found to form the sulfahydantoin at rt, over time, and in small amounts during column chromatography.



Scheme 5.

Despite these concerns, our initial 3-component coupling reaction with allylated amino ester **13a–c** and CSI produced sulfamoyl ureas **28a–c** in good overall yields (Scheme 6). Furthermore, optimal results were obtained with 1.2 equiv of Et_3N and 2.2 equiv of the amino ester. Use of lesser equivalents of the amino ester gave a complex mixture of product, sulfahydantoin and sulfamoyl chloride. For stability reasons, benzylation was therefore utilized as a means of both protection and functionalization. The standard K_2CO_3 promoted benzylation of **28a–c** resulted in moderate yields of benzyl-protected RCM precursors **30a–c**

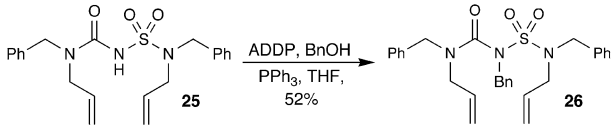


Scheme 6.

(43–65%). Surprisingly, these conditions produced only minor amounts of the sulfahydantoin despite elevated temperatures, with no single entry yielding more than 5% of hydantoin byproduct.

Metathesis of the amino ester-derived sulfamoyl ureas met with consistent results as treatment of **30a–c** with 6 mol% of cat-**B** afforded the desired cyclic sulfamoyl ureas **31a–c** in good yields (71–81%). Importantly, no byproducts via X-MET were observed during the RCM.

An alternate route of benzylation was sought in order to circumvent problems associated with generating benzylated sulfamoyl ureas. We felt that if a Mitsunobu reaction could be initiated at the sulfamoyl urea nitrogen, the potential for derivatization would greatly improve. The difficulty is encountered in the inability of the DEAD/PPh_3 complex to deprotonate the sulfamoyl ureas containing a less acidic N–H moiety. Mitsunobu reactions with higher pK_a nucleophiles have been realized with the advent of 1,1′-(azodicarbonyl)dipiperidine-tributylphosphine (ADDP)[33] as a more powerful DEAD equivalent. To test the efficacy of this method, benzylamine-derived sulfamoyl urea **25** was subjected to modified conditions with ADDP, to afford benzylated sulfamoyl urea **26** in 52% yield (Scheme 7). To our knowledge, this is the first example of a Mitsunobu reaction using a sulfamoyl urea as the nucleophile. Though the yield was less than that obtained via standard alkylation conditions, these results are encouraging. In addition to nitrogen protection, utilization of more elaborate non-racemic secondary alcohols will provide an excellent pathway for diversification of these sulfamoyl ureas.



Scheme 7.

3. Conclusion

In conclusion, we have described the first synthesis of both cyclic sulfamoyl carbamates and ureas utilizing RCM. This method represents an extension of our recent sulfamide research and a new direction in the synthesis of novel *S*-heterocycles. Further research on sulfamoyl carbamates will focus on functionalization of the sulfamoyl carbamate nitrogen utilizing secondary allylic alcohols and amines in the 3-component coupling reaction to generate a variety of novel sulfamoyl carbamates and sulfamoyl ureas. In addition, the Mitsunbou reaction will be optimized and exploited as an important means to functionalize the sulfamoyl ureas. Biological screening and further refinement of these compounds is underway and will be reported in due course.

4. Experimental

4.1. General

All reactions were carried out in flame-dried glassware

under argon. Toluene, THF, Et_2O, and CH_2Cl_2 were purified by passage through a purification system (Solv-Tek) employing activated Al_2O_3.[34] Et_3N was distilled from CaH_2. Flash column chromatography was performed with Merck silica gel (EM-9385-9, 230–400 mesh). Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5715-7, Merck). All amino acid precursors were purchased from Advanced Chem Tech. ^1H and ^{13}C spectra were recorded in $CDCl_3$ on either a Bruker DRX-400 or a Bruker AM-500 spectrometer operating at 400/100 MHz and 500/125 MHz, respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained on a VG Instrument ZAB double-focusing mass spectrometer. Infrared data was obtained on a Nicolet 320 Fourier Transform Infrared Spectrophotometers. Melting points were obtained on a Thomas Hoover capillary melting point apparatus. Optical rotations were carried out on a Rudolph Automatic Polarimeter (AUTOPOL IV).

4.1.1. *N*-[[[(2-Propenyloxy)carbonyl]amino]sulfonyl]-*N*-(2-propenyl)-(*S*)-valine methyl ester (14a). To a stirring solution of chlorosulfonyl isocyanate (CSI) (0.61 mL, 7.01 mmol) and CH_2Cl_2 (25 mL) at 0 °C was added allyl alcohol (0.40 mL, 7.01 mmol) in CH_2Cl_2 (3 mL) and stirred 10 min. The mixture was then transferred, via cannula, to a stirring solution of allylvaline methyl ester (1.23 g, 7.71 mmol) and Et_3N (1.17 mL, 8.41 mmol) in CH_2Cl_2 (35 mL) at 0 °C. The resulting mixture was stirred for 12 h. The solvent was removed and EtOAc (80 mL) was added. The solution was washed with 10% $NaHSO_4$ (60 mL), $NaHCO_3$ (2×50 mL), brine (60 mL), dried with $MgSO_4$, filtered, and the solvent removed. Flash chromatography (SiO_2, hexanes/EtOAc) afforded 1.86 g (79%) of **14a** as a yellow solid. TLC R_f=0.28 (3:1 hexanes/EtOAc). Mp 72 °C; $[\alpha]_D^{25}$ −67.7 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50 (s, 1H), 5.97 (dddd, *J*=17.5, 10.1, 7.7, 5.4 Hz, 1H), 5.89 (dddd, *J*=16.2, 11.6, 5.8, 5.8 Hz, 1H), 5.33 (dd, *J*=17.1, 1.4 Hz, 1H), 5.25 (dd, *J*=10.5, 1.2 Hz, 1H), 5.22 (dd, *J*=17.2, 1.4 Hz, 1H), 5.13 (dd, *J*=10.1, 1.1 Hz, 1H), 4.62–4.59 (m, 2H), 4.24 (ddd, *J*=16.4, 5.4, 1.4 Hz, 1H), 4.12–4.06 (m, 1H), 4.12–4.06 (m, 1H), 3.69 (s, 3H), 2.21–2.15 (m, 1H), 1.02 (d, *J*=6.6 Hz, 3H), 0.94 (d, *J*=6.6 Hz, 3H); ^{13}C ($CDCl_3$, 100 MHz) δ 170.9, 150.6, 134.8, 131.3, 119.2, 117.8, 67.1, 66.8, 51.7, 49.6, 28.7, 19.6, 19.4; FTIR (neat) 3260, 2967, 1747, 1456, 1370, 1142 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{13}H_{23}N_2O_6S$ 335.1277, found 335.1283.

4.1.2. *N*-[[[(2-Propenyloxy)carbonyl]amino]sulfonyl]-*N*-(2-propenyl)-benzylamine (14b). In a procedure similar to the preparation of sulfamoyl carbamate **14a**, allyl alcohol (0.48 mL, 7.08 mmol) and allylbenzylamine (1.25 g, 8.48 mmol) were subjected to 3-component coupling conditions. Flash chromatography (SiO_2, hexanes/EtOAc) yielded 1.98 g (90%) of **14b** as a clear liquid. TLC R_f=0.27 (3:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65 (bs, 1H), 7.35–7.8 (m, 5H), 5.90 (dddd, *J*=16.4, 1.5, 5.8, 5.8 Hz, 1H), 5.78 (dddd, *J*=16.8, 12.9, 6.5, 6.5 Hz, 1H), 5.36 (dd, *J*=17.2, 1.2 Hz, 1H), 5.28 (dd, *J*=10.4, 1.0 Hz, 1H), 5.19 (d, *J*=8.9 Hz, 1H), 5.16 (dd, *J*=16.7, 1.1 Hz, 1H), 4.64 (d, *J*=5.8 Hz, 2H), 4.55 (s, 2H), 3.91 (d, *J*=6.4 Hz, 2H); ^{13}C ($CDCl_3$, 100 MHz) δ 150.9, 135.7, 132.1, 131.2, 128.6, 128.4, 127.9, 119.4, 119.3, 67.1, 51.9, 50.6; FTIR (neat) 3620, 3600, 3260, 3087, 3031, 2928, 1747, 1647, 1606, 1455, 1352, 1150, 778, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{14}H_{19}N_2O_4S$ 311.1066, found 311.1050.

4.1.3. *N*-[[[(2-Propenyloxy)carbonyl]amino]sulfonyl]-*N*-(2-propenyl)-(*S*)-leucine methyl ester (14c). In a procedure similar to the preparation of sulfamoyl carbamate **14a**, coupling and flash chromatography (SiO_2, hexanes/EtOAc) yielded 727 mg (85%) of the sulfamoyl carbamate **14c** as a clear yellow oil. TLC R_f=0.28 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −88 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (bs, 1H), 6.00–5.87 (m, 1H), 6.00–5.87 (m, 1H), 5.35 (dd, *J*=17.2, 1.4 Hz, 1H), 5.26 (dd, *J*=10.5, 1.2 Hz, 1H), 5.20 (dd, *J*=17.2, 1.2 Hz, 1H), 5.13 (dd, *J*=10.1, 1.1 Hz, 1H), 4.63–4.60 (m, 2H), 4.63–4.60 (m, 1H), 4.20 (dd, *J*=16.7, 5.4 Hz, 1H), 3.92 (dd, *J*=16.5, 7.3 Hz, 1H), 3.71 (s, 3H), 1.78–1.63 (m, 2H), 1.78–1.63 (m, 1H), 0.96 (d, *J*=6.2 Hz, 3H), 0.91 (d, *J*=6.2 Hz, 3H); ^{13}C ($CDCl_3$, 100 MHz) δ 172.1, 150.9, 134.9, 131.4, 119.1, 117.6, 67.5, 59.5, 52.2, 49.6, 38.9, 24.3, 22.5, 21.3; FTIR (neat) 3620, 3600, 3033, 2954, 1747, 1647, 1606, 1455, 1379, 1147 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{14}H_{25}N_2O_6S$ 349.1433, found 349.1421.

4.1.4. *N*-[[[(2-Propenyloxy)carbonyl]amino]sulfonyl]-*N*-(2-propenyl)-(*S*)-phenylalanine methyl ester (14d). In a procedure similar to the preparation of sulfamoyl carbamate **14a**, coupling and flash chromatography (SiO_2, hexanes/EtOAc) yielded 1.36 g (86%) of **14d** as a yellow oil. TLC R_f=0.21 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −29.3 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.53 (bs, 1H), 7.31–7.21 (m, 5H), 5.95–5.80 (m, 1H), 5.95–5.80 (m, 1H), 5.35 (dd, *J*=17.2 Hz, 1.4 Hz, 1H), 5.26 (dd, *J*=10.4, 1.1 Hz, 1H), 5.24 (dd, *J*=18.1, 1.2 Hz, 1H), 5.16 (dd, *J*=10.2, 1.1 Hz, 1H), 4.79 (dd, *J*=7.5, 7.5 Hz, 1H), 4.62 (dd, *J*=5.7, 1.1 Hz, 1H), 4.15 (ddd, *J*=16.4, 6.0, 1.0 Hz, 1H), 4.01 (ddd, *J*=16.3, 6.4 Hz, 1H), 3.67 (s, 3H), 3.32 (dd, *J*=14.0, 7.8 Hz, 1H), 3.32 (dd, *J*=14.0, 7.8 Hz, 1H), 3.11 (dd, *J*=14.1, 7.5 Hz, 1H); ^{13}C ($CDCl_3$,100 MHz) 170.9, 150.6, 136.5, 134.2, 131.3, 129.2, 128.5, 127.0, 119.2, 118.4, 67.1, 62.2, 52.3, 50.2, 36.8; FTIR (neat) 3620, 3600, 3262, 3029, 2953, 1747, 1648, 1605, 1496, 1455, 1367, 1159, 750, 700 cm^{-1}; (HRMS $(M+H)^+$ calcd for $C_{17}H_{23}N_2O_6S$ 383.1277, found 383.1275.

4.1.5. *N*-[[[(2-Propenyloxy)carbonyl]-*N'*-(benzyl)amino]-sulfonyl]-*N*-(2-propenyl)-(*S*)-valine methyl ester (15a). To a stirring solution of sulfamoyl carbamate **14a** (1.00 g, 3.4 mmol) and DEAD (0.562 mL, 3.57 mmol) in THF (1 mL) under argon, was added a mixture of BnOH (0.370 mL, 3.57 mmol) and PPh_3 (936 mg, 3.57 mmol) in THF (1 mL) via dropwise addition from a syringe. The solution was stirred for 6 h, the solvent removed, and purified by flash chromatography to yield 1.20 g (92%) of **15a** as a clear oil. TLC R_f=0.45 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −65.9 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, *J*=7.9 Hz, 2H), 732–7.23 (m, 3H), 5.97 (dddd, *J*=18.0, 13.0, 7.8, 5.2 Hz, 1H), 5.88 (dddd, *J*=16.3, 10.5, 5.8, 5.8 Hz, 1H), 5.30, (dd, *J*=17.2, 1.4 Hz, 1H), 5.24 (dd, *J*=10.5, 1.1 Hz, 1H), 5.20 (dd, *J*=18.3, 1.1 Hz, 1H), 5.11 (dd, *J*=10.1, 1.0 Hz, 1H), 4.90 (s, 2H), 4.63 (dd, *J*=5.8, 1.2 Hz, 2H), 4.25 (ddd, *J*=16.4, 5.1, 1.4 Hz, 1H), 4.10 (dd, *J*=16.4,

7.9 Hz, 1H), 3.89 (d, $J=10.4$ Hz, 1H), 3.66 (s, 3H), 2.19–2.09 (m, 1H), 1.02 (d, $J=6.6$ Hz, 3H), 0.88 (d, $J=6.6$ Hz, 3H); ^{13}C ($CDCl_3$, 100 MHz) δ 170.7, 152.5, 137.1, 135.3, 131.3, 128.3, 128.1, 127.6, 119.2, 117.2, 67.6, 66.3, 52.3, 51.4, 49.7, 28.7, 19.6, 19.2; FTIR (neat) 3033, 2967, 1739, 1649, 1607, 1497, 1435, 1370, 1142, 701, 768 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{20}H_{29}N_2O_6S$ 425.1746, found 425.1729.

4.1.6. *N*-[[[(2-Propenyloxy)carbonyl]-*N'*-(benzyl)amino]-sulfonyl]-*N*-(2-propenyl)-benzylamine (15b). In a procedure similar to the preparation of sulfamoyl carbamate **15a**, Mitsunobu reaction and flash chromatography (SiO_2, hexanes/EtOAc) afforded 1.19 g (92%) of **15b** as a clear liquid. TLC $R_f=0.51$ (3:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, $J=8.5$ Hz, 2H), 7.35–7.24 (m, 8H), 5.92 (dddd, $J=16.4$, 11.7, 5.9, 5.9 Hz, 1H), 5.65 (dddd, $J=16.8$, 10.5, 6.5, 6.5 Hz, 1H), 5.35 (dd, $J=17.4$, 1.2 Hz, 1H), 5.28 (d, $J=10.4$ Hz, 1H), 5.14 (d, $J=10.2$ Hz, 1H), 5.06 (dd, $J=17.2$, 1.2 Hz, 1H), 4.94 (s, 2H), 4.70 (d, $J=5.8$ Hz, 2H), 4.46 (s, 2H), 3.77 (d, $J=6.4$ Hz, 2H); ^{13}C ($CDCl_3$, 100 MHz) δ 152.8, 137.2, 136.0, 132.0, 131.4, 128.5, 128.4, 128.3, 128.2, 127.7, 127.7, 119.4, 119.0, 67.6, 52.0, 51.8, 50.3; FTIR (neat) 3086, 3033, 2983, 1732, 1650, 1606, 1496, 1455, 1372, 1158, 750, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{21}H_{25}N_2O_4S$ 401.1535, found 401.1517.

4.1.7. *N*-[[[(2-Propenyloxy)carbonyl]-*N'*-(benzyl)amino]-sulfonyl]-*N*-(2-propenyl)-(*S*)-leucine methyl ester (15c). In a procedure similar to the preparation of sulfamoyl carbamate **15a**, Mitsunobu reaction and flash chromatography (SiO_2, hexanes/EtOAc) afforded 721 mg (87%) of **15c** as a clear yellow liquid. TLC $R_f=0.49$ (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −81.5 (*c* 5.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, $J=7.1$ Hz, 2H), 7.33–7.23 (m, 3H), 5.99–5.86 (m, 1H), 5.99–5.86 (m, 1H), 5.33 (dd, $J=17.2$, 1.3 Hz, 1H), 5.26 (dd, $J=10.4$, 1.0 Hz, 1H), 5.16 (dd, $J=17.2$, 1.2 Hz, 1H), 5.10 (dd, $J=10.2$, 1.0 Hz, 1H), 4.93 (d, $J=15.7$ Hz, 1H), 4.75 (d, $J=15.6$ Hz, 1H), 4.67 (d, $J=5.7$ Hz, 2H), 4.40 (dd, $J=8.6$, 6.0 Hz, 1H), 4.17 (d, $J=16.7$, 5.3 Hz, 1H), 3.91 (dd, $J=16.7$, 7.4 Hz, 1H), 3.65 (s, 3H), 1.71–1.56 (m, 2H), 1.71–1.56 (m, 1H), 0.93 (d, $J=6.2$ Hz, 3H), 0.88 (d, $J=6.4$ Hz, 3H); ^{13}C ($CDCl_3$,100 MHz) δ 171.9, 153.1, 137.6, 136.0, 131.8, 128.7, 128.6, 128.0, 119.5, 117.4, 68.6, 59.3, 52.6, 52.2, 50.1, 39.8, 24.7, 22.7, 21.8; FTIR (neat) 3033, 2955, 1747, 1649, 1607, 1497, 1455, 1380, 1147, 770, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{21}H_{31}N_2O_6S$ 439.1903, found 439.1904.

4.1.8. *N*-[[[(2-Propenyloxy)carbonyl]-*N'*-(benzyl)amino]-sulfonyl]-*N*-(2-propenyl)-(*S*)-phenylalanine methyl ester (15d). In a procedure similar to the preparation of sulfamoyl carbamate **15a**, Mitsunobu and flash chromatography (SiO_2, hexanes/EtOAc) afforded 1.24 (81%) of **15d** as a clear oil. TLC $R_f=0.40$ (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −27.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, $J=7.1$ Hz, 2H), 7.33–7.23 (m, 6H), 7.17 (d, $J=6.9$ Hz, 2H), 5.98–5.86 (m, 1H), 5.98–5.86 (m, 1H), 5.33 (dd, $J=17.2$, 1.2 Hz, 1H), 5.27 (dd, $J=10.4$, 1.3 Hz, 1H), 5.26 (dd, $J=16.7$, 1.3 Hz, 1H), 5.17 (dd, $J=10.2$, 1.1 Hz, 1H), 4.94 (d, $J=15.6$ Hz, 1H), 4.86 (d, $J=15.7$ Hz, 1H), 4.69–4.65 (m, 2H), 4.69–4.65 (m, 1H), 4.21 (dd, $J=16.7$, 5.8 Hz, 1H), 4.06 (dd, $J=16.6$, 6.7 Hz, 1H), 3.61 (s, 3H), 3.26 (dd, $J=13.8$, 9.0 Hz, 1H), 3.04 (dd, $J=13.8$, 9.0 Hz, 1H); ^{13}C ($CDCl_3$,100 MHz) 170.4, 152.6, 137.1, 136.5, 135.1, 131.4, 129.2, 128.5, 128.4, 128.2, 127.7, 126.9, 119.2, 117.6, 67.7, 61.6, 52.2, 51.9, 50.1, 37.1; FTIR 3031, 2952, 1732, 1649, 1605, 1496, 1454, 1384, 1170, 750, 700 cm^{-1}; HRMS (neat) $(M+H)^+$ calcd for $C_{24}H_{29}N_2O_6S$ 473.1746, found 473.1744.

4.1.9. (2*S*)-2-(3-Benzyl-2,4,4-trioxo-3,4,6,9-tetrahydro-2*H*-4λ^6-[1,4,3,5]oxathiadiazonin-5-yl)-3-methyl-butyric acid methyl ester (16a). Sulfamoyl carbamate **15a** (200 mg, 0.471 mmol), and CH_2Cl_2 (50 mL) were placed in a 100 mL round-bottomed flask and degassed with argon gas for 15 min. Catalyst **B** (12 mg, 0.014 mmol) was added, the flask was quickly fitted with a condenser under argon balloon, and the solution heated to reflux for 12 h. Another equivalent of catalyst was added (12 mg, 0.014 mmol) and the solution stirred for 6 h. The solution was cooled to rt, DMSO (0.2 mL) added, and the solution stirred for 12 h. The solvent was removed under reduced pressure and the material was subjected to flash chromatography (SiO_2, hexanes/EtOAc) to yield 128 mg (69%) of **16a** as a white solid. TLC $R_f=0.23$ (3:1 hexanes/EtOAc). Mp 97–98 °C $[\alpha]_D^{25}$ −27.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, $J=7.2$ Hz, 2H), 7.34–7.25 (m, 3H), 5.73 (dddd, $J=11.4$, 3.6, 1.6, 1.6 Hz, 1H), 5.60–5.53 (m, 1H), 5.30 (d, $J=16.0$ Hz, 1H), 5.00 (d, $J=15.5$ Hz, 1H), 4.90 (d, $J=15.5$ Hz, 1H), 4.82–4.77 (m, 1H), 4.67 (d, $J=16.5$ Hz, 1H), 3.92 (d, $J=11.0$ Hz, 1H), 3.60–3.50 (m, 1H), 3.54 (s, 3H), 2.35–2.26 (m, 1H), 1.02 (d, $J=6.3$ Hz, 3H), 0.99 (d, $J=6.7$ Hz, 3H); ^{13}C ($CDCl_3$, 100 MHz) δ 170.7, 153.1, 136.8, 131.3, 128.4, 128.2, 127.7, 125.4, 64.5, 63.7, 52.2, 51.5, 43.3, 25.8, 20.9, 18.6; FTIR (neat) 3023, 2967, 1741, 1600, 1507, 1386, 1136, 767, 701 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{18}H_{25}N_2O_6S$ 397.1433, found 397.1429.

4.1.10. 2,9-Dibenzyl-1,1-dioxo-1,2,4,5,8,9-hexahydro-1λ^6-[1,4,2,9]thiaoxdiazonin-3-one (16b). In a procedure similar to that used for the preparation of **16a**, sulfamoyl carbamate **15b** (200 mg, 0.50 mmol) and cat-**B** (13 mg, 0.015 mmol) in CH_2Cl_2 (50 mL) were subjected to RCM. Flash chromatography (SiO_2, 3:1 hexane/EtOAc) afforded 74 mg (40%) of **16b** as a brown oil. TLC $R_f=0.40$ (3:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, $J=7.2$ Hz, 2H), 7.37–7.26 (m, 8H), 5.93 (dt, $J=11.5$, 3.2 Hz, 1H), 5.58–5.50 (m, 1H), 5.50 (bs, 2H), 4.92 (s, 2H), 4.14–3.86 (m, 2H), 3.96 (bs, 2H); ^{13}C ($CDCl_3$, 100 MHz) δ 153.5, 137.7, 134.6, 132.9, 128.8, 128.6, 128.5, 128.3, 128.2, 127.9, 125.8, 64.6, 51.4, 48.7, 44.3; FTIR (neat) 3220, 3030, 2980, 1729, 1508, 1370, 1167, 753, 699 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{19}H_{21}N_2O_4S$ 373.1222, found 373.1220.

4.1.11. (2*S*)-2-(3-Benzyl-2,4,4-trioxo-3,4,6,9-tetrahydro-2*H*-4λ^6-[1,4,3,5]oxathiadiazonin-5-yl)-4-methyl-pentanoic acid methyl ester (16c). In a procedure similar to that used for the preparation of **16a**, sulfamoyl carbamate **15c** (121 mg, 0.28 mmol) and cat-**B** (17 mg, 0.020 mmol) in CH_2Cl_2 (56 mL) were subjected to RCM. Flash chromatography (SiO_2, 10:1 heptane/EtOAc) afforded 58 mg (51%) of **16c** as a white solid. TLC $R_f=0.26$ (3:1 hexanes/EtOAc). Mp 78–80 °C; $[\alpha]_D^{25}$ −54.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, $J=7.0$ Hz, 2H), 7.33–7.23

(m, 3H), 5.73 (dddd, J=11.7, 3.7, 1.8, 1.8 Hz, 1H), 5.56–5.51 (m, 1H), 5.28 (dd, J=16.7, 3.7 Hz, 1H), 4.96 (d, J=15.4, Hz, 1H), 4.89 (d, J=15.4 Hz, 1H), 4.79 (dd, J=15.2, 7.1 Hz, 1H), 4.71 (d, J=16.7 Hz, 1H), 4.45 (dd, J=9.2, 5.6 Hz. 1H), 3.69–3.63 (m, 1H), 3.56 (s, 3H), 1.83 (ddd, J=14.5, 8.8, 5.7 Hz, 1H), 1.69 (ddd, J=14.2, 9.4, 4.7 Hz, 1H), 1.69–1.59 (m, 1H), 0.97 (d, J=6.5 Hz, 3H), 0.97 (J=6.5 Hz, 3H); ^{13}C ($CDCl_3$,100 MHz) δ 171.6, 153.4, 137.0, 131.9, 128.4, 128.4, 127.7, 124.9, 64.9, 56.9, 52.3, 51.4, 43.3, 37.0, 24.3, 22.9, 21.6; FTIR (neat) 3033, 2954, 1739, 1505, 1450, 1385, 1272, 1157, 772, 701 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{19}H_{27}N_2O_6S$ 411.1590, found 411.1583.

4.1.12. (2*S*)-2-(3-Benzyl-2,4,4-trioxo-3,4,6,9-tetrahydro-2*H*-4λ^6-[1,4,3,5]oxathiadiazonin-5-yl)-3-phenyl-propionic acid methyl ester (16d). In a procedure similar to that used for the preparation of **16a**, RCM and flash chromatography (SiO_2, hexanes/EtOAc) yielded 122 mg (52%) of **16d** as a brown solid. TLC R_f=0.26 (3:1 hexanes/EtOAc). Mp 83 °C; $[\alpha]_D^{25}$ −45 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, J=7.1 Hz, 2H), 7.33–7.23 (m, 8H), 5.75 (ddd, J=11.5, 1.9, 1.9 Hz, 1H), 5.66–5.59 (m, 1H), 5.22 (d, J=16.2 Hz, 1H), 4.94 (d, J=15.5 Hz, 1H), 4.89 (d, J=15.5 Hz, 1H), 4.73 (d, J=16.8 Hz, 1H), 4.67 (d, J=7.5 Hz, 1H), 4.65 (d, J=7.5 Hz, 1H), 3.89–3.81 (m, 1H), 3.58 (s, 3H), 3.43 (dd, J=14.4, 7.5 Hz, 1H), 3.02 (dd, J=14.4, 7.5 Hz, 1H); ^{13}C ($CDCl_3$,100 MHz) 170.6, 153.2, 136.9, 136.9, 131.9, 129.1, 128.6, 128.4, 128.4, 127.7, 127.0, 125.0, 65.0, 59.9, 52.4, 51.4, 44.1, 35.2; FTIR (neat) 3030, 2950, 1740, 1498, 1386, 1168, 753, 699 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{22}H_{25}N_2O_6S$ 445.1433, found 445.1433.

4.1.13. *N*-[[[(2-Propenyloxy)carbonyl]amino]sulfonyl]-(*S*)-phenylalanine methyl ester (17a). To a stirring solution of CSI (1.97 g, 13.9 mmol) in CH_2Cl_2, (10 mL) at 0 °C was added allyl alcohol (0.95 mL, 13.9 mmol) via syringe and the reaction was stirred for 1 h. This solution was transferred via cannula to a stirring solution of phenylalanine ester hydrochloride (3.0 g, 13.9 mmol) and Et_3N (3.87 mL, 27.8 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The resulting mixture was stirred under Ar for 12 h. The product of the reaction was dissolved in 100 mL of H_2O and extracted with CH_2Cl_2 (4×50 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash chromatography (SiO_2, 3:1 heptane/EtOAc) to afford 2.65 g (56%) of carbamate **17a** as white solid. TLC R_f=0.38 (1:1 heptane/EtOAc). Mp 101–102.5 °C $[\alpha]_D^{25}$ +32.9 (c 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33–7.27 (m, 3H and N–H), 7.16 (d, J=7.0 Hz, 2H), 5.88 (dddd, J=16.6, 11.3, 5.8, 5.6 Hz, 1H), 5.58 (d, J=8.5 Hz, 1H), 5.34 (d, J=17.1 Hz, 1H), 5.27 (d, J=10.4 Hz, 1H), 4.61, (d, J=5.8 Hz, 2H), 4.55–4.51 (m, 1H), 3.72, (s, 3H), 3.13 (d, J=5.9 Hz, 2H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 150.6, 134.7, 130.9, 129.4, 128.7, 127.5, 119.5, 67.4, 57.7, 52.7, 39.0; FTIR (neat) 3271, 1740, 1732, 1647 cm$^{-1;}$ HRMS $(M+H)^+$ calcd for $C_{14}H_{19}N_2O_6S$ 343.0964, found 343.0957.

4.1.14. *N*-[[[(2-Butenyloxy)carbonyl]amino]sulfonyl]-(*S*)-phenylalanine methyl ester (17b). In a procedure similar to the preparation of sulfamoyl carbamate **17a**, CSI (1.21 mL, 13.9 mmol), 3-buten-1-ol (1.2 mL, 13.9 mmol), and (L)-phenylalanine methyl ester hydrochloride (3.0 g, 13.9 mmol) and Et_3N (3.87 mL, 27.8 mmol) were subjected to 3-component coupling conditions. Flash chromatography (SiO_2, 2:1 heptane/EtOAc) afforded 3.60 g (73%) of the desired carbamate **17b** as a white solid. TLC R_f=0.38 (1:1 heptane/EtOAc). Mp 95–97 °C $[\alpha]_D^{25}$ +38.3 (c 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32–7.25 (m, 3H and N–H), 7.15 (d, J=6.8 Hz, 2H), 5.75 (dddd, J=17.0, 10.2, 6.7, 6.7 Hz, 1H), 5.11 (d, J=17.1 Hz, 1H), 5.07 (d, J=10.3 Hz, 1H), 4.51 (t, J=5.8 Hz, 1H), 4.18 (t, J=6.6 Hz, 2H), 3.72 (s, 3H), 3.13 (d, J=5.8 Hz, 2H), 2.39 (dd, J=13.1, 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 150.8, 134.7, 133.3, 129.4, 128.8, 127.5, 117.8, 65.9, 57.6, 52.7, 38.8, 32.8; FTIR (neat) 3273, 2955, 1744, 1642 cm^{-1} HRMS $(M+H)^+$ calcd for $C_{15}H_{21}N_2O_6S$ 357.1120, found 357.1099.

4.1.15. *N*-[[[(2-Pentenyloxy)carbonyl]amino]sulfonyl]-(*S*)-phenylalanine methyl ester (17c). In a procedure similar to the preparation of sulfamoyl carbamate **17a**, CSI (1.21 mL, 13.9 mmol), 4-penten-1-ol (1.44 mL, 13.9 mmol), (L)-phenyl alanine methyl ester hydrochloride (3.0 g, 13.9 mmol) and Et_3N (3.87 mL, 27.8 mmol) were subjected to 3-component coupling conditions. Flash chromatography (SiO_2, 3:1 heptane/EtOAc) afforded 3.17 g (62%) of the desired carbamate **17c** as white solid. TLC R_f=0.21 (2:1 heptane/EtOAc). Mp 101–103 °C $[\alpha]_D^{25}$ +35.0 (c 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.25 (m, 3H), 7.16 (d, J=7.1 Hz, 2H), 5.77 (dddd, J=16.9, 10.2, 6.6, 6.6 Hz, 1H), 5.58 (dd, J=12.6, 8.5 Hz, 1H), 5.04 (dd, J=17.2, 1.0 Hz, 1H), 5.00 (dd, J=10.2, 1.1 Hz, 1H), 4.52 (dd, J=14.3, 5.9 Hz, 1H), 4.14 (t, J=6.6 Hz, 2H), 3.72 (s, 3H), 3.13 (d, J=5.9 Hz, 2H), 2.08 (q, J=7.1 Hz, 2H), 1.73 (quintet, J=7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 150.9, 137.0 134.7, 129.4 128.7, 127.4, 115.7, 66.5, 57.7, 52.7, 39.0, 29.7, 27.6; FTIR (neat) 3271, 1744, 1641 cm$^{-1;}$ HRMS $(M+H)^+$ calcd for $C_{16}H_{23}N_2O_6S$ 371.1277, found 371.1280.

4.1.16. *N*-[[[(2-Propenyloxy)carbonyl]-*N*′-(4-methoxybenzyl)-amino]sulfonyl]-(*S*)-phenylalanine methyl ester (18a). To a stirring solution of Ph_3P (1.85 g, 7.04 mmol) in THF (4 mL) at rt was added PMBOH (973 mg, 7.04 mmol) via syringe and the solution stirred for 30 min. This mixture was transferred via cannula to a stirring solution of sulfamoyl carbamate **17a** (2.41 g, 7.04 mmol) and DIAD (1.42 g, 7.04 mmol) in THF (5 mL) and the reaction was stirred for 3 h and concentrated under reduced pressure. Flash chromatography (SiO_2, 4:1 heptane/EtOAc) afforded 3.17 g (97%) of the desired alkylated sulfamoyl carbamate **18a** as a yellow oil. TLC R_f=0.49 (1:1 heptane/EtOAc). $[\alpha]_D^{25}$ +2.9 (c 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (d, J=8.6 Hz, 2H), 7.31–7.28 (m, 3H), 7.07 (d, J=6.3 Hz, 2H), 6.87 (d, J=8.5 Hz, 2H), 5.90 (dddd, J=16.6, 11.2, 5.8, 5.4 Hz, 1H), 5.74 (d, J=8.2 Hz, 1H), 5.36 (d, J=17.2 Hz, 1H), 5.28 (d, J=10.4 Hz, 1H), 4.85 (d, J=15.3 Hz, 1H), 4.73 (d, J=15.3 Hz, 1H), 4.71–4.74 (m, 2H), 4.06 (dd, J=14.0, 5.9 Hz, 1H), 3.82 (s, 3H), 3.61 (s, 3H), 3.03 (d, J=9.4 Hz, 2H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 159.4, 152.6, 136.2, 134.8, 131.0, 130.1, 129.3, 128.6, 127.3, 119.4, 113.9, 67.4, 57.0, 55.2, 52.4, 50.3, 38.9; FTIR (neat) 3304, 2979, 1736, 1728, 1612, 1514 cm^{-1}

HRMS $(M+H)^+$ calcd for $C_{22}H_{27}N_2O_7S$ 463.1539, found 463.1566.

4.1.17. *N*-[[[(2-Butenyloxy)carbonyl]-*N′*-(4-methoxybenzyl)-amino]sulfonyl]-(*S*)-phenylalanine methyl ester (18b). In a procedure similar to the preparation of sulfamoyl carbamate **18a**, compound **17b** (3.56 g, 9.99 mmol), DIAD (1.97 mL, 9.99 mmol), Ph_3P (2.62 g, 9.99 mmol) and PMBOH (1.25 mL g, 9.99 mmol) were utilized in the Mitsunobu reaction. Flash chromatography (SiO_2, 5:1 heptane/EtOAc) afforded 3.94 g (83%) of the desired alkylated product **18b** as a yellow oil. TLC $R_f=0.55$ (1:1 heptane/EtOAc). $[\alpha]_D^{25}$ +3.0 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.33 (d, $J=8.5$ Hz, 2H), 7.27–7.24 (m, 3H), 7.05 (d, $J=7.0$ Hz, 2H), 6.84 (d, $J=8.5$ Hz, 2H), 5.75–5.69 (m, 1H and N–H), 5.10 (d, $J=17.2$ Hz, 1H), 5.00 (d, $J=10.2$ Hz, 1H), 4.82 (d, $J=15.2$ Hz, 1H), 4.68 (d, $J=15.2$ Hz, 1H), 4.24 (t, $J=6.5$ Hz, 2H), 4.02 (dd, $J=14.2$, 5.9 Hz, 1H), 3.80 (s, 3H), 3.59 (s, 3H), 2.98 (d, J=5.9 Hz, 2H), 2.40 (dd, $J=12.8$, 6.4 Hz, 2H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 159.3, 152.8, 134.8, 134.0, 130.2, 129.4, 129.2, 128.6, 127.3, 117.8, 113.8, 66.4, 56.9, 55.3, 52.4, 50.2, 39.0, 32.9; FTIR (neat) 3319, 3055, 2926, 1744, 1728, 1612, 1514 cm^{-1} HRMS $(M+NH_4)^+$ calcd for $C_{23}H_{32}N_3O_7S$ 494.1961, found 494.1953.

4.1.18. *N*-[[[(2-Pentenyloxy)carbonyl]-*N′*-(4-methoxybenzyl)-amino]sulfonyl]-(*S*)-phenylalanine methyl ester (18c). In a procedure similar to the preparation of sulfamoyl carbamate **18a**, compound **17c** (3.0 g, 8.1 mmol), DIAD (1.59 mL, 8.1 mmol), Ph_3P (2.12 g, 8.1 mmol) and PMBOH (1.0 mL, 8.1 mmol) were utilized in the Mitsunobu reaction. Flash chromatography (SiO_2, 4:1 heptane/EtOAc) afforded 3.08 g (78%) of the desired alkylated product **18c** as a yellow oil. TLC $R_f=0.54$ (1:1 heptane/EtOAc). $[\alpha]_D^{25}$ +3.3 (*c* 1.01, $CHCl_3$);^1H ($CDCl_3$, 500 MHz) δ 7.34 (d, $J=8.6$ Hz, 2H), 7.31–7.27 (m, 3H), 7.08 (d, $J=6.5$ Hz, 2H), 6.87 (d, $J=8.6$ Hz, 2H), 5.78 (dddd, $J=16.9$, 10.2, 6.6, 6.6 Hz, 1H), 5.73 (d, $J=5.5$ Hz, 1H), 5.03 (dd, $J=16.9$, 1.5 Hz, 1H), 5.00 (d, $J=9.0$ Hz, 1H), 4.85 (d, $J=15.3$ Hz, 1H), 4.72 (d, $J=15.3$, 1H), 4.24–4.17 (m, 2H), 4.06 (dd, $J=13.9$, 5.9 Hz, 1H), 3.82 (s, 3H), 3.62 (s, 3H), 3.01 (d, $J=5.8$ Hz, 2H), 2.08 (dt, $J=7.4$, 7.1 Hz, 2H), 1.75 (quintet, $J=7.1$ Hz, 2H); ^{13}C ($CDCl_3$, 125 MHz) δ 170.6, 159.3, 152.8, 137.0, 134.8, 129.9, 129.3, 129.1, 128.6, 127.3, 115.6, 113.8, 67.0, 57.0, 55.2, 52.4, 50.2, 38.9, 29.7, 27.6; FTIR (neat) 3296, 1728, 1612, 1514 cm^{-1}; HRMS $(M+NH_4)^+$ calcd for $C_{24}H_{34}N_3O_7S$ 508.2117, found 508.2094.

4.1.19. *N*-(2-Propenyl)-*N*-[[[(2-propenyloxy)carbonyl]-*N′*-(4-methoxybenzyl)-amino]sulfonyl]-(*S*)-phenylalanine methyl ester (19a). To a stirring solution of **18a** (3.06 g, 6.62 mmol) in CH_3CN (25 mL) was added K_2CO_3 (9.15 g, 66.2 mmol), and allyl bromide (2.86 mL, 33.1 mmol). The reaction was stirred under reflux for 24 h. The product was filtered and purified by flash chromatography (SiO_2, 5:1 heptane/EtOAc) to afford 2.01 g (60%) of the pure product **19a** as a yellow oil. TLC $R_f=0.51$ (1:1 heptane/EtOAc). $[\alpha]_D^{25}$ −15.1 (*c* 1.09, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, $J=8.6$ Hz, 2H), 7.30–7.21 (m, 3H), 7.12 (d, $J=6.9$ Hz, 2H), 6.82 (d, $J=8.6$ Hz, 2H), 5.97–5.85 (m, 2H), 5.35 (d, $J=17.1$ Hz, 1H), 5.28 (d, $J=10.4$ Hz, 1H), 5.25 (d, $J=17.6$ Hz, 1H), 5.17 (d, $J=10.2$ Hz, 1H), 4.87 (d, $J=15.4$ Hz, 1H), 4.77 (d, $J=15.4$ Hz, 1H), 4.65 (d, $J=5.9$ Hz, 2H), 4.55 (dd, $J=8.9$, 6.2 Hz, 1H), 4.17 (dd, $J=16.7$, 5.7 Hz, 1H), 4.00 (dd, $J=16.7$, 6.8 Hz, 1H), 3.77 (s, 3H), 3.59 (s, 3H), 3.22 (dd, $J=13.7$, 9.0 Hz, 1H), 2.97 (dd, $J=13.7$, 6.2 Hz, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 159.1, 152.5, 136.2, 134.9, 131.2, 129.9, 129.1, 129.0, 128.4, 126.8, 119.4, 117.6, 113.6, 67.7, 61.1, 55.1, 52.0, 51.4, 50.0, 36.8; FTIR (neat) 3350, 2982, 1732, 1649, 1612, 1585, 1514 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{25}H_{31}N_2O_7S$ 503.1852, found 503.1863.

4.1.20. *N*-(2-Propenyl)-*N*-[[[(2-butenyloxy)carbonyl]-*N′*-(4-methoxybenzyl)amino]sulfonyl]-(*S*)-phenylalanine methyl ester (19b). In a procedure similar to the preparation of sulfamoyl carbamate **19a**, **18b** (1.58 g, 3.3 mmol), K_2CO_3 (912 mg, 6.6 mmol), and allyl bromide (0.29 mL, 3.30 mmol) was subjected to the allylation procedure. Flash chromatography (SiO_2, 100% EtOAc) afforded 1.68 g (98%) of **19b** as a yellow oil. TLC $R_f=0.60$ (1:1 heptane/EtOAc). $[\alpha]_D^{25}$ −19.8 (*c* 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35 (d, $J=8.6$ Hz, 2H), 7.29–7.22 (m, 3H), 7.13 d, $J=7.0$ Hz, 2H), 6.81 (d, $J=11.5$ Hz, 2H), 5.91 (dddd, $J=16.9$, 10.2, 6.3, 6.1 Hz, 1H), 5.75 (dddd, $J=17.0$, 10.3, 6.7, 6.7 Hz, 1H), 5.25 (dd, $J=17.2$, 1.1 Hz, 1H), 5.16 (dd, $J=10.3$, 1.0 Hz, 1H), 5.12 (dd, $J=17.2$, 1.5 Hz, 1H), 5.10 (dd, $J=9.3$, 1.3 Hz, 1H), 4.83 (d, $J=15.5$ Hz, 1H), 4.74 (d, $J=15.5$ Hz, 1H), 4.58 (dd, $J=8.9$, 6.2 Hz, 1H), 4.20 (t, $J=6.3$ Hz, 2H), 4.17 (d, $J=5.7$ Hz, 1H)), 4.02 (dd, $J=16.6$, 6.7 Hz, 1H), 3.77 (s, 3H), 3.59 (s, 3H), 3.22 (dd, $J=13.7$, 9.0 Hz, 1H), 2.97 (dd, $J=13.7$, 6.1 Hz, 1H), 2.42 (dd, $J=13.5$, 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 159.3, 152.7, 136.3, 135.0, 133.3, 129.9, 129.2, 129.1, 128.4, 126.8, 117.8, 117.7, 113.7, 66.3, 61.2, 55.2, 52.0, 51.4, 49.9, 36.9, 33.0; FTIR (neat) 2955, 1728, 1612, 1514 cm^{-1}; HRMS $(M+Na)^+$ calcd for $C_{26}H_{32}N_2O_7SNa$ 539.1828, found 539.1834.

4.1.21. *N*-(2-Propenyl)-*N*-[[[(2-pentenyloxy)carbonyl]-*N′*-(4-methoxybenzyl)amino]sulfonyl]-(*S*)-phenylalanine methyl ester (19c). In a procedure similar to the preparation of sulfamoyl carbamate **19a**, **18c** (513 mg, 3.3 mmol), K_2CO_3 (1.45 g, 10.5 mmol), allyl bromide (0.45 mL, 5.23 mmol) in CH_3CN (20 mL) was subjected to the allylation procedure. Flash chromatography (SiO_2, 4:1 heptane/EtOAc) afforded 506 mg (91%) of **19c** as a yellow oil. TLC $R_f=0.67$ (1:1 heptane/EtOAc). $[\alpha]_D^{25}$ −20.2 (*c* 0.92, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, $J=8.7$ Hz, 2H), 7.33–7.25 (m, 3H), 7.17 (d, $J=6.8$ Hz, 2H), 6.86 (d, $J=8.7$ Hz, 2H), 5.95 (dddd, $J=16.9$, 10.2, 6.5, 5.9 Hz. 1H), 5.80 (dddd, $J=16.9$, 10.2, 6.6, 6.6 Hz, 1H), 5.29 (dd, $J=17.2$, 1.2 Hz, 1H), 5.20 (dd, $J=10.2$, 1.1 Hz, 1H), 5.05 (dd, $J=17.1$, 1.6 Hz, 1H), 5.04 (d, $J=10.0$, 1.5 Hz, 1H), 4.89 (d, $J=15.5$ Hz, 1H), 4.79 (d, $J=15.5$ Hz, 1H), 4.61 (dd, $J=8.9$, 6.2 Hz, 1H), 4.22 (dd, $J=16.3$, 5.7 Hz, 1H), 4.19 (t, $J=7.0$ Hz, 2H), 4.07 (dd, $J=16.6$, 6.7 Hz, 1H), 3.80 (s, 3H), 3.63 (s, 3H), 3.26 (dd, $J=13.7$, 8.9 Hz, 1H), 3.01 (dd, $J=13.7$, 6.2 Hz, 1H), 2.11 (q, $J=7.1$ Hz, 2H), 1.79 (quintet, $J=7.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 159.1, 152.7, 136.9, 136.2, 134.9, 129.6, 129.1, 129.0, 128.3, 126.8, 117.6, 115.5, 113.6, 66.5, 61.1, 55.1, 52.0, 51.4, 49.9, 36.8, 29.6, 27.6;

FTIR (neat) 1728, 1612, 1514 cm^{-1}; HRMS $(M+NH_4)^+$ calcd for $C_{27}H_{38}N_3O_7S$ 548.2430, found 540.2431.

4.1.22. (2*S*)-2-[3-(4-Methoxy)benzyl)-2,4,4-trioxo-3,4,6,9-tetrahydro-2*H*-4λ^6-[1,4,3,5]oxathiadiazonin-5-yl]-3-phenyl-propionic acid methyl ester (20a). Compound **19a** (202 mg, 0.40 mmol) was dissolved in DCE (80 mL, 0.005 *M*) and the solution was degassed with Ar for 15 min followed by reflux for 30 min. Cat-**B** (75 mg, 22 mol%) was added to the refluxing solution in three equal portions over a period of 48 h. The reaction was cooled to rt, DCE was removed under reduced pressure, followed the addition of DMSO (0.32 mL, 50 equiv relative to catalyst) in CH_2Cl_2 (50 mL). The reaction was stirred at rt for 24 h and the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 4:1 heptane/EtOAc) afforded 124 mg (65%) of **19b** as a yellow oil. TLC R_f=0.47 (1:1 heptane/EtOAc). $[\alpha]_D^{25}$ −60.6 (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, *J*=8.9 Hz, 2H), 7.30 (d, *J*=7.4 Hz, 2H), 7.24–7.22 (m, 3H), 6.81 (d, *J*=8.7 Hz, 2H), 5.74 (dd, *J*=11.5 Hz, 1.7 Hz, 1H), 5.59 (dd, *J*=9.2, 1.8 Hz, 1H), 5.24–5.14 (m, 1H), 4.83 (s, 2H), 4.71–4.67 (m, 1H), 4.61 (t, *J*=7.3 Hz, 1H), 3.80–3.75 (m, 1H), 3.75 (s, 3H), 3.53 (s, 3H), 3.41 (dd, *J*=14.4, 7.6 Hz, 1H), 2.98 (dd, *J*=14.4, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 159.2, 153.1, 136.1, 132.0, 130.1, 129.0, 128.8, 128.6, 127.0, 124.5, 113.7, 64.9, 59.4, 55.2, 52.5, 50.7, 43.6, 34.8; FTIR (neat) 2950, 1740, 1612, 1514 cm^{-1}; HRMS $(M+NH_4)^+$ calcd for $C_{23}H_{29}N_3O_7S$ 492.1804, found 492.1793.

4.1.23. (2*S*)-2-[3-(4-Methoxybenzyl)-2,4,4-trioxo-3,4,9,10 tetrahydro-2*H*,6*H*-4λ^6-[1,4,3,5]oxathiadiazonin-5-yl]-3-phenyl-propionic acid methyl ester (20b). In a procedure similar to the preparation of cyclic sulfamoyl carbamate **20a**, **19b** (209 mg, 0.40 mmol) and cat-**B** (34 mg, 10 mol%) in DCE (80 mL) was subjected to the RCM procedure. Flash chromatography (SiO_2, 4:1 heptane/EtOAc) afforded 173 mg (87%) of **20b** as an ivory-colored solid, Mp=43–50 °C. TLC R_f=0.16 (2:1 heptane/EtOAc). $[\alpha]_D^{25}$ −97.5 (*c* 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, *J*=8.6 Hz, 2H), 7.31 (d, *J*=7.2 Hz, 2H), 7.27–7.24 (m, 3H). 6.78 (d, *J*=8.6 Hz, 2H), 5.85 (dd, *J*=16.6, 5.2 Hz, 1H), 5.62 (ddd, *J*=11.0, 11.0, 5.5 Hz, 1H), 4.82 (d, *J*=15.1 Hz, 1H), 4.76 (d, *J*=15.1 Hz, 1H), 4.59 (bs,1H), 4.52 (t, *J*=7.4 Hz, 1H), 4.18–4.14 (m, 1H), 4.08 (dd, *J*=11.3, 1.1 Hz, 1H), 3.74 (s, 4H), 3.52 (s, 3H), 3.45 (dd, *J*=14.4, 7.0 Hz, 1H), 3.00 (dd, *J*=14.4, 7.8 Hz, 1H), 2.74–2.68 (m, 1H), 2.25–2.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3, 159.2, 152.5, 136.5, 131.5, 130.3, 129.1, 129.1, 128.5, 126.9, 113.5, 65.6, 59.2, 55.2, 52.5, 50.8, 44.7, 35.0, 25.3; FTIR (neat) 1732, 1612, 1514 cm^{-1}; HRMS $(M+NH_4)^+$ calcd for $C_{24}H_{32}N_3O_7S$ 506.1961, found 506.1955.

4.1.24. (2*S*)-2-[3-(4-Methoxybenzyl)-2,4,4-trioxo-1-oxa-4λ^6-thia-3,5-diaza-cycloundec-7-en-5-yl]-3-phenyl-propionic acid methyl ester (20c) (hydrogenated for characterization). In a procedure similar to the preparation of cyclic sulfamoyl carbamate **20a**, **19c** (206 mg, 0.39 mmol) and cat-**B** (43 mg, 0.05 mmol) in DCE (78 mL) was subjected to the RCM procedure. Flash chromatography (SiO_2, 5:1 heptane/EtOAc) afforded 170 mg (87%) of **20c** (1.6:1 E:Z) as a yellow oil. TLC R_f=0.50 (1:1 heptane/EtOAc); HRMS $(M+NH_4)^+$ calcd for $C_{25}H_{34}N_3O_7S$ 520.2117, found 520.2091. A portion of this compound was immediately subjected to the following hydrogenation protocol: Cyclic sulfamoyl carbamate **20c** (57 mg, 0.11 mmol) was weighed into a round-bottomed flask followed by the addition of 5% Pd/C (29 mg) and EtOAc (10 mL). The flask was evacuated using suction followed by the insertion of two H_2 balloons. The reaction was stirred at rt for 2 h. The crude product was filtered through celite and concentrated under reduced pressure to afford 54 mg (95%) of a white solid. TLC R_f=0.49 (1:1 heptanes/EtOAc). Mp 99–102 °C; $[\alpha]_D^{25}$ −9.7 (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, *J*=8.5 Hz, 2H), 7.24–7.17 (m, 3H), 6.91 (d, *J*=6.0 Hz, 2H), 6.76 (d, *J*=8.5 Hz, 2H), 5.03 (d, *J*=15.0 Hz, 1H), 4.81 (d, *J*=15.0 Hz, 1H), 4.22 (m, 1H), 4.10 (t, *J*=10.1 Hz, 1H), 3.90 (dd, *J*=9.8, 3.7 Hz, 1H), 3.73 (s, 3H), 3.68–3.51 (m, 2H), 3.58 (s, 3H), 3.17 (t, *J*=10.5 Hz, 1H), 2.87 (dd, *J*=13.3, 4.2 Hz, 1H), 2.05–1.92 (m, 2H), 1.78–1.66 (m, 2H), 1.56–1.51 (m, 2H), 1.32–1.28 (m, 2H); ^{13}C ($CDCl_3$, 100 MHz) δ 169.9, 159.2, 152.9, 136.0, 130.5, 129.1, 129.0, 128.4, 126.7, 113.6, 69.2, 60.6, 55.1, 52.0, 51.5, 46.9, 34.9, 25.8, 23.4, 23.3, 22.1; FTIR (neat) 2953, 1743, 1726, 1612, 1514 cm^{-1}; HRMS $(M+Na)^+$ calcd for $C_{25}H_{32}N_2O_7SNa$ 527.1828, found 527.1820.

4.1.25. *N*-[[[(2-Propenyloxy)carbonyl]amino]sulfonyl]-(*S*)-valine methyl ester (21). CSI (29.8 mmol; 4.2 g) was dissolved in CH_2Cl_2 (10 mL), the solution was cooled to 0 °C, and allyl alcohol (1.73 g, 29.8 mmol) was added via syringe. In an adjacent round-bottomed flask, valine methyl ester hydrochloride (5.0 g, 29.8 mmol) was dissolved in CH_2Cl_2 (25 mL), cooled to 0 °C, and Et_3N (6.03 g, 59.6 mmol) was added via syringe. Each solution was stirred at 0 °C under Ar for approximately 1h. The CSI/alcohol solution was cannulated into the amino acid solution and the reaction was stirred for 12 h under Ar at 0 °C while slowly warming to rt. The crude product was dissolved in H_2O (100 mL) and extracted with CH_2Cl_2 (4×50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 4:1 heptane/EtOAc) afforded 6.12 g (70%) of the desired carbamate **21** as white solid. TLC R_f=0.35 (1:1 heptane/EtOAc). Mp 93–95 °C $[\alpha]_D^{25}$ +43.6 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.92 (dddd, *J*=17.0, 10.4, 5.8, 5.8 Hz, 1H), 5.67 (d, *J*=9.4 Hz, 1H), 5.37 (dd, *J*=17.2, 1.3 Hz, 1H), 5.29 (dd, *J*=10.4, 1.1 Hz, 1H), 4.66–4.63 (m, 2H), 4.07 (dd, *J*=9.4, 5.0 Hz, 1H), 3.75 (s, 3H), 2.20–2.11 (m, 1H), 1.02 (d, *J*=6.8 Hz, 3H), 0.91 (d, *J*=6.9 Hz, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 150.7, 131.0, 119.4, 67.3, 62.2, 52.5, 31.4, 18.8, 17.2; FTIR (neat) 3276, 3205, 2966, 1744, 1720, 1651 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{10}H_{19}N_2O_6S$ 295.0964, found 295.0947.

4.1.26. *N*-[[[[*N*′-(2-Propenyloxy)carbonyl]-*N*′-(1*R*)-1-ethoxycarbonyl-ethyl]amino]sulfonyl]-(*S*)-valine methyl ester (22). Compound **21** (2.66 g, 9.0 mmol) was dissolved in THF (3 mL) followed by the addition of DIAD (1.82 g, 9.0 mmol) dropwise via syringe. In an adjacent round-bottomed flask, Ph_3P (2.37 g, 9.0 mmol) was dissolved in THF (4 mL) followed by the addition of (*S*)-ethyl lactate (1.02 mL, 9.0 mmol) via syringe. Each solution was stirred under Ar atmosphere at rt for 1 h after which the Ph_3P/ethyl lactate solution was cannulated into the solution of

21/DIAD and the resulting reaction mixture stirred under at rt for 24 h. The reaction was concentrated under reduced pressure. Flash chromatography (SiO_2, 9:1 heptane/EtOAc) afforded 2.30 g (65%) of the desired alkylated product **22** as a yellow oil. TLC R_f=0.53 (1:1 heptane/EtOAc). $[\alpha]_D^{25}$ + 73.0 (*c* 1.18, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.08 (d, J=7.4 Hz, 1H), 5.95 (dddd, J=16.6, 11.1, 5.7, 5.4 Hz, 1H), 5.39 (d, J=17.2 Hz, 1H), 5.30 (d, J=10.5 Hz, 1H), 4.96 (q, J=7.0 Hz, 1H), 4.71 (t, J=5.6 Hz, 2H), 4.23–4.17 (m, 2H), 4.12 (dd, J=7.0, 3.5 Hz, 1H), 3.77 (s, 3H), 2.22–2.15 (m, 1H), 1.59 (d, J=7.0 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.02 (d, J=6.8 Hz, 3H), 0.86 (d, J=6.9 Hz, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 170.0, 151.7, 131.0, 119.3, 68.1, 61.9, 61.8, 56.6, 52.5, 31.9, 18.8, 17.0, 16.5, 14.1; FTIR (neat) 3304, 2966, 1740, 1726, 1649 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{15}H_{27}N_2O_8S$ 395.1488, found 395.1472.

4.1.27. *N*-(2-Propenyl)-*N*-[[[[*N′*-(2-propenyloxy)carbonyl]-*N′*-(1*R*)-1-ethoxycarbonyl-ethyl]amino]sulfonyl]-(*S*)-valine methyl ester (23). Compound **22** (1.10 g, 2.79 mmol) was weighed into a round-bottomed flask, followed by the addition of K_2CO_3 (771 mg, 5.58 mmol), allyl bromide (0.24 mL, 2.79 mmol) and CH_3CN (25 mL). The reaction was stirred under reflux at 85 °C for 6 h. The product was filtered and concentrated under reduced pressure. Flash chromatography (SiO_2, 6:1 heptane/EtOAc) afforded 825 mg (68%) of **23** as a yellow oil. TLC R_f=0.38 (2:1 heptane/EtOAc). $[\alpha]_D^{25}$ −22.2 (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.02 (dddd, J=17.3, 10.2, 5.8, 5.8 Hz, 1H), 5.90 (dddd, J=16.4, 10.6, 5.8, 5.8 Hz, 1H), 5.36 (dd, J=17.2, 1.2 Hz, 1H), 5.29 (dd, J=10.2, 1.0 Hz, 1H), 5.22 (dd, J=17.3, 1.2 Hz, 1H), 5.12 (dd, J=10.2, 1.1 Hz, 1H), 4.99 (q, J=7.0 Hz, 1H), 4.64 (d, J=5.8 Hz, 2H), 4.23–4.21 (m, 2H), 4.19 (d, J=7.1 Hz, 2H), 4.13 (d, J=10.3 Hz, 1H), 3.70 (s, 3H), 2.22–2.14 (m, 1H), 1.61 (d, J=7.0 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.03 (d, J=6.6 Hz, 3H), 0.94 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 170.0, 151.9, 135.3, 131.0, 119.6, 117.5, 67.9, 66.2, 61.7, 56.8, 51.7, 49.5, 28.9, 19.7, 19.4, 16.1, 14.0; FTIR (neat) 2968, 1742, 1647 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{18}H_{31}N_2O_8S$ 435.1801, found 435.1778.

4.1.28. (2*S*)-2-((1*R*)-1-Ethoxycarbonyl-ethyl])-2,4,4-trioxo-3,4,6,9-tetrahydro-2*H*-4λ⁶-[1,4,3,5]oxathiadiazonin-5-yl)-3-methyl-butyric acid methyl ester (24). In a procedure similar to the preparation of cyclic sulfamoyl carbamate **20a**, **23** (24 mg, 0.055 mmol), cat-**B** (4 mg, 8 mol%) in DCE (11 mL) was subjected to the RCM procedure. Flash chromatography (SiO_2, 9:1 heptane/EtOAc) afforded 15 mg (68%) of **24** as a yellow oil. TLC R_f=0.45 (1:1 heptane/EtOAc). $[\alpha]_D^{25}$ −77.9 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.72–5.69 (m, 1H), 5.54–5.51 (m, 1H), 5.33–5.29 (m, 1H), 4.95 (q, J=7.0 Hz, 1H), 4.89–4.85 (m, 1H), 4.73–4.69 (m, 1H), 4.33–4.18 (m, 2H), 3.96 (d, J=10.9 Hz, 1H), 3.57 (s, 3H), 3.57 (m, 1H), 2.37–2.27 (m, 1H), 1.62 (d, J=7.0 Hz, 3H), 1.31 (t, J=7.1 Hz, 3H), 1.04 (d, J=6.3 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 169.7, 152.6, 130.9, 124.6, 65.3, 61.8, 56.0, 51.8, 43.2, 29.7, 25.9, 20.5, 18.6, 15.6, 14.0; FTIR (neat) 2970, 1744, 1647, 1450, 1386 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{16}H_{27}N_2O_8S$ 407.1488, found 407.1497.

4.1.29. *N*-(Benzyl)-*N*-(2-propenyl)-*N′*-[[*N″*-(2-propenyl)-*N″*-(benzyl)amino]sulfonyl]-urea (25). To a stirring solution of benzylallylamine (2.18 g, 14.8 mmol) and Et_3N (2.96 mL, 21.2 mmol) in CH_2Cl_2 (45 mL) at 0 °C under argon was added CSI (615 μL, 2.40 mmol) in CH_2Cl_2 (3 mL) dropwise over 5 min. The solution was stirred for 12 h, and CH_2Cl_2 (130 mL) added. The solution was washed with 10% $NaHSO_4$ (50 mL), $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and the solvent removed. Flash chromatography (SiO_2, hexanes/EtOAc) afforded 2.75 g of **25** (97%) as a white solid. TLC R_f=0.30 (2:1 hexanes/EtOAc). Mp 54–58 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.26 (m, 10H), 5.87–5.71 (m, 1H), 5.87–5.71 (m, 1H), 5.25–5.20 (m, 1H), 5.25–5.20 (m, 1H), 5.15–5.11 (m, 1H), 5.15–5.11 (m, 1H), 4.57 (s, 2H), 4.50 (s, 2H), 3.91 (d, J=5.6 Hz, 2H), 3.85 (d, J=5.1 Hz, 2H); ^{13}C ($CDCl_3$,125 MHz) 152.8, 136.6, 132.8, 128.9, 128.9, 128.5, 128.5, 128.4, 127.9, 127.7, 127.6, 118.7, 118.0, 52.1, 50.6, 50.4, 49.7; FTIR (neat) 3306, 3031, 2927, 1696, 1651, 1606, 1586, 1455, 1392, 1153, 740, 699 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{21}H_{26}N_3O_3S$ 400.1695, found 400.1711.

4.1.30. *N*-(Benzyl)-*N*-(2-propenyl)-*N′*-(benzyl)-*N′*-[[*N″*-(2-propenyl)-*N″*(benzyl)amino]sulfonyl]-urea (26). Sulfamoyl urea **25** (500 mg, 1.25 mmol), K_2CO_3 (863 mg, 6.25 mmol), CH_3CN (40 mL) and BnBr (744 μL, 6.25 mmol) were added sequentially to a 100 mL round-bottomed flask, a condenser was attached, and the mixture stirred at 70 °C for 16 h. The solution was filtered, the solvent removed under reduced pressure, and the crude mixture was submitted to flash chromatography (SiO_2, hexanes/EtOAc) to yield 355 mg (58%) of **26** as a clear oil. TLC R_f=0.44 (3:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.17 (m, 15H), 5.91 (dddd, J=16.9, 10.4, 6.5, 6.5 Hz, 1H), 5.77 (dddd, J=16.3, 10.4, 5.9, 5.9, 1H), 5.48 (s, 2H), 5.19, (dd, J=10.2, 1.0 Hz, 1H), 5.11 (dd, J=15.4, 1.1 Hz, 1H), 5.10 (dd, J=8.6, 1.2 Hz, 1H), 5.09 (dd, J=18.3, 1.2 Hz, 1H), 4.56 (s, 2H), 4.30 (s, 2H), 3.96 (d, J=5.9 Hz, 2H), 3.75 (d, J=6.5 Hz, 2H); ^{13}C ($CDCl_3$, 100 MHz) 157.1, 137.2, 136.3, 135.4, 133.8, 132.3, 129.1, 128.8, 128.7, 128.6, 128.5, 128.2, 127.7, 127.5, 127.3, 118.4, 118.0, 74.0, 51.5, 51.4, 51.0, 50.9; FTIR (neat) 3031, 2925, 1743, 1566, 1496, 1454, 1313, 1153, 739, 699 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{28}H_{32}N_3O_3S$ 490.2168, found 490.2158.

4.1.31. 2,4,9-Tribenzyl-1,1-dioxo-1,2,4,5,8,9-hexahydro-1λ⁶-[1,2,4,9]thiatriazonin-3-one (27). Sulfamoyl urea **26** (53 mg, 0.72 mmol), and CH_2Cl_2 (50 mL) were placed in a 100 mL round-bottomed flask and degassed with argon gas for 10 min. Cat-**B** (3 mg, 0.023 mmol) was added, the flask was quickly fitted with a condenser containing an argon balloon, and the solution was heated to reflux for 10 h during which another equivalent of cat-**B** was added. The solution was cooled to rt, DMSO (0.1 mL) added, and the solution stirred for 12 h. The solvent was removed and flash chromatography (SiO_2, hexanes/EtOAc) gave 41 mg (74%) of **27** as a white solid. Mp 92 °C; TLC R_f=0.24 (3:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.27 (m, 15H), 5.87 (dd, J=15.4, 7.6 Hz, 1H), 5.45 (dd, J=17.0,

8.4 Hz, 1H), 5.33 (s, 2H), 4.60 (s, 2H), 4.35 (s, 2H), 3.71 (s, 2H), 3.71 (s, 2H); ^{13}C ($CDCl_3$, 100 MHz) δ 154.0, 136.6, 135.6, 135.2, 129.3, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.6, 71.1, 55.6, 50.7, 46.8, 40.6; FTIR (neat) 3030, 2956, 1741, 1680, 1508, 1455, 1365, 1163, 751, 699 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{26}H_{28}N_3O_3S$ 462.1851, found 462.1861.

4.1.32. *N*-(2-Propenyl)-*N*-[[[*N′*-(2-propenyl)-*N′*-(1*S*)-1-methoxycarbonyl-3-methyl-butyl]carbonyl]amino]-sulfonyl]-(*S*)-leucine methyl ester (28a). To a stirring solution of *N*-allyl (L)-leucine methyl ester (975 mg, 5.26 mmol) and Et_3N (0.40 mL, 2.90 mmol) in CH_2Cl_2 at 0 °C under argon was added CSI (0.21 mL, 2.40 mmol) in CH_2Cl_2 (3 mL) slowly over 10 min. The solution was stirred for 12 h while slowly being raised to rt. The solvent was removed under reduced pressure and EtOAc (80 mL) added. The solution was washed with 10% $NaHSO_4$ (50 mL), $NaHCO_3$ (50 mL), brine (50 mL), dried with $MgSO_4$, and the solvent removed. Column chromatography (SiO_2, hexanes/EtOAc) afforded 890 mg (78%) of **28a** as a yellow oil. TLC R_f=0.20 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −131.6 (*c* 3.1, $CHCl_3$); FTIR (neat) 3347, 2958, 2870, 1732, 1682, 1642, 1549, 1455, 1368, 1168 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{21}H_{38}N_3O_7S$ 476.2430, found 476.2433.

4.1.33. *N*-(2-Propenyl)-*N*-[[[*N′*-(2-propenyl)-*N′*-(1*S*)-1-methoxycarbonyl-2-methyl-propyl]carbonyl]amino]-sulfonyl]-(*S*)-valine methyl ester (28b). In a procedure similar to the preparation of **28a**, 3-component coupling and flash chromatography (SiO_2, hexanes/EtOAc) yielded 921 mg (56%) of **28b** as a clear oil, which was taken on directly to the next step. TLC R_f=0.17 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −87.3 (*c* 1.05, $CHCl_3$); FTIR (neat) 3292, 3081, 2967, 1740, 1684, 1551, 1458, 1355, 1164 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{19}H_{34}N_3O_7S$ 448.2117, found 448.2118.

4.1.34. *N*-(2-Propenyl)-*N*-[[[*N′*-(2-propenyl)-*N′*-(1*S*)-1-methoxycarbonyl-2-phenyl-ethyl]carbonyl]amino]-sulfonyl]-(*S*)-phenylalanine methyl ester (28c). In a procedure similar to the preparation of sulfamoyl urea **28a** coupling and flash chromatography (SiO_2, hexanes/EtOAc) yielded 1.01 g (90%) of **28c** as a clear oil, which was taken on directly to the next step. TLC R_f=0.28 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −30.8 (*c* 1.1, $CHCl_3$); FTIR (neat) 3306, 3032, 2964, 1738, 1556, 1455, 1327, 1155, 745, 699 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{27}H_{34}N_3O_7S$ 544.2117, found 544.2118.

4.1.35. *N*-(2-Propenyl)-*N*-[[[*N′*-(2-propenyl)-*N′*-(1*S*)-1-methoxycarbonyl-3-methyl-butyl]carbonyl]-*N″*-(benzyl)-amino]sulfonyl]-(*S*)-leucine methyl ester (30a). In a procedure similar to the preparation of **26**, benzylation and flash chromatography (SiO_2, hexanes/EtOAc) gave 140 mg (43%) of **30a** as a white solid. TLC R_f=0.46 (3:1 hexanes/EtOAc). Mp 46–47 °C; $[\alpha]_D^{25}$ −47.3 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.29 (m, 5H), 6.02 (dddd, *J*=17.0, 10.2, 6.6, 6.6 Hz, 1H), 5.41 (dddd, *J*=16.9, 10.1, 6.7, 6.7 Hz, 1H), 5.22 (dd, *J*=17.2, 1.0 Hz, 1H), 5.14 (d, *J*=10.2 Hz, 1H), 5.04 (dd, *J*=17.9, 1.2 Hz, 1H), 5.01 (d, *J*=10.6, Hz, 1H), 4.52–4.49 (m, 1H), 4.50 (s, 2H), 4.17–4.01 (m, 2H), 4.17–4.01 (m, 2H), 3.85 (dd, *J*=15.4, 7.2 Hz, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 1.82–1.71 (m, 2H), 1.82–1.71 (m, 2H), 1.65–1.55 (m, 1H), 1.55–1.45 (m, 1H), 0.99 (d, *J*=5.5 Hz, 3H), 0.94 (d, *J*=6.0 Hz, 3H), 0.82 (d, *J*=6.5 Hz, 3H), 0.82 (d, *J*=6.5 Hz, 3H); ^{13}C ($CDCl_3$,100 MHz) 172.1, 171.1, 155.4, 135.3, 135.3, 133.8, 129.8, 128.4, 128.1, 118.5, 117.6, 74.5, 59.1, 57.3, 52.0, 51.6, 51.5, 49.5, 39.5, 376, 24.6, 24.4, 22.8, 22.4, 21.9, 21.8; FTIR (neat) 3347, 3080, 2958, 2870, 1732, 1681, 1642, 1548, 1455, 1368, 1168 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{28}H_{44}N_3O_7S$ 566.2900, found 566.2875.

4.1.36. *N*-(2-Propenyl)-*N*-[[[*N′*-(2-propenyl)-*N′*-(1*S*)-1-methoxycarbonyl-2-methyl-propyl]carbonyl]-*N″*-(benzyl)amino]-sulfonyl]-(*S*)-valine methyl ester (30b). In a procedure similar to the preparation of **26**, benzylation and flash chromatography (SiO_2, hexanes/EtOAc) gave 117 mg (62%) of **30b** as a clear oil. TLC R_f=0.43 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −56.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.25 (m, 5H), 6.06 (dddd, *J*=17.2, 10.1, 6.1, 6.1 Hz, 1H), 5.50–5.38 (m, 1H), 5.21 (dd, *J*=17.2, 1.1 Hz, 1H), 5.12 (dd, *J*=10.1, 1.0 Hz, 1H), 5.04 (d, *J*=17.2 Hz, 1H), 4.97 (d, *J*=10.1 Hz, 1H), 4.44 (s, 2H), 4.17 (d, *J*=10.3 Hz, 1H), 4.16–4.11 (m, 2H), 4.07 (dd, *J*=19.1, 5.8 Hz, 1H), 4.03–3.99 (m, 1H), 3.98–3.93 (m, 1H), 3.72 (s, 3H), 3.53 (s, 3H), 2.25–2.18 (m, 2H), 1.10 (d, *J*=6.6 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H), 0.87 (d, *J*=6.5 Hz, 3H), 0.48 (bs, 3H); ^{13}C ($CDCl_3$, 125 MHz) δ 171.4, 170.5, 156.0, 135.2, 133.8, 129.9, 128.6, 128.5, 128.2, 118.0, 117.8, 67.1, 65.3, 51.6, 51.3, 48.8, 28.9, 28.2, 20.3, 19.9, 19.6, 18.9, 17.9, 17.8; FTIR (neat) 3080, 2966, 2877, 1742, 1676, 1456, 1436, 1364, 1161, 749, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{26}H_{40}N_3O_7S$ 538.2587, found 538.2571.

4.1.37. *N*-(2-Propenyl)-*N*-[[[*N′*-(2-propenyl)-*N′*-(1*S*)-1-methoxy-carbonyl-2-phenyl-ethyl]carbonyl]-*N″*-(benzyl)-amino]-sulfonyl]-(*S*)-phenylalanine methyl ester (30c). In a procedure similar to the preparation of sulfamoyl urea **26**, benzylation and flash chromatography (SiO_2, hexanes/EtOAc) afforded 505 mg (65%) of **30c** as a clear oil. TLC R_f=0.36 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −104.9 (*c* 3.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.26 (m, 8H), 7.22–7.14 (m, 5H), 7.06–7.04 (m, 2H), 6.02 (dddd, *J*=16.8, 10.2, 6.5, 6.5 Hz, 1H), 5.39–5.33 (m, 1H), 5.28 (dd, *J*=17.2, 1.3 Hz, 1H), 5.22 (dd, *J*=10.2, 1.1 Hz, 1H), 4.97 (dd, *J*=10.1, 1.1 Hz, 1H), 4.94 (d, *J*=17.2 Hz, 1H), 4.78 (dd, *J*=7.9, 6.8 Hz, 1H), 4.29 (s, 2H), 4.14–4.02 (m, 2H), 4.14–4.02 (m, 2H), 3.70 (s, 3H), 3.52–3.44 (m, 1H), 3.50–3.40 (m, 1H), 3.46 (s, 3H), 3.43–3.37 (m, 1H), 3.18 (dd, *J*=13.9, 6.7 Hz, 1H), 2.89 (dd, *J*=14.2, 7.2 Hz, 1H); ^{13}C ($CDCl_3$,100 MHz) 170.9, 170.1, 155.4, 138.2, 137.1, 135.3, 134.6, 133.4, 129.5, 129.5, 129.4, 128.6, 128.5, 128.4, 128.1, 127.0, 126.5, 119.2, 118.7, 62.2, 61.4, 52.1, 51.9, 51.4, 49.4, 49.4, 36.8, 35.2; FTIR (neat) 3064, 3030, 2951, 1744, 1675, 1605, 1586, 1496, 1455, 1367, 1160, 749, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{34}H_{40}N_3O_7S$ 634.2587, found 634.2582.

4.1.38. (2*S*)-2-[2-Benzyl-4-[(1*S*)-1-methoxycarbonyl-3-methyl-butyl]-1,1,3-trioxo-1,2,3,4,5,8-hexahydro-1λ^6-[1,2,4,9] thiatriazonin-9-yl]-4-methyl-pentanoic acid methyl ester (31a). In a procedure similar to that used for the preparation of **27**, RCM and flash chromatography (SiO_2, hexanes/EtOAc) afforded 35 mg (74%) of **31a** as a

white solid. Mp 86–87 °C; TLC R_f=0.31 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −91.8 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.37 (m, 2H), 7.40–7.26 (m, 3H), 5.78 (dd, *J*=18.7, 8.7 Hz, 1H), 5.51 (dd, *J*=18.8, 8.6, Hz, 1H), 4.90–4.86 (m, 1H), 4.80 (dd, *J*=8.4, 5.6 Hz, 1H), 4.55 (d, *J*=13.2 Hz, 1H), 4.47 (d, *J*=13.2 Hz, 1H), 4.09 (dd, *J*=15.0, 8.8 Hz, 1H), 3.95–3.78 (m, 2H), 3.95–3.78 (m, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 1.86–1.77 (m, 2H), 1.76–1.61 (m, 2H), 1.57–1.48 (m, 2H), 1.02 (d, *J*=6.0 Hz, 3H), 1.02 (d, *J*=6.0 Hz, 3H), 0.84 (d, *J*=6.5 Hz, 3H), 0.84 (d, *J*=6.5 Hz, 3H); ^{13}C ($CDCl_3$,100 MHz) 172.3, 171.7, 154.7, 134.5, 130.7, 130.2, 128.2, 128.0, 127.8, 59.7, 58.3, 52.3, 51.9, 51.6, 42.0, 40.2, 39.7, 38.3, 24.9, 24.3, 23.1, 22.9, 21.7, 21.7; FTIR (neat) 3033, 2956, 1742, 1693, 1680, 1380, 1164, 752, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{26}H_{40}N_3O_7S$ 53.2587, found 538.2573.

4.1.39. (2*S*)-2-[2-Benzyl-4-[(1*S*)-1-methoxycarbonyl-2-methyl-propyl)-1,1,3-trioxo-1,2,3,4,5,8-hexahydro-1λ^6-[1,2,4,9] thiatriazonin-9-yl]-3-methyl-butyric acid methyl ester (31b). In a procedure similar to that used for the preparation of **27**, RCM and flash chromatography (SiO_2, hexanes/EtOAc) afforded 75 mg (71%) of **31b** as a clear oil. TLC R_f=0.13 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −101.2 (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.29 (m, 5H), 5.95 (dd, *J*=18.6, 8.6 Hz, 1H), 5.62 (dd, *J*=18.0, 8.7 Hz, 1H), 5.45 (d, *J*=12.2 Hz, 1H), 5.37 (d, *J*=12.2 Hz, 1H), 4.48 (dd, *J*=13.8, 9.3 Hz, 1H), 4.29–4.12 (m, 2H), 4.29–4.12 (m, 2H), 4.01 (dd, *J*=15.3, 7.7 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 2.23–2.13 (m, 1H), 2.15–2.05 (m, 1H), 1.07 (d, *J*=6.7 Hz, 3H),) 0.95 (d, *J*=6.5 Hz, 3H), 0.89 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.7 Hz, 3H);); ^{13}C ($CDCl_3$,100 MHz) 172.5, 170.4, 156.1, 135.1, 131.8, 128.6, 128.6128.5, 126.2, 72.4, 67.1, 65.9, 51.9, 51.4, 42.9, 40.0, 29.3, 28.7, 19.8, 19.5, 19.4, 19.3; FTIR (neat) 3030, 2965, 1740, 1579, 1472, 1291, 1156, 753, 701 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{24}H_{36}N_3O_7S$ 510.2274, found 510.2273.

4.1.40. (2*S*)-2-[2-Benzyl-4-[(1*S*)-1-methoxycarbonyl-2-phenyl-ethyl]-1,1,3-trioxo-1,2,3,4,5,8-hexahydro-1λ^6-[1,2,4,9] thiatriazonin-9-yl]-3-phenyl-propionic acid methyl ester (31c). In a procedure similar to that used for the preparation of cyclic sulfamoyl urea **27**, RCM and flash chromatography (SiO_2, hexanes/EtOAc) afforded 84 mg (81%) of **31c** as a clear oil. TLC R_f=0.20 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ −110.3 (*c* 0.82, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.24 (m, 8H), 7.23–7.16 (m, 5H), 7.06–7.02 (m, 2H), 5.69 (dd, *J*=18.3, 7.7 Hz, 1H), 5.24 (dd, *J*=19.0, 8.6 Hz, 1H), 4.96 (dd, *J*=7.8, 7.8 Hz, 1H), 4.57 (dd, *J*=7.6, 6.7 Hz, 1H), 4.47 (d, *J*=13.4 Hz, 1H), 4.23–4.19 (m, 1H), 4.10 (dd, *J*=15.6, 8.0 Hz, 1H), 4.03 (dd, *J*=14.7, 8.9 Hz, 1H), 3.91 (dd, *J*=15.6, 7.5 Hz, 1H), 3.73 (s, 3H), 3.64 (dd, *J*=14.7, 8.1 Hz, 1H), 3.60 (s, 3H), 3.40 (dd, *J*=14.4, 7.1 Hz, 1H), 3.29 (dd, *J*=14.3, 6.4 Hz, 1H), 3.07 (dd, *J*=14.3, 8.2 Hz, 1H), 2.91 (dd, *J*=14.3, 7.9 Hz, 1H); ^{13}C ($CDCl_3$,100 MHz) 171.1, 170.4, 159.3, 137.4, 136.1, 134.7, 130.5, 129.2, 129.2, 128.7, 128.4, 128.2, 128.2, 128.1, 127.9, 127.2, 126.6, 63.4, 62.2, 52.2, 52.2, 51.7, 44.3, 41.4, 36.9, 35.4; FTIR (neat) 3032, 2958, 1742, 1649, 1545, 1455, 1365, 1164, 750, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{32}H_{36}N_3O_7S$ 606.2274, found 606.2281.

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References and notes

1. (a) Hill, D. C. *Curr. Opin. Drug Dis. Dev.* **1998**, *1*, 92–97. (b) Silverman, L.; Campbell, R.; Broach, J. R. *Curr. Opin. Chem. Biol.* **1998**, *2*, 397–403. (c) Mere, L.; Bennett, T.; Coassin, P.; England, P.; Hamman, B.; Rink, T.; Zimmerman, S.; Negulescu, P. *Drug Disc. Tod.* **1999**, *4*, 363–369.
2. (a) *A Practical Guide to Combinatorial Chemistry*; Czarnik, A. W., DeWitt, S. H., Eds.; American Chemical Society: Washington, DC, 1997. (b) Merritt, A. T. *Comb. Chem. High Thr. Screen.* **1998**, *1*, 57–72. (c) Patel, D. V.; Campbell, D. A. *Comb. Chem. Mol. Div. Drug Dis.* **1998**, 189–199. (d) Bunin, B. A. *The Combinatorial Index*; Academic: New York, 1998. (e) *Combinatorial Chemistry: a Practical Approach*; Fenniri, H., Ed.; The practical approach series 233; Oxford Unversity Press: New York, 2000.
3. (a) Tan, D. S.; Foley, M. A.; Stockwell, B. R.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9073–9087. (b) Bergnes, G.; Gilliam, C. L.; Boisclair, M. D.; Blanchard, J. L.; Blake, K. V.; Epstein, D. M.; Pal, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2849–2854. (c) Wood, P. L. *Curr. Opin. Drug Disc. Dev.* **1998**, *1*, 34–40. (d) Burke, M. D.; Schreiber, S. L. *Chem. Rev.* **2002**, *102*, 515–553. (e) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
4. (a) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *J. Org. Chem.* **1995**, *60*, 5157–5169 and references cited therein. (b) Decicco, C. P.; Seng, J. L.; Kennedy, K. E.; Covington, M. B.; Welch, P. K.; Arner, E. C.; Magolda, R. L.; Nelson, D. J. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2331–2336. (c) Roush, W. R.; Gwaltney, S. L., II; Cheng, J.; Scheidt, K. A.; McKerrow, J. H.; Hansel, E. *J. Am. Chem. Soc.* **1998**, *120*, 10994–10995.
5. (a) Jadhav, P. K.; Woerner, F. J. *Tetrahedron Lett.* **1995**, *36*, 6383–6386. (b) Hultén, J.; Andersson, H. O.; Schaal, W.; Danielson, H. U.; Classon, B.; Kvarnströem, I.; Karlén, A.; Unge, T.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 4054–4061 and references cited therein. Sul (c) Winum, J.-Y.; Toupet, L.; Barragan, V.; Dewynter, G.; Montero, J.-L. *Org. Lett.* **2001**, *3*, 2241–2243.
6. (a) Berredjem, M.; Djebbar, H.; Regainia, Z.; Aouf, N.-E.; Dewynter, G.; Winum, J.-Y.; Montero, J.-L. *Phosphorus, Sulfur Silicon* **2003**, *178*, 693–705. (b) Winum, J.-Y.; Bouissiere, J.-L.; Passagne, I.; Evrard, A.; Montero, V.; Cuq, P.; Montero, J.-L. *Eur. J. Med. Chem.* **2003**, *38*, 319–324. (c) Picard, J. A.; O'Brien, P. M.; Sliskovic, D. R.; Anderson,

M. K.; Bousley, R. F.; Hamelehle, K. L.; Krause, B. R.; Stanfield, R. L. *J. Med. Chem.* **1996**, *39*, 1243–1252.
7. Kuang, R.; Epp, J. B.; Ruan, S.; Yu, H.; Huang, P.; He, S.; Tu, J.; Schechter, N. M.; Turbov, J.; Froelich, C. J.; Groutas, W. C. *J. Am. Chem. Soc.* **1999**, *121*, 8128–8129 and references cited therein.
8. (a) Sarges, R.; Kuhla, D. E.; Wiedermann, H. E.; Mayhew, D. A. *J. Med. Chem.* **1976**, *19*, 695–709. (b) McManus, J. M.; McFarland, J. W.; Gerber, C. F.; McLamore, W. M.; Laubach, G. D. *J. Med. Chem.* **1965**, *8*, 766–776. (c) McManus, J. M. *J. Med. Chem.* **1966**, *9*, 967–968. (d) McManus, J. M.; Gerber, C. F. *J. Med. Chem.* **1966**, *9*, 256–257.
9. (a) de Bont, D. B. A.; Dijkstra, G. D. H.; den Hartog, J. A. J.; Liskamp, R. M. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3035–3040. (b) Raju, B.; Kogan, T. P. *Tetrahedron Lett.* **1997**, *38*, 3373–3376. (c) Gordeev, M. F.; Gordon, E. M.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 8177–8181. (d) Kim, S. W.; Hong, C. Y.; Lee, K.; Lee, E. J.; Koh, J. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 735–738. (e) Brown, R. C. D.; Castro, J. L.; Moriggi, J.-D. *Tetrahedron Lett.* **2000**, *41*, 3681–3685.
10. Fitzpatrick, L. J.; Rivero, R. A. *Tetrahedron Lett* **1997**, *38*, 7479–7482.
11. (a) Tremblay, M.; Voyer, N.; Boujabi, S.; Dewynter, G. F. *J. Comb. Chem.* **2002**, *4*, 429–435. (b) Albericio, F.; Bryman, L. M.; Garcia, J.; Michelotti, E. L.; Nicolas, E.; Tice, C. M. *J. Comb. Chem.* **2001**, *3*, 290–300.
12. Esteve, C.; Vidal, B. *Tetrahedron Lett.* **2002**, *43*, 1019–1021.
13. McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239–2258.
14. For additional RCM routes to *S*-heterocycles, see (a) Brouwer, A. J.; Liskamp *J. Org. Chem.* **2004**, *69*, 3662–3668. (b) Salim, S. S.; Bellingham, R. K.; Brown, R. C. D. *Eur. J. Org. Chem.* **2004**, *4*, 800–806. (c) Moriggi, J.-D.; Brown, L. J.; Castro, J. L.; Brown, R. C. D. *Org. Biomol. Chem.* **2004**, *2*, 835–844. (d) Bolm, C.; Müller, D.; Hackenberger, C. P. R. *Org. Lett.* **2002**, *4*, 893–896.
15. (a) Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, J. D.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron* **2000**, *56*, 9781–9790. (b) Jun, J. H.; Dougherty, J. M.; Jiménez, M. d. S.; Hanson, P. R. *Tetrahedron* **2003**, *59*, 8901–8912.
16. Groutas, W. C.; Kuang, R.; Venkataraman, R. *Biochem. Biophys. Res. Commun.* **1994**, *198*, 341–349.
17. (a) Montero, J. L.; Dewynter, G.; Agoh, B.; Delaunay, B.; Imbach, J. L. *Tetrahedron Lett.* **1983**, *24*, 3091–3094. (b) Lee, C. H.; Korp, J. D.; Kohn, H. *J. Org. Chem.* **1989**, *54*, 3077–3083.
18. (a) Berredjem, M.; Djebbar, H.; Regainia, Z.; Aouf, N.-E.; Dewynter, G.; Winum, J.-Y.; Montero, J.-L. *Phosphorus, Sulfur Silicon* **2003**, *178*, 693–705. (b) Winum, J.-Y.; Bouissiere, J.-L.; Passagne, I.; Evrard, A.; Montero, V.; Cuq, P.; Montero, J.-L. *Eur. J. Med. Chem.* **2003**, *38*, 319–324. (c) Doherty, A. M.; Sircar, I.; Kornberg, B. E.; Quin, J., III; Winters, R. T.; Kaltenbronn, J. S.; Taylor, M. D.; Batley, B. L.; Rapundalo, S. R.; et al *J. Med. Chem.* **1992**, *35*, 2–14.
19. Disselnkoetter, H. (Farbenfabriken Bayer A.-G.). Ger. Offen. De, 1971, 14.
20. Winum, J.-Y.; Toupet, L.; Barragan, V.; Dewynter, G.; Montero, J.-L. *Org. Lett.* **2001**, *3*, 2241–2243.
21. Picard, J. A.; O'Brien, P. M.; Sliskovic, D. R.; Anderson, M. K.; Bousley, R. F.; Hamelehle, K. L.; Krause, B. R.; Stanfield, R. L. *J. Med. Chem.* **1996**, *39*, 1243–1252.
22. Bryuzgin, A. A.; Levkovskaya, G. G.; Mirskova, A. N. *Zh. Org. Khim.* **1994**, *30*, 63–65.
23. (a) Sarges, R.; Kuhla, D. E.; Wiedermann, H. E.; Mayhew, D. A. *J. Med. Chem.* **1976**, *19*, 695–709. (b) McManus, J. M.; McFarland, J. W.; Gerber, C. F.; McLamore, W. M.; Laubach, G. D. *J. Med. Chem.* **1965**, *8*, 766–776. (c) McManus, J. M. *J. Med. Chem.* **1966**, *9*, 967–968. (d) McManus, J. M.; Gerber, C. F. *J. Med. Chem.* **1966**, *9*, 256–257.
24. (a) Fahmy, M. A. H.; Fukuto, T. R. (University of California, Berkeley, USA). Eur. Pat. Appl. Ep, 1980, 36. (b) Levitt, G. US Patent 4,786,311.
25. Otto, E., Duerckheimer, W., Muschaweck, R. (Hoechst A.-G., Fed. Rep. Ger.). Ger. Offen. De, 1975, 18.
26. For recent reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013–3043. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (e) Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633.
27. (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
28. Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077.
29. (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041. (b) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511. (c) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
30. An unidentifiable byproduct presumed to be a cross-metathesis dimer was formed in significant amounts ($\sim$30%). The difficulty in confirming such a product is the result of carbamate C–N bond rotamers that occur in two-fold vis-à-vis the cross-metathesized product. Proton NMR experiments on these sulfamoyl carbamates were conducted at 50 °C in order to attempt to overcome the rotational barrier but were unsuccessful.
31. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
32. Ahn, Y.; Yang, K.-L.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411–1413.
33. Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639–1642.
34. Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

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Gold catalysis: five new bonds by a domino hydroarylation/cycloisomerization

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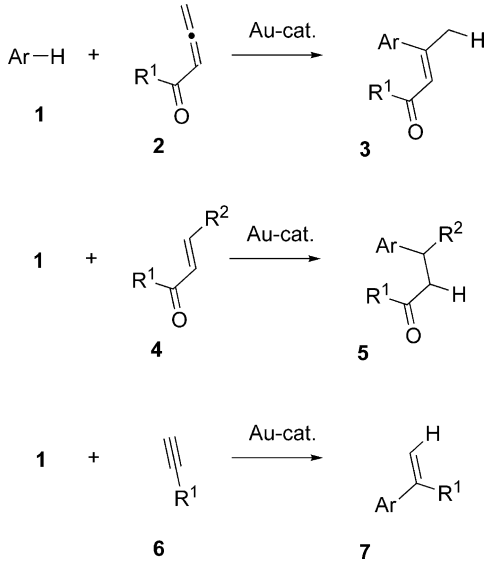
Abstract—The gold-catalyzed reaction of furans possessing one unsubstituted 2-position with ethynyl vinyl ketones bearing alkyl groups on the alkene led to interesting phenols of the indan-1-one-type by a domino hydroarylation/cycloisomerization. The yields were moderate but higher than in longer routes described before. With ethynyl vinyl ketones that have an aryl substituent, the chemoselectivity of the reaction was different. Then products from an initial reaction at the ethynyl group were observed.

1. Introduction

Gold-catalyzed organic reactions are still quite rare but an increasing number of remarkable chemical transformations have been published in the past few years.[1–5] The gold-catalyzed hydroarylation of allenyl ketones **2** and vinyl ketones **4** was first reported in 2000 (Scheme 1).[6] Electron-rich furans were used as heterocyclic aryl compounds, $AuCl_3$ was the catalyst. Recently, the analogous reaction of indoles with vinyl ketones, using $Na[AuCl_4]\cdot 2H_2O$ as the catalyst, was observed.[7] Work by Dyker, Muth and us showed that other arenes like electron-rich benzene-derivatives and azulenes also react under similar conditions.[8] At the same time, Reetz and Sommer achieved hydroarylation reactions with alkynes **6** (Scheme 1); $AuCl_3$ catalysts in combination with two equivalents $AgSbF_6$ were most effective for the reactions of arylethynes, acetylene carboxylic acid esters delivered the best results with (trialkylphosphane)- or (triarylphosphane)gold(I)-chloride and silver(I) or $BF_3\cdot OEt_2$ as the co-catalyst.[9] With internal electron-poor alkynes no reaction was observed. Shi and He reported analogous reactions of electron-rich arenes with acceptor-substituted alkenes and alkynes to be catalyzed by $AuCl_3$ and three equivalents of AgOTf even under solvent-free conditions.[10] There non-terminal alkynes reacted only in intramolecular reactions. While in all these reactions it is uncertain whether a C–H activation is involved or the C–C double or triple bonds are activated by gold as a carbophilic Lewis acid and then attacks the arene in an electrophilic manner, recent work of Shi and He, reporting an unusual regioselectivity in the gold-catalyzed reaction of epoxides and arenes[11] and a S_N2-like reaction mode in the gold-catalyzed alkylation of primary sulfonate esters with arenes,[12] points towards a contribution of arylgold species.



Scheme 1. Different substrates for the gold-catalyzed hydroarylation.

No matter what the exact mechanism of these hydroarylations in each of the examples discussed above is, a domino reaction[13] of such a hydroarylation of **9** with furans like **8** and the gold-catalyzed phenol synthesis would be a synthetically useful reaction. The phenol synthesis is an

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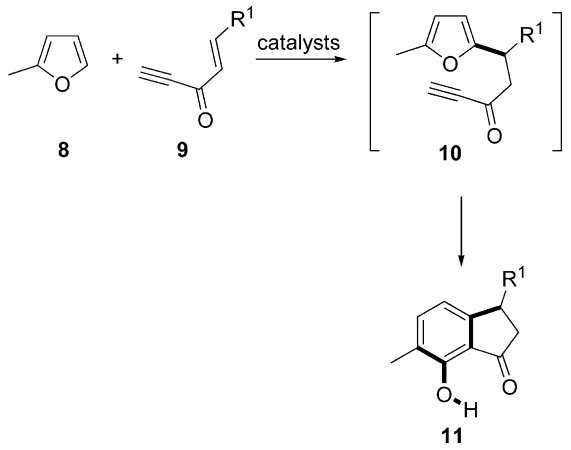


Scheme 2. Five new bonds (shown in bold) are formed in the domino hydroarylation/cycloisomerization.

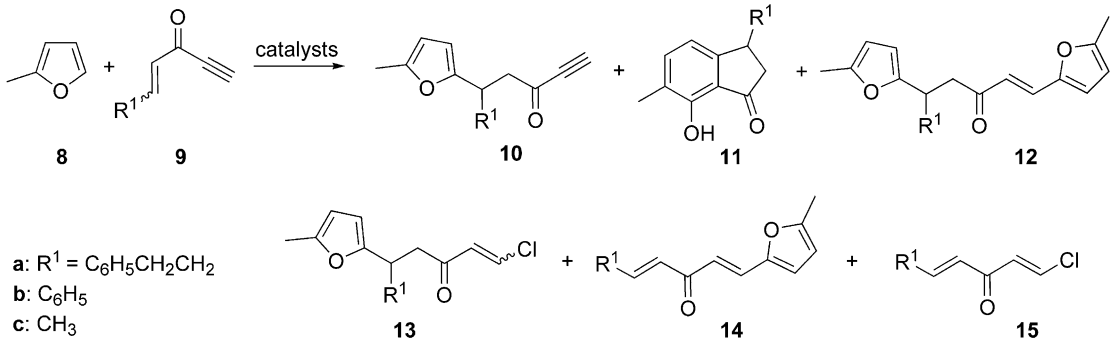
efficient method for the synthesis of highly substituted 5- or 6-ring annelated arenes like **11** from **10**.[14–18]

For a combination of these two reaction modes, ethynyl vinyl ketones must first undergo a intermolecular hydroarylation with furans at the vinyl moiety and then the furan must react intramolecularly with the remaining alkynone (Scheme 2). The competition for the enone and the alkynone subunit of these substrates in the hydroarylation has not been investigated yet. Here we report our results on this chemoselectivity problem and the combination of the two gold-catalyzed reactions.

2. Results and discussion

For the investigation we used three different ethynyl vinyl ketones **9a–c**, all easily available substrates.[19–21] Their reaction with 2-methylfuran **8** was tested first (Scheme 3, Table 1). Using 12 mol% of $AuCl_3$ in acetonitrile, the reaction of **8** with the alkyl-substituted **9a** delivered a 43% yield of the desired **11a** accompanied by a 4% yield of the bis-hydroarylation product **12a** (entry 1). The conversion was not complete, 23% of **9a** could be re-isolated. Reducing the amount of $AuCl_3$ to 5 mol% gave almost the same result, only the portion of **12a** increased (entry 2), with only 3 mol% of $AuCl_3$ the yield of **11a** dropped to 21%, 40% of **9a** were recovered (entry 3). Switching to dichloromethane gave a lower conversion due to a shorter lifetime of the catalyst (entry 4).

With the $Na[AuCl_4]\cdot 2H_2O$ catalyst in acetonitrile comparable results were obtained with different amounts of

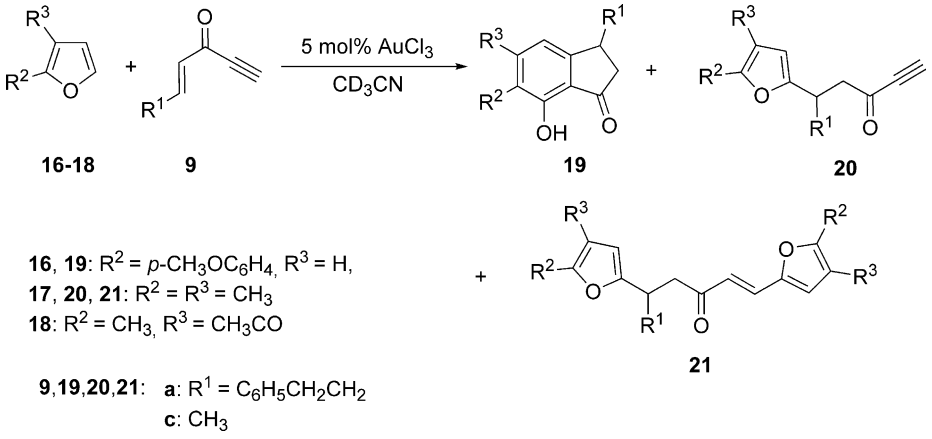


Scheme 3. Experiments with 2-methylfurans and different catalysts.

Table 1. Results of the addition reactions of 5-methyl-furan (**8**) to en-yn-ketone (**9**)

Entry	9	Cat.[a] (mol%)	Temp.	Solvent	Time (h)	Recovered starting material	Product (yield, %)			
1	**9a**	i (12)	rt	CD_3CN	0.3	**9a** (23)	**11a** (43)	**12a** (4)		
2	**9a**	i (5)	rt	CD_3CN	0.3	**9a** (23)	**11a** (45)	**12a** (11)		
3	**9a**	i (3)	rt	CD_3CN	0.3	**9a** (40)	**11a** (21)	**12a** (12)		
4	**9a**	i (5)	rt	CD_2Cl_2	16	**9a** (49)	**11a** (16)	**12a** (6)		
5	**9a**	ii (12)	rt	CD_3CN	36	**9a** (25)	**11a** (33)	**12a** (10)	**15a** (8)	
6	**9a**	ii (10)	50 °C	CD_3CN	16	**9a** (9)	**11a** (35)	**12a** (10)	**15a** (12)	
7	**9a**	ii (5)	rt	CH_3CN	72	**9a** (25)	**11a** (30)	**12a** (8)	**15a** (9)	**13a** (1)
8	**9a**	ii (5)	50 °C	CD_3CN	16	**9a** (23)	**11a** (32)	**12a** (10)	**15a** (4)	
9	**9a**	iii (10)	rt	CD_3CN	24	No reaction				
10	**9a**	iii (10)	50 °C	CD_3CN	16	Polymerization of **9a**				
11	**9a**	iv (10)	50 °C	CD_3CN	16	No reaction				
12	**9b**	i (5)	rt	CD_3CN	16	**9b** (14)	**14b** (45)	**15b** (7)		
13	**9b**	i (10)	rt	CD_3CN	16	**9b** (18)	**14b** (54)	**15b** (4)		
14	**9b**	ii (10)	50 °C	CD_3CN	14	**9b** (n.o.)	**14b** (46)	**15b** (20)		
15	**9b**	ii (5)	rt	CD_3CN	36	**9b** (10)	**14b** (41)	**15b** (12)		
16	**9c**	i (5)	rt	CD_3CN	0.5	**9c** (48)	**11c** (15)	**12c** (8)	**10c** (19)	
17	**9c**	i (2.3)	0 °C	CH_2Cl_2	7	**9c** (−)	**11c** (43)	**12c** (22)		
18	**9c**	ii (5)	rt	CD_3CN	40	**9c** (−)	**11c** (33)	**12c** (13)	**13c** (12)	

[a] i $AuCl_3$; ii. $Na[AuCl_4]\cdot 2H_2O$; iii. $PdCl_2(MeCN)_2$; iv. $PtCl_2(MeCN)_2$.



Scheme 4. Experiments with different other furans and $AuCl_3$.

Table 2. Results of the addition reactions of other furan derivatives (**16–18**) to en-yn-one (**9**)

Entry	9	Furans	Temp.	Time(h)	Product (yield, %)	
1	**9a**	**16**	rt	0.3	**16** (28)	**19a** (22)
2	**9c**	**17**	rt	0.3	**20c** (6)	**21c** (18)
3	**9c**	**18**	50 °C	24	No reaction	

catalysts and at different temperatures (entries 5–8). The most significant difference is the slower reaction and the occurrence of two new side-products **15a**, the product of a hydrochlorination[22] of the alkyne, and **13a**, the product of a hydrochlorination of the alkyne and a hydroarylation of the alkene.

The tests of $PdCl_2(MeCN)_2$ (entry 9 and 10) and $PtCl_2(MeCN)_2$ (entry 11) were completely unsuccessful, no reaction at rt or a polymerization of **9a** at higher temperature were the outcome. This again shows the unique catalytic activity of the Au(III) catalyst.

The use of the phenyl-substituted **9b** completely changed the chemoselectivity of the reaction. With both $AuCl_3$ (entry 12 and 13) and $Na[AuCl_4]\cdot 2H_2O$ (entry 14 and 15) a hydroarylation of the alkyne leading to **7** was the major pathway, it was accompanied by the hydrochlorination to **15b**.

Then **9c** was used. In the reaction with 5 mol% $AuCl_3$ at rt the catalyst was deactivated fast, 48% of **9c** could be reisolated (entry 16). Furthermore, **11c**, **12c** and even **10c**, the product of the hydroarylation of the alkene and thus the precursor of **11c**, were isolated. The deactivation could be avoided by reducing the amount of catalyst and conducting the reaction at 0 °C; still the 43% yield of **11c** were accompanied by 22% of **12c** (entry 17). $Na[AuCl_4]\cdot 2H_2O$ led to lower yields, another side-reaction was the hydrochlorination of the alkyne and the hydroarylation of the olefin to **13c** (entry 18). This reaction to **11c** is a formal total synthesis of Jungianol,[17] and even though a yield of 43% (corresponding to 66% for each of the two one-pot reactions, overall five new bonds were formed!) sounds not too impressive, it significantly shortened the previous route, which in the three steps leading to **11c** only delivered a 42% yield.

These reactions clearly show that with alkyl substituents on the alkene, the one-pot combination of a hydroarylation and a cycloisomerization is possible. The isolation of **11** and **12** and the absence of **14** with $AuCl_3$ suggest that the olefin in the substrates **9** reacts faster under these conditions. The absence of **10** (with the exception of entry 16) shows that the intramolecular cycloisomerization step is faster than the hydroarylation. With the *aryl* substituent on the alkene on the other hand, the alkyne unit is more reactive, **14** and **15** are formed.

Finally, we investigated other furans (Scheme 4, Table 2). 2-Methoxyphenylfuran **16** with **9a** and $AuCl_3$ led to a 22% yield of **19a** (entry 1). When using the 2,3-dimethylfuran **17** and **9c**, 18% of the alkynone **21c** was isolated (hydroarylation of the alkene, entry 2). The side-product was the di-furylated **20c** (6%). The acceptor-substituted 2-methyl-3-acetylfuran **18** and **9c** did not react (entry 3).

3. Conclusion

This investigation provides a proof of principle that a domino hydroarylation/cycloisomerization is successful. The yields are relatively low, but already comparable to the yields from known multistep-routes to these substrates. Nevertheless, more active catalysts are necessary, a complete conversion cannot be achieved with the simple salt $AuCl_3$. The so far barely explored influence of ligands on the activity and selectivity of gold catalysts will probably be the key to more efficient catalysts.

4. Experimental

4.1. General procedure

To the mixture of 0.1 mmol of both **8** and **9** in about 500 mg

of CD_3CN, the catalyst was added as a solid. The reactions were carried out at the temperature given in the Tables and monitored by NMR. The time listed in the Tables is the time when no further progress was observed. Then the solvent was removed and the residue was worked up by column chromatography on silica gel using mixtures of petrol ether (PE) and ethyl acetate (EA) as eluent.

4.1.1. 7-Phenyl-hept-4-en-1-yn-3-ol. R_f (PE/EA, 9:1)=0.15. IR (film): ν=3286 cm^{-1}, 3026, 2926, 1496, 1453, 1082, 1006, 965, 746, 698, 653. ^1H NMR (CD_3CN, 500 MHz): δ=2.38–2.43 (m, 2H), 2.57 (s, 1H), 2.72–2.75 (m, 2H), 4.84 (br s, 1H), 5.65 (dm, 1H, $^3J_{H,H}$=15.8 Hz), 5.94–6.00 (m, 2H), 7.18–7.22 (m, 3H), 7.28–7.31 (m, 2H). ^{13}C NMR (CD_3CN, 126 MHz): δ=34.1 (t), 35.6 (t), 63.1 (d), 74.5 (s), 83.6 (d), 126.4 (d), 128.76 (d, 2C), 128.83 (d, 2C), 129.5 (d), 133.8 (d), 141.9 (s). MS (EI): *m/z* (%): 185 (6) [$(M-H)^+$], 91 (100). $C_{13}H_{14}O$ (186.3): calcd C 83.83, H 7.58; found C 83.34, H 7.63.

4.1.2. (4*E*)-7-Phenyl-hept-4-en-1-yn-3-one (9a) from the oxidation of 7-phenyl-hept-4-en-1-yn-3-ol. R_f (PE/EA, 8:2)=0.34. IR (film) ν=3260 cm^{-1}, 3027, 2928, 2096, 1644, 1626, 1496, 1453, 1227, 969, 745, 697, 664, 648. ^1H NMR (CD_3CN, 500 MHz): δ=2.62–2.67 (m, 2H), 2.83–2.86 (m, 2H), 3.70 (s, 1H), 6.18 (dm, 1H, $^3J_{H,H}$=15.8 Hz), 7.21–7.26 (m, 3H), 7.29–7.34 (m, 3H). ^{13}C NMR (CD_3CN, 126 MHz): δ=33.0 (t), 33.4 (t), 78.7 (d), 79.5 (s), 125.6 (d), 127.9 (d, 2C), 128.0 (d, 2C), 131.5 (d), 140.5 (s), 154.6 (d), 177.1 (s). MS (EI): *m/z* (%): 184 (4) [M^+], 91 (100). $C_{13}H_{12}O$ (184.2): calcd C 84.75, H 6.57; found C 84.70, H 6.58.

4.1.3. Hex-4-en-1-yn-3-one (9c).[23] ^1H NMR ($CDCl_3$, 500 MHz): δ=2.00 (dd, 3H, $^3J_{H,H}$=6.9 Hz, $^4J_{H,H}$=1.4 Hz), 3.21 (s, 1H), 6.21 (dm, 1H, $^3J_{H,H}$=15.6 Hz), 7.25–7.30 (m, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=18.6 (q), 78.9 (d), 79.7 (s), 133.5 (d), 151.1 (d), 177.7(s).

4.1.4. 5-(5-Methyl-2-furyl)-hex-1-yn-3-one (10c). This compound has been reported earlier.[13]

4.1.5. 7-Hydroxy-6-methyl-3-(2-phenylethyl)-indan-1-one (11a). R_f (PE/EA, 8:2)=0.43. IR (film): ν=3027 cm^{-1}, 2924, 1674, 1628, 1498, 1455, 1437, 1332, 1286, 1252, 1097, 699, 669, 646. ^1H NMR ($CDCl_3$, 500 MHz): δ=1.77–1.85 (m, 1H), 2.18–2.26 (m, 4H, including s at 2.24 with 3H), 2.45 (dd, 1H, $^2J_{H,H}$=19.1 Hz, $^3J_{H,H}$=3.2 Hz), 2.69–2.74 (m, 2H), 2.91 (dd, 1H, $^2J_{H,H}$=19.1 Hz, $^3J_{H,H}$=11.7 Hz), 3.34–3.36 (m, 1H), 6.87 (d, 1H, $^3J_{H,H}$=7.6 Hz), 7.19–7.22 (m, 3H), 7.29–7.32 (m, 2H), 7.34 (d, 1H, $^3J_{H,H}$=7.6 Hz), 9.23 (s, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=14.5 (q), 34.2 (t), 37.9 (t), 38.0 (d), 43.3 (t), 116.2 (d), 122.2 (s), 123.4 (s), 126.4 (d), 128.7 (d, 2C), 128.9 (d, 2C), 139.2 (d), 141.7 (s), 155.6 (s), 156.5 (s), 209.6 (s). MS (EI): *m/z* (%): 266 (18) [M^+], 91 (100). $C_{18}H_{18}O_2$ (266.3): calcd C 81.17, H 6.81; found C 80.80, H 6.84.

4.1.6. 1,5-bis-(5-Methyl-2-furyl)-7-phenylhept-1-en-3-one (12a). R_f (PE/EA, 8:2)=0.36. ^1H NMR ($CDCl_3$, 500 MHz): δ=1.94–2.01 (m, 2H), 2.29 (s, 3H), 2.38 (s, 3H), 2.56–2.64 (m, 2H), 2.84 (dd, 1H, $^2J_{H,H}$=15.8 Hz, $^3J_{H,H}$=7.3 Hz), 3.00 (dd, 1H, $^2J_{H,H}$=15.8 Hz, $^3J_{H,H}$=7.0 Hz), 3.36–3.39 (m, 1H), 5.87 (d, 1H, $^3J_{H,H}$=2.2 Hz), 5.96 (d, 1H, $^3J_{H,H}$=2.9 Hz), 6.12 (d, 1H, $^3J_{H,H}$=3.0 Hz), 6.53 (d, 1H, $^3J_{H,H}$=15.7 Hz), 6.57 (d, 1H, $^3J_{H,H}$=3.1 Hz), 7.17–7.36 (m, 6H). MS (EI): *m/z* (%): 348 (98) [M^+], 212 (26), 199 (30), 135 (100), 91 (21).

4.1.7. 1,5-bis-(5-Methyl-2-furyl)-hex-1-en-3-one (12c). R_f (PE/EA, 9:1)=0.43. IR (film): ν=2925 cm^{-1}, 1695, 1682, 1613, 1569, 1369, 1021, 781. ^1H NMR ($CDCl_3$, 500 MHz): δ=1.27 (d, 3H, $^3J_{H,H}$=6.9 Hz), 2.25 (s, 3H), 2.36 (s, 3H), 2.69 (dd, 1H, $^2J_{H,H}$=15.6 Hz, $^3J_{H,H}$=8.5 Hz), 3.01 (dd, 1H, $^2J_{H,H}$=15.6 Hz, $^3J_{H,H}$=5.6 Hz), 3.38–3.42 (m, 1H), 5.83 (d, 1H, $^3J_{H,H}$=3.0 Hz), 5.87 (d, 1H, $^3J_{H,H}$=3.0 Hz), 6.10 (d, 1H, $^3J_{H,H}$=3.1 Hz), 6.56 (d, 1H, $^3J_{H,H}$=3.3 Hz), 6.56 (d, 1H, $^3J_{H,H}$=15.6 Hz), 7.25 (d, 1H, $^3J_{H,H}$=15.8 Hz). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=13.9 (q), 14.3 (q), 19.3 (q), 29.9 (d), 47.3 (t), 104.8 (d), 106.1 (d), 109.6 (d), 118.0 (d), 122.3 (d), 129.3 (d), 150.1 (s), 150.8 (s), 156.2 (s), 157.8 (s), 198.9 (s). MS (EI): *m/z* (%): 258 (50) [M^+], 135 (61), 122 (53), 109 (100), 95 (24).

4.1.8. 1-Chloro-5-(5-methyl-2-furyl)-7-phenyl-hept-1-en-3-one (13a). R_f (PE/EA, 8:2)=0.48. IR (film): ν=3027 cm^{-1}, 2926, 1659, 1626, 1584, 1496, 1454, 1356, 1198, 1111, 1080, 972, 854, 711, 664. ^1H NMR ($CDCl_3$, 500 MHz): δ=1.81–1.90 (m, 2H), 2.19 (s, 3H), 2.45–2.51 (m, 2H), 2.66 (dd, 1H, $^2J_{H,H}$=16.0 Hz, $^3J_{H,H}$=6.8 Hz), 2.83 (dd, 1H, $^2J_{H,H}$=16.0 Hz, $^3J_{H,H}$=7.4 Hz), 3.18–3.21 (m, 1H), 5.78 (d, 1H, $^3J_{H,H}$=2.8 Hz), 5.85 (d, 1H, $^3J_{H,H}$=2.9 Hz), 6.35 (d, 1H, $^3J_{H,H}$=13.5 Hz), 7.06–7.26 (m, 6H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=14.0 (q), 33.8 (t), 34.9 (d), 35.8 (t), 46.1 (t), 106.2 (d), 107.0 (d), 126.2 (d), 128.7 (d, 2C), 128.8 (d, 2C), 132.9 (d), 137.2 (d), 142.2 (s), 151.2 (s), 154.8 (s), 196.3 (s). MS (EI): *m/z* (%): 302 (12) [M^+], 267 (16), 91 (100). HRMS (70 eV): $C_{18}H_{19}ClO_2$: calcd 302.1074; found 302.1074.

4.1.9. 1-Chloro-5-(5-methyl-2-furyl)-hex-1-en-3-one (13c) *trans*-13c. R_f (PE/EA, 9:1)=0.55. IR (film): ν=2924 cm^{-1}, 2926, 1721, 1682, 1586, 1366, 1173, 1111, 1088, 1028, 943, 843, 789, 679. ^1H NMR ($CDCl_3$, 500 MHz): δ=1.25 (d, 3H, $^3J_{H,H}$=6.9 Hz), 2.24 (s, 3H), 2.63 (dd, 1H, $^2J_{H,H}$=16.0 Hz, $^3J_{H,H}$=8.1 Hz), 2.94 (dd, 1H, $^2J_{H,H}$=16.0 Hz, $^3J_{H,H}$=5.8 Hz), 3.22–3.38 (m, 1H), 5.83 (d, 1H, $^3J_{H,H}$=3.1 Hz), 5.85 (d, 1H, $^3J_{H,H}$=3.0 Hz), 6.49 (d, 1H, $^3J_{H,H}$=13.8 Hz), 7.27 (d, 1H, $^3J_{H,H}$=14.0 Hz). MS (EI): *m/z* (%): 210 (37), 212 (13) [$M-2H]^+$, 195 (40), 197 (13), 149 (11), 89 (40), 87 (13). *cis*-**13c**: R_f (PE/EA, 9:1)=0.60. IR (film): ν=2024 cm^{-1}, 1671, 1585, 1365, 1253, 1085, 943, 856, 677. ^1H NMR ($CDCl_3$, 500 MHz): δ=1.25 (d, 3H, $^3J_{H,H}$=7.0 Hz), 2.24 (s, 3H), 2.77 (dd, 1H, $^2J_{H,H}$=16.6 Hz, $^3J_{H,H}$=8.0 Hz), 3.05 (dd, 1H, $^2J_{H,H}$=16.6 Hz, $^3J_{H,H}$=5.7 Hz), 3.38–3.42 (m, 1H), 5.84 (d, 1H, $^3J_{H,H}$=3.0 Hz), 5.86 (d, 1H, $^3J_{H,H}$=3.0 Hz), 6.36 (d, 1H, $^3J_{H,H}$=8.3 Hz), 6.59 (d, 1H, $^3J_{H,H}$=8.3 Hz). MS (EI): *m/z* (%): 210 (80), 212 (27) [$M-2H]^+$, 195 (100), 197 (33), 175 (24), 149 (28), 89 (54), 87 (28), 43 (60).

4.1.10. 1-(5-Methyl-2-furyl)-5-phenylpenta-1,4-dien-3-one (14b). R_f (PE/EA, 9:1)=0.26. IR (film): ν=2921 cm^{-1}, 1657, 1616, 1565, 1522, 1447, 1372, 1333, 1198, 1176, 1100, 1022, 975, 792, 753, 696. ^1H NMR

($CDCl_3$, 500 MHz): δ=2.38 (s, 3H), 6.12 (d, 1H, $^3J_{H,H}$=3.1 Hz), 6.60 (d, 1H, $^3J_{H,H}$=3.2 Hz), 6.92 (d, 1H, $^3J_{H,H}$=15.5 Hz), 6.99 (d, 1H, $^3J_{H,H}$=15.9 Hz), 7.39–7.43 (m, 3H), 7.45 (d, 1H, $^3J_{H,H}$=15.6 Hz), 7.58–7.60 (m, 2H), 7.70 (d, 1H, $^3J_{H,H}$=16.0 Hz). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=14.3 (q), 106.2 (d), 109.7(d), 118.4 (d), 121.2 (d), 126.5 (d), 128.6 (d, 2C), 129.2 (d, 2C), 129.9 (d), 130.6 (d), 135.2 (s), 142.9 (d), 150.4 (s), 156.2 (s), 188.8 (s). MS (EI): *m/z* (%): 238 (59) [M^+], 131 (100), 146 (86), 103 (73). HRMS (70 eV): $C_{16}H_{14}O_2$: calcd 238.0994; found 238.0994.

4.1.11. 1-Chloro-7-phenylhepta-1,4-dien-3-one (15a). R_f (PE/EA, 8:2)=0.31. IR (film): ν=2923 cm^{-1}, 2859, 1717, 1679, 1580, 1563, 1518, 1495, 1453, 1216, 1164, 1098, 1026, 938, 838, 785, 747, 698. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.50–2.54 (m, 2H), 2.72–2.75 (m, 2H), 6.25 (d, 1H, $^3J_{H,H}$=15.8 Hz), 6.45 (d, 1H, $^3J_{H,H}$=8.3 Hz), 6.53 (d, 1H, $^3J_{H,H}$=8.3 Hz), 6.86 (dt, 1H, $^3J_{H,H}$=15.8 Hz, 7.0 Hz), 7.07–7.15 (m, 3H), 7.19–7.24 (m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=34.7 (t, 2C), 126.7 (d), 128.1 (d), 128.7 (d), 128.8 (d, 2C), 128.9 (d, 2C), 131.3 (d), 141.0 (s), 149.1 (d), 189.2 (s). MS (EI): *m/z* (%): 220 (0.4) [M^+], 185 (41), 91 (100). HRMS (70 eV): $C_{13}H_{13}ClO$: calcd 220.0655; found 220.0653.

4.1.12. 1-Chloro-5-phenylpenta-1,4-dien-3-one (15b). R_f (PE/EA, 9:1)=0.40. IR (film): ν=3073 cm^{-1}, 1648, 1597, 1198, 981, 943. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=6.85 (d, 1H, $^3J_{H,H}$=16.0 Hz), 6.90 (d, 1H, $^3J_{H,H}$=13.3 Hz), 7.40–7.44 (m, 4H), 7.57–7.59 (m, 2H), 7.66 (d, 1H, $^3J_{H,H}$=16.0 Hz). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=125.2 (d), 128.8 (d, 2C), 129.4 (d, 2C), 131.3 (d), 131.4 (d), 134.6 (s), 137.4 (d), 145.0 (d), 186.7 (s). MS (EI): *m/z* (%): 192 (88) [M^+], 194 (28), 191 (100), 193 (40), 157 (24), 131 (26), 103 (26), 77 (22). HRMS (70 eV): $C_{11}H_9ClO$: calcd 192.0342; found 192.0339.

4.1.13. 7-Hydroxy-6-(4-methoxyphenyl)-3-(2-phenylethyl)-indan-1-one (19a). R_f (PE/EA, 8:2)=0.35. ^{1}H NMR (CD_3CN, 500 MHz): δ=1.80–1.88 (m, 1H), 2.25–2.32 (m, 1H), 2.56 (dd, 1H, $^2J_{H,H}$=19.1 Hz, $^3J_{H,H}$=3.2 Hz), 2.76 (t, 2H, $^3J_{H,H}$=7.5 Hz), 2.97 (dd, 1H, $^2J_{H,H}$=19.2 Hz, $^3J_{H,H}$=7.3 Hz), 3.40–3.44 (m, 1H), 3.84 (s, 3H), 7.01 (d, 2H, $^3J_{H,H}$=8.8 Hz), 7.14 (d, 1H, $^3J_{H,H}$=7.7 Hz), 7.20–7.23 (m, 1H), 7.28–7.34 (m, 4H), 7.56 (d, 2H, $^3J_{H,H}$=8.8 Hz), 7.63 (d, 1H, $^3J_{H,H}$=7.7 Hz), 9.63 (s, 1H). ^{13}C NMR (CD_3CN, 126 MHz): δ=33.4 (t), 36.9 (t), 37.7 (d), 42.4 (t), 54.9 (q), 113.6 (d, 2C), 116.8 (d), 122.6 (s), 125.8 (d), 125.9 (s), 128.32 (d, 2C), 128.34 (d, 2C), 128.5 (s), 130.1 (d, 2C), 138.0 (d), 142.0 (s), 153.8 (s), 158.1 (s), 159.0 (s), 209.8 (s).

4.1.14. 5-(4,5-Dimethyl-2-furyl)-hex-1-yn-3-one (20c). R_f (PE/EA, 95:5)=0.40. IR (film): ν=3250 cm^{-1}, 2976, 2929, 2092, 1765, 1682, 1570, 1121. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.25 (d, 3H, $^3J_{H,H}$=6.9 Hz), 1.88 (s, 3H), 2.15 (s, 3H), 2.67 (dd, 1H, $^2J_{H,H}$=16.4 Hz, $^3J_{H,H}$=8.1 Hz), 2.98 (dd, 1H, $^2J_{H,H}$=16.4 Hz, $^3J_{H,H}$=6.2 Hz), 3.21 (s, 1H), 3.38–3.44 (m, 1H), 5.77 (s, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=10.2 (q), 11.6 (q), 19.2 (q), 29.4 (d), 59.5 (t), 79.0 (d), 81.8 (s), 106.8 (d), 114.5 (s), 146.2 (s), 155.3 (s), 186.3 (s). MS (EI): *m/z* (%): 190 (27) [M^+], 123 (100). HRMS (70 eV): $C_{12}H_{14}O_2$: calcd 190.0994; found 190.0994.

4.1.15. 1,5-bis(4,5-Dimethyl-2-furyl)-hex-1-en-3-one (21c). R_f (PE/EA, 95:5)=0.42. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.23 (d, 3H, $^3J_{H,H}$=7.0 Hz), 1.87 (s, 3H), 1.95 (s, 3H), 2.15 (s, 3H), 2.26 (s, 3H), 2.66 (dd, 1H, $^2J_{H,H}$=15.7 Hz, $^3J_{H,H}$=8.5 Hz), 2.97 (dd, 1H, $^2J_{H,H}$=15.7 Hz, $^3J_{H,H}$=5.6 Hz), 3.33–3.39 (m, 1H), 5.76 (s, 1H), 6.45 (s, 1H), 6.52 (d, 1H, $^3J_{H,H}$=15.6 Hz), 7.20 (d, 1H, $^3J_{H,H}$=15.7 Hz). MS (FAB+): *m/z* (%): 285 (23) [$M-1$]$^+$, 189 (20).

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References and notes

1. Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51–65.
2. Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3–9.
3. (a) Dyker, G. *Angew. Chem.* **2000**, *112*, 4407–4409. (b) *Angew. Chem.* **2000**, *39*, 4237–4239.
4. Dyker, G. In *Organic synthesis highlights V*; Schmalz, H. G., Wirth, T., Eds.; Wiley-VCH: Weinheim, 2003; pp 48–55.
5. (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem.* **2000**, *112*, 2382–2385. (b) *Angew. Chem. Int., Ed.* **2000**, *39*, 2285–2288.
6. For some remarkable recent examples, see: (a) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546–2547. (b) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859.
7. Arcadi, A.; Bianchi, G.; Chiarini, M.; D'Anniballe, G.; Marinelli, F. *Synlett* **2004**, 944–950.
8. Dyker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L. *Adv. Synth. Catal.* **2003**, *345*, 1247–1252.
9. Reetz, M. T.; Sommer, K.; Eur *J. Org. Chem.* **2003**, 3485–3496.
10. Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669–3671.
11. Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964–5965.
12. Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596–13597.
13. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
14. Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.
15. Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769–3771.
16. Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Catal. Today* **2002**, *72*, 19–27.
17. Hashmi, A. S. K.; Ding, L.; Bats, J. W.; Fischer, P.; Frey, W. *Chem. Eur. J.* **2003**, 4339–4345.
18. (a) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejović, E. *Angew. Chem.* **2004**, *116*, 6707–6709. (b) *Angew. Chem. Int., Ed.* **2004**, *43*, 6545–6547.
19. Prepared in analogy to Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283–5287 and a subsequent Dess–Martin oxidation of the alcohol..
20. (a) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45–56. (b) Miller, R. D.; Reiser, O. *J. Heterocycl. Chem.*

1993, *30*, 755–764. (c) Maeda, Y.; Kakiuchi, N.; Matsumura, S.; Nishimura, T.; Kawamura, T.; Uemura, S. *J. Org. Chem.* **2002**, *67*, 6718–6724.

21. (a) Bowden, K.; Jones, E. R. H. *J. Chem. Soc.* **1946**, 52–54. (b) Crout, D. H. G.; Hassall, C. H.; Jones, T. L. *J. Chem. Soc.* **1964**, 2187–2194. (c) Lee, P. H.; Park, J.; Lee, K.; Kim, H.-C. *Tetrahedron Lett.* **1999**, *40*, 7109–7112.
22. In order to make the application as simple as possible, whenever possible we work in normal, water-containing solvents and not in absolute solvents. This explains the source of the protons.
23. (a) Bondarev, G. N.; Petrov, A. A. *J. Org. Chem. USSR (Engl. Transl.)* **1966**, *2*, 785–790. (b) *Zh. Org. Khim.* **1966**, *2*, 782–788.

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Enantioselective addition of amines to alkenoyl-*N*-oxazolidinones

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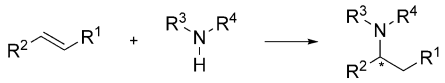
Abstract—Investigations of cationic Pd(II) complex **1** as hydroamination catalysts led to the development of highly enantioselective addition of aromatic amines to alkenoyl-*N*-oxazolidinones, with ee values up to 93%. Factors affecting the yield and selectivity of the reaction were described. Addition of substituted benzylamines to these Michael acceptors was also attempted, and was found to be reversible under catalytic conditions.

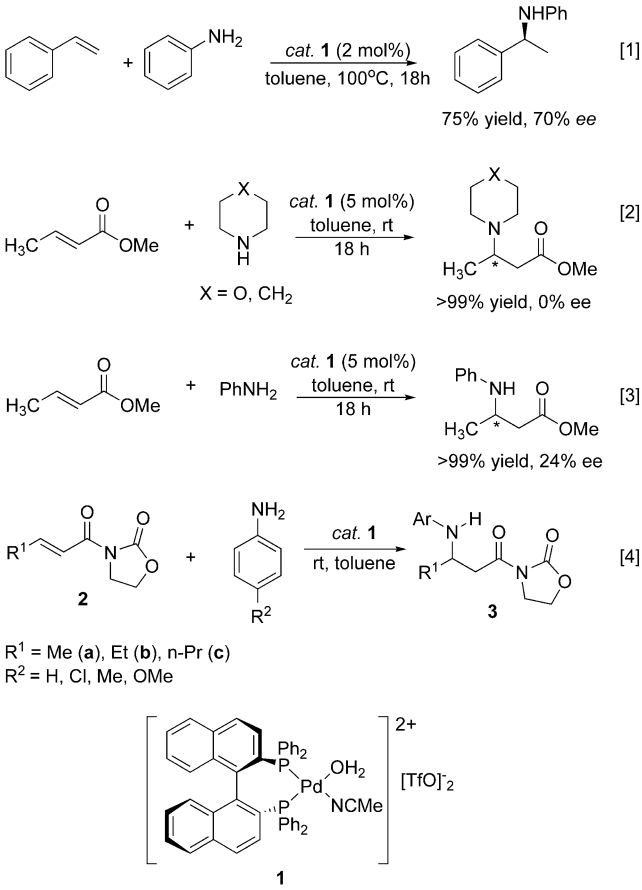
1. Introduction

The catalysed addition of N–H across C–C double bonds (hydroamination) is one of the most attractive atom-economical processes (Scheme 1). If the alkene substrate is activated towards nucleophilic attack by the presence of electron-withdrawing substituents (e.g., keto, ester or nitrile groups), the reaction is also sometimes referred to as an aza-Michael (1,4-conjugate) addition. With prochiral alkenes, the reaction poses additional challenges in regio- and enantioselectivity.



Scheme 1. Asymmetric hydroamination reaction.

Previously, we reported the development of air- and moisture-stable palladium catalysts for the hydroamination of olefins under pH neutral conditions at low catalytic loadings,[1,2] including a class of air- and moisture-stable dicationic palladium complexes that mediates the addition of a range of amines to acyclic olefins. Among these, the chiral complex $[(BINAP)Pd(solvent)]^{2+}[TfO]^{-}_{2}$ (**1**) catalyses the enantioselective addition of aniline to styrene at elevated temperatures (Scheme 2, Eq. 1).[2] With methyl crotonate, addition of cyclic and aromatic amines may be effected at room temperature (Scheme 2, Eqs. 2 and 3), but ee's were disappointingly low (no more than 24%). Introducing an achiral template on the olefin substrate, the addition of primary aromatic amines to the alkenoyl-*N*-oxazolidinones **2** at room temperature were accomplished with good enantioselectivity (Scheme 2, Eq. 4).[3] This paper will detail the course of our investigation of this latter



Scheme 2. Asymmetric hydroamination reactions catalysed by complex **1**.

Keywords: Enantioselective addition; Hydroamination; Alkenoyl-*N*-oxazolidinones.
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Table 1. Effect of solvent, catalyst loading and ratio of substrate on the hydroamination of **2a** with aniline (Scheme 2, **Eq. 4**)[a]

Entry	Catalyst loading (mol%)	**2a**: aniline	Solvent	Yield[b] (%)	ee[c] (%)
1	2	1:1.5	Toluene	25	10
2	2	1:1.5	CH_3CN	4	19
3	2	1:1.5	CH_2Cl_2	16	6
4	2	1:1.5	THF	19	1
5	5	1:1.5	Toluene	34	45
6	10	1:1.5	Toluene	48	51
7	20	1:1.5	Toluene	80	85
8	10	1:4	Toluene	45	22
9	10	1:1	Toluene	64	89
10	10	1.5:1	Toluene	93	93
11	10	1.5:1	THF	31	60

[a] Reactions were conducted in toluene at 25 °C for 18 h.
[b] Calculated by ^{1}H NMR spectroscopy.
[c] Determined by chiral HPLC (Daicel Chiralpak AD).

process, and subsequent exploration of its scope and limitations.[4]

2. Results and discussion

2.1. Effect of catalyst loading, solvent and ratio of substrates

Effects of solvent, catalyst loading and substrate ratios on the addition of aniline to **2a** were studied and results are summarised in Table 1. Employing an initial catalyst loading of 2 mol% at room temperature, the highest conversion was obtained with toluene as the solvent, but ee was low (Table 1, entry 1). In contrast, an improved ee may be obtained in acetonitrile, but the yield was extremely low (entry 2). Dichloromethane furnished low yield and ee (entry 3), whereas THF afforded practically very low enantioselectivity (entries 4 and 11). These observations led us to conclude that coordinating solvents are detrimental to the catalytic activity, hence, toluene was employed as the solvent of choice in further studies.

Unsurprisingly, increased catalyst loading from 2 to 20 mol% resulted in improvements in yield and ee of the process (entries 5–7). Although a high ee of 85% may be obtained with 20, 10 mol% of catalyst were consequently employed in the following optimisation work.

Interestingly, employing an excess of the aniline substrate has a negative effect on the enantioselectivity of the reaction (entry 8). More crucially, catalyst decomposition was observed when an excess of the amine substrate was employed, leading to a poor yield of the product. Increasing the relative stoichiometry of the olefin substrate led to improvements in the turnover and selectivity (entry 9). The optimal ratio appears to be 1.5:1 where 93% yield and 93% ee were obtained (entry 10).

2.2. Reaction scope and reactivity

Having established the most favourable reaction conditions, the addition of different aromatic amines to alkenoyl oxazolidinones **2a–c** was examined (Table 2).

The addition of primary aromatic amines to crotonyl oxazolidinone **2a** generally proceeded with good yields at room temperature. In all cases, very good conversions (85–90%) were obtained in 18 h. Among the primary aromatic amines, addition of aniline proceeded with the best ee (93%, entry 1). Interestingly, the presence of an electron-withdrawing Cl substituent did not appear to alter the yield or selectivity significantly (entry 2), whereas the addition of increasingly electron-rich amines such as *p*-toluidine and *p*-anisidine gave products with significantly reduced ee values (entries 3 and 4).

Changing the substituent of the alkenoyl functionality retarded the rate of the reactions dramatically—the addition to pentenoyl oxazolidinone **2b** was considerably slower at room temperature. Performing these reactions at an elevated temperature (60 °C), modest ee of 47% was obtained for aniline (entry 5), compared with the electron rich *p*-toluidine (32% ee, entry 7). But for 4-chloroaniline, good yield and ee of 93 and 75% were obtained, respectively (entry 6). The addition of the more nucleophilic *p*-anisidine may be effected at room temperature, but enantioselectivity was low (entry 8). Extending the homology, the addition to hexenoyl oxazolidinone **2c** proceeded in even lower selectivity, ranging from 10 to 50% (entries 9–10).

The results presented above suggests there is no apparent correlation between the nucleophilicity of the amine and reactivity, as might be expected. In the addition to **2a**, aniline appears to have the same activity as *p*-chloroaniline (entries 1 and 2). On the other hand, the addition of the least nucleophilic amine to **2b** appeared to be faster than aniline and toluidine at 60 °C (entries 5–7), while at the same time, the addition of anisidine proceeded at room temperature (entry 8). A different order of activity was again observed for the addition to **2c**: *p*-chloroaniline ~ *p*-toluidine > *p*-anisidine > aniline (entries 9–12). In light of these observations, it is highly unlikely that the reactions proceed solely via Lewis-acid catalysis.

2.3. Generating the catalyst in situ

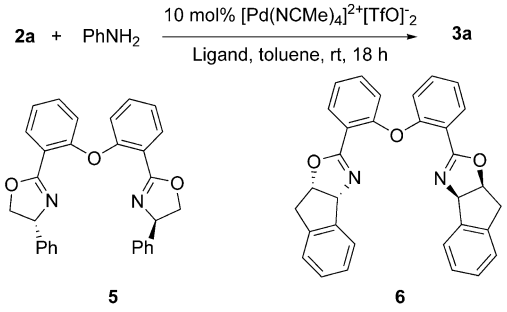
It is often possible, and more convenient, to generate active catalysts in situ from suitable catalyst precursors, as this will also greatly facilitate ligand screening and catalyst discovery. To this end, we attempted to generate catalyst **1** by mixing $[Pd(NCMe)_4]^{2+}[OTf]^-_2$ with BINAP in toluene

Table 2. Addition of anilines to α,β-unsaturated oxazolidinones (Scheme 2, **Eq. 4**)[a]

Entry	R^1	R^2	Product	*T* (°C)	Yield[b] (%)	ee[c] (%)
1	Me (**2a**)	H	**3a**	25	90	93
2	Me (**2a**)	Cl	**3b**	25	90	92
3	Me (**2a**)	Me	**3c**	25	85	68
4	Me (**2a**)	OMe	**3d**	25	85	24
5	Et (**2b**)	H	**3e**	60	70	47
6	Et (**2b**)	Cl	**3f**	60	93	75
7	Et (**2b**)	Me	**3g**	60	54	32
8	Et (**2b**)	OMe	**3h**	25	50	9
9	^{n}Pr (**2c**)	H	**3i**	60	69	50
10	^{n}Pr (**2c**)	Cl	**3j**	60	85	26
11	^{n}Pr (**2c**)	Me	**3k**	60	86	18
12	^{n}Pr (**2c**)	OMe	**3l**	60	75	10

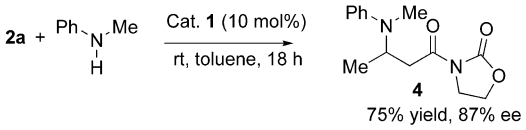
[a] Reactions were conducted in toluene with 10 mol% catalyst **1** for 18 h.
[b] Isolated yields after column chromatography.
[c] Determined by chiral HPLC (Daicel Chiralpak AD).

(metal-to-ligand ratio of 1:1), for the addition of aniline to **2a** (Scheme 3). However, the catalyst generated in this way is not as active as the isolated complex **1**—affording the product **3a** in only 57% yield with an ee of 78% after 18 h. In fact, more than 40 h were required before the reaction gave comparable results to that afforded by the isolated catalyst **1** (89% yield and 81% ee). The catalyst turnover was also found to be sensitive to the relative quantity of the ligand employed: A mere 0.2 equiv excess (i.e., 1:1.2 metal-to-ligand ratio) led to a decrease in yield and selectivity (59% yield and 65% ee after 40 h). We speculate that this is due to the formation of a catalytically less active species, such as $[Pd(BINAP)_2]^{2+}[OTf]^-_2$. Attempts were also made to generate active catalysts in situ by mixing chiral bis-oxazolidine ligands **5** and **6** and $[Pd(NCMe)_4]^{2+}[OTf]^-_2$ in a metal-to-ligand ratio of 1:1. In both cases, the addition of aniline to **2a** only gave **3a** as a racemic mixture in less than 30% yield (18 h).



Scheme 3. Generating catalysts in situ.

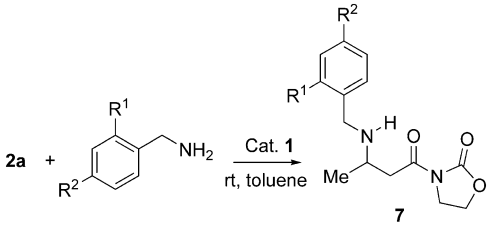
Previously, the addition of the secondary aromatic amine *N*-methyl aniline to substrate **2a** has been effected by a catalyst generated in situ from $Ni(ClO_4)_2$ and chiral bis-oxazolidine ligand **5**: the product **4** was found to have a high ee (90%), but the yield obtained after 40 h was only moderate (62%).[5] In comparison, complex **1** catalysed the addition of the secondary amine to **2a** with comparable selectivity (Scheme 4). It is somewhat surprising that the palladium complex should catalyse the addition of both primary and secondary aromatic amines with equal efficacy, given the different electronic and steric natures of these substrates.



Scheme 4. Addition of *N*-methyl aniline to **2a**.

2.4. Addition of benzylamine

Uncatalysed addition of benzylamines to **2a** occurs slowly in toluene under ambient conditions. In the presence of **1**, low to moderate yields and ee's of products **7** may be obtained in 2 h (Scheme 5, Table 3).



Scheme 5.

However, the optical activity of the reaction mixture plummets to between 3 and 7% ee after 18–48 h, whilst the conversion remained unchanged, thus, signifying that the addition of benzyl amines to **2a** is reversible under these conditions.[6]

2.5. Amine salt control

Sodeoka et al. reported an improvement in the yield and selectivity by employing trifluoromethanesulfonate salts of the aromatic amines as substrates,[4] as they postulate that the use of the free amine leads to an uncatalysed reaction. Indeed, uncatalysed slow addition of *p*-anisidine (1.5 equiv) to *N*-oxazolidinone **2a** do occur slowly in solution (12%, 18 h, 25 °C), which was inhibited when *p*-anisidine·HOTf salt was used. Nevertheless, we failed to observe any addition of the *p*-anisidine·HOTf to **2a** in the presence of catalyst **1**.

3. Conclusion

Various aspects of the enantioselective addition of amines to

Table 3. Addition of substituted benzyl amines to **2a**[a]

Entry	R^1	R^2	Product	Yield[b] (%)	ee (%)[c]
1	H	H	**7a**	57	41
2	OCH_3	OCH_3	**7b**	52	46
3	H	OCH_3	**7c**	52	39
4	Br	H	**7d**	61	7
5	H	CH_3	**7e**	47	33

[a] Reaction were conducted in toluene with 10 mol% catalyst **1** at 25 °C for 2 h.
[b] Calculated by ^{1}H NMR spectroscopy.
[c] Determined by chiral HPLC (Daicel Chiralpak AD).

N-alkenoyl oxazolidinones catalysed by the cationic diphosphine–palladium complex **1** have been presented. The catalytic activity and selectivity are much more sensitive to the steric and electronic nature of the olefin substrate. Hence, the chelating dicarbonyl moiety of the olefin substrate was identified as the key stereocontrolling element. In subsequent work, we modified the achiral template by replacing the oxazolidinone ring by a carbamate moiety (substrate **8**, Fig. 1), which led to a significant enhancement in the activity and selectivity of the conjugate addition process.[7] Recently, highly enantioselective addition of carbamates to the α'-hydroxy enone **9** (Fig. 1) was reported by Palomo et al.[8] (using Evan's bis-oxazoline copper complexes as catalysts), capitalising a hydroxyketone moiety in the olefin substrate as a mode of chelation to the metal centre, presumably promoted by the *gem*-dialkyl groups.

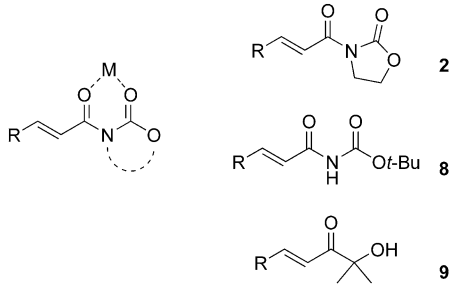


Figure 1. Olefin substrates **2**, **8** and **9** containing chelating functionalities.

Work is currently underway to discern the mechanism of these addition reactions and to examine the conjugate addition of amines to other modified olefin substrates, these will be reported in due course. Current endeavours also include the design and identification of more active and selective catalysts for other asymmetric hydroamination reactions.

4. Experimental

All manipulations were performed using standard Schlenk techniques. Dichloromethane, toluene and acetonitrile were dried over CaH_2, distilled and stored under a nitrogen atmosphere. THF was dried over Na/benzophenone. NMR spectra were recorded on a Bruker Avance 360 instrument (^{1}H at 360 MHz and ^{13}C at 90.6 MHz). The chemical shifts are reported in δ (ppm) referenced to residual protons and ^{13}C signals of deuterated chloroform. Infra-red spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer. Elemental analysis was provided by the Elemental Analysis Service at University of North London. High Resolution Mass spectra (HRMS) were recorded using Electrospray (ES) ionisation technique on a Micromass 'Q-TOF' spectrometer. Optical purity were measured using a Gilson HPLC system fitted with a Daicel Chiralpak AD column, with UV detection at 215 nm. Optical rotation values were measured on a Perkin–Elmer polarimeter 343 using a 10 cm solution cell, concentration of the samples was indicated as g/mL, given in the parenthesis. Melting points (uncorrected) were determined on an Electrothermal Gallenhamp apparatus. 3-(*E*)-2-butenoyl-1,3-oxazolidin-2-one,[9] 3-(*E*)-2-pentenoyl-2-oxazolidinone,[10] 3-(*E*)-2-hexenoyl-1,3-oxazolidin-2-one,[11] and $[Pd(NCMe)_4]^{2+}(OTf)^-{}_2$[12] were synthesised according to literature methods. All other compounds were procured from commercial sources and used as received. Palladium salts were obtained from Johnson Matthey plc through a loan agreement.

4.1. General procedure for the hydroamination of compound 2 with primary amines

0.022 g (0.020 mmol) of complex **1** and the olefin substrate **2** (0.30 mmol) were placed in a thick-walled Young's tube, which was purged with N_2. 1.0 mL of toluene and the appropriate amine (0.20 mmol) were added. The tube was sealed via a PTFE tap and the reaction mixture was stirred and heated in a thermostatic oil bath. After the appropriate time, the homogeneous solution was subjected to column chromatography (SiO_2) to furnish the product.

4.1.1. 3-(3-Anilinobutanoyl)-1,3-oxazolidin-2-one (3a). Purified by column chromatography (ether/pentane = 1:3, R_f 0.3) gave a white solid (Found: C, 62.7; H, 6.8; N, 11.0%; M^+, 248.1155. $C_{13}H_{16}N_2O_3$ requires C, 62.9; H, 6.5; N, 11.3%; M^+ 248.1161); mp 114–115 °C (from EtOAc/hexane); 86% ee (Chiral HPLC, *i*-PrOH/hexane = 20:80, 1.0 mL/min, t_{major} 14.2 min, t_{minor} 18.8 min); $[\alpha]_D^{20} = +8.1$ ($c = 0.017$ in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3363, 1771, 1694, 1605, 1392, 1140, 760, 700; δ_H (360 MHz, $CDCl_3$) 7.16 (2H, t, $J = 7.7$ Hz, Ph), 6.68 (1H, t, $J = 7.3$ Hz, Ph), 6.62 (2H, d, $J = 7.3$ Hz, Ph), 4.24–4.36 (2H, m, OCH_2), 4.08–4.17 (1H, m, NHC*H*), 3.84–3.95 (2H, m, NCH_2), 3.79 (1H, br s, PhN*H*), 3.34 (1H, dd, $J = 7.3$, 15.4 Hz, $COCH_2$), 3.00 (1H, dd, $J = 5.9$, 15.4 Hz, $COCH_2$), 1.30 (3H, d, $J = 6.4$ Hz, $CHCH_3$); δ_C (90.6 MHz, $CDCl_3$) 171.7 (CO), 153.7 CO), aromatic C [146.9, 129.3, 117.6, 113.6], 61.9 (OCH_2), 46.3 (NCH_2), 42.4 (CH), 41.4 ($COCH_2$), 21.3 (CH_3).

4.1.2. 3-[3-(4-Chlorophenylamino)butanoyl]-1,3-oxazolidin-2-one (3b). Purified by column chromatography (ether/pet. ether = 3:1, R_f 0.35) gave a white solid (Found: C, 55.1; H, 5.5; N, 9.9%; M^+, 282.0767. $C_{13}H_{15}ClN_2O_3$

requires C, 55.2; H, 5.35; N, 9.9%; M^+ 282.0771); mp 84–85 °C (from EtOAc/hexane); 92% ee (Chiral HPLC, *i*-PrOH/hexane=30:70, 1.0 mL/min, t_{major} 12.6 min, t_{minor} 16.2 min); $[\alpha]_D^{20}=-0.7$ ($c=0.017$ in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3374, 1771, 1691, 1604, 1514, 1390, 814; δ_H (360 MHz, $CDCl_3$) 7.09 (2H, d, $J=9.1$ Hz, Ph), 6.57 (2H, d, $J=9.1$ Hz, Ph), 4.29–4.40 (2H, m, OCH_2), 4.01–4.10 (1H, m, NHC*H*), 3.88–3.99 (2H, m, NCH_2), 3.83 (1H, br s, NH), 3.32 (1H, dd, $J=6.8$, 15.4 Hz, $COCH_2$), 2.98 (1H, dd, $J=5.5$, 15.4 Hz, $COCH_2$), 1.28 (3H, d, $J=6.4$ Hz, $CHCH_3$); δ_C (90.6 MHz, $CDCl_3$) 171.6 (CO), 153.7 CO), aromatic C (145.5, 129.1, 122.1, 114.6), 62.0 (OCH_2), 46.4 (NCH_2), 42.4 (CH), 41.2 ($COCH_2$), 21.0 (CH_3).

4.1.3. 3-{3-[(4-Methylphenyl)amino]butanoyl}-1,3-oxazolidin-2-one (3c). Purified by column chromatography (ether/pentane=1:1, R_f 0.18) gave a white solid (Found: C, 64.2; H, 7.05; N, 10.6%; M^+, 262.1312. $C_{14}H_{18}N_2O_3$ requires C, 64.1; H, 6.9; N, 10.7%; M^+, 262.1317); mp 70–71 °C (from EtOAc/hexane); 68% ee (Chiral HPLC, *i*-PrOH/hexane=30:70, 1.0 mL/min, t_{major} 11.7 min, t_{minor} 17.1 min); $[\alpha]_D^{20}=+0.47$ ($c=0.021$ in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1770, 1684, 1522, 1395, 1210, 810; δ_H (360 MHz, $CDCl_3$) 6.97 (2H, d, $J=8.2$ Hz, Ph), 6.55 (2H, d, $J=8.2$ Hz, Ph), 4.26–4.37 (2H, m, OCH_2), 4.03–4.12 (1H, m, NHC*H*), 3.88–3.96 (2H, m, NCH_2), 3.65 (1H, br s, NH), 3.32 (1H, dd, $J=7.3$, 15.4 Hz, $COCH_2$), 2.99 (1H, dd, $J=5.9$, 15.4 Hz, $COCH_2$), 2.22 (3H, s, PhCH_3), 1.28 (3H, d, $J=6.4$ Hz, $CHCH_3$); δ_C (90.6 MHz, $CDCl_3$) 171.8 (CO), 153.7 (CO), aromatic C [144.6, 129.8, 126.9, 113.9], 61.9 (OCH_2), 46.7 (NCH_2), 42.5 (CH), 41.4 ($COCH_2$), 21.2 ($CHCH_3$), 20.3 (PhCH_3).

4.1.4. 3-[3-[(4-Methoxyphenyl)amino]butanoyl]-1,3-oxazolidin-2-one (3d). Purified by column chromatography (ether, R_f 0.38) gave a white solid (Found: C, 60.7; H, 6.45; N, 9.9%; M^+, 278.1261. $C_{14}H_{18}N_2O_4$ requires C, 60.4; H, 6.5; N, 10.0%; M^+, 278.1267); mp 110–111 °C; $[\alpha]_D^{20}=-1.0$ ($c=0.023$ in $CHCl_3$); 24% ee (Chiral HPLC, *i*-PrOH/hexane=3:97, 1.0 mL/min, t_{major} 11.3 min, t_{minor} 22.6 min); ν_{max} (KBr)/cm^{-1} 3344, 1768, 1688, 1513, 1394, 1234, 1025, 824; δ_H (360 MHz, $CDCl_3$) 6.77 (2H, d, $J=8.9$ Hz, Ph), 6.62 (2H, d, $J=8.9$ Hz, Ph), 4.28–4.36 (2H, m, OCH_2), 4.01–4.06 (1H, m, NHC*H*), 3.90–3.95 (2H, m, NCH_2), 3.75 (3H, s, OCH_3), 3.51 (1H, br s, NH), 3.34 (1H, dd, $J=7.1$, 15.4 Hz, $COCH_2$), 2.98 (1H, dd, $J=5.7$, 15.4 Hz, $COCH_2$), 1.28 (d, 3H, $J=6.4$ Hz, $CHCH_3$); δ_C (90.6 MHz, $CDCl_3$) 171.9 (CO), 153.7 (CO), aromatic C [152.3, 141.0, 115.4, 114.8], 61.9 (OCH_2), 55.7 (OCH_3), 47.5 (NCH_2), 42.4 (CH), 41.4 ($COCH_2$), 21.2 ($CHCH_3$).

4.1.5. 3-(3-Anilinopentanoyl)-1,3-oxazolidin-2-one (3e). Purified by column chromatography (*i*-PrOH/pet. ether=1:2, R_f 0.71) gave a white solid (Found: C, 63.9; H, 6.85; N, 10.55%; M^+, 262.1312. $C_{14}H_{18}N_2O_3$ requires C, 64.1; H, 6.9; N, 10.7%; M^+, 262.1317); mp 77–78 °C (from EtOAc/hexane); 47% ee (Chiral HPLC, *i*-PrOH/hexane=8:92, 1.0 mL/min, t_{major} 24.2 min, t_{minor} 26.3 min); $[\alpha]_D^{20}=-3.8$ ($c=0.049$ in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3368, 1772, 1681, 1601, 1407, 1122, 1039, 749, 705; δ_H (360 MHz, $CDCl_3$) 7.14 (2H, t, $J=7.3$ Hz, Ph), 6.66 (1H, t, $J=7.3$ Hz, Ph), 6.61 (2H, d, $J=7.3$ Hz, Ph), 4.16–4.29 (2H, m, OCH_2), 3.90–3.98 (1H, m, NHC*H*), 3.75–3.87 (2H, m, NCH_2), 3.77 (1H, br s, PhNH), 3.30 (1H, dd, $J=8.2$, 15.0 Hz, $COCH_2$), 3.02 (1H, dd, $J=5.0$, 15.0 Hz, $COCH_2$), 1.61–1.69 (2H, m, CH_2CH_3), 0.99 (3H, t, $J=7.3$ Hz, CH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 171.9 (CO), 153.7 (CO), aromatic C [147.4, 129.2, 117.3, 113.2], 61.8 (OCH_2), 52.0 (NCH_2), 42.4 (CH), 39.5 ($COCH_2$), 28.4 (CH_2CH_3), 10.4 (CH_2CH_3).

4.1.6. 3-{3-[(4-Chlorophenyl)amino]pentanoyl}-1,3-oxazolidin-2-one (3f). Purified by column chromatography (*i*-PrOH/pet. ether=1:4, R_f 0.65) gave a white solid (Found: C, 56.75; H, 5.85; N, 9.3%; M^+, 296.0922. $C_{14}H_{17}ClN_2O_3$ requires C, 56.65; H, 5.75; N, 9.45%; M^+, 296.0928); mp 69–70 °C (from EtOAc/hexane); $[\alpha]_D^{20}=-9.8$ ($c=0.023$ in $CHCl_3$). 75% ee (Chiral HPLC, *i*-PrOH/hexane=6:94, 1.0 mL/min, t_{major} 36.4 min, t_{minor} 42.4 min); ν_{max} (KBr)/cm^{-1} 1772, 1687, 1602, 1509, 1390, 822; δ_H (360 MHz, $CDCl_3$) 7.08 (2H, d, $J=8.8$ Hz, Ph), 6.53 (2H, d, $J=8.8$ Hz, Ph), 4.24–4.36 (2H, m, OCH_2); 3.81–3.93 (3H, m, NCH_2 and NHC*H*), 3.79 (1H, br s, PhNH), 3.29 (1H, dd, $J=7.7$, 15.0 Hz, $COCH_2$), 3.00 (1H, dd, $J=5.0$, 15.0 Hz, $COCH_2$), 1.59–1.67 (2H, m, CH_2CH_3), 0.97 (3H, t, $J=7.3$ Hz, CH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 171.8 (CO), 153.7 (CO), aromatic C [146.0, 129.1, 121.8, 114.4], 61.9 (OCH_2), 52.4 (NCH_2), 42.5 (CH), 39.4 ($COCH_2$), 28.4 (CH_2CH_3), 10.4 (CH_2CH_3).

4.1.7. 3-{3-[(4-Methylphenyl)amino]pentanoyl}-1,3-oxazolidin-2-one (3g). Purified by column chromatography (ether, R_f 0.9) gave a white solid (Found: C, 65.25; H, 7.05; N, 10.0%; M^+, 276.1468. $C_{15}H_{20}N_2O_3$ requires C, 65.2; H, 7.3; N, 10.15%; M^+, 276.1474); mp 88–89 °C (from EtOAc/hexane); 32% ee (Chiral HPLC, *i*-PrOH/hexane=10:90, 1.0 mL/min, t_{major} 19.6 min, t_{minor} 26.0 min); $[\alpha]_D^{20}=-4.4$ ($c=0.011$ in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3369, 1768, 1685, 1522, 1391, 1228, 806; δ_H (360 MHz, $CDCl_3$) 6.95 (2H, d, $J=8.3$ Hz, Ph), 6.54 (1H, d, $J=8.3$ Hz, Ph), 4.20–4.33 (2H, m, OCH_2), 3.79–3.94 (3H, m, NCH_2 and NHC*H*), 3.62 (1H, br s, PhNH), 3.29 (1H, dd, $J=8.2$, 15.0 Hz, $COCH_2$), 3.01 (1H, dd, $J=5.0$, 15.0 Hz, $COCH_2$), 2.21 (3H, s, PhCH_3), 1.59–1.67 (2H, m, CH_2CH_3), 0.98 (3H, t, $J=7.3$ Hz, CH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 172.1 (CO), 153.7 (CO), aromatic C [145.1, 129.7, 126.6, 113.6], 61.9 (OCH_2), 52.6 (NCH_2), 42.5 (CH), 39.5 ($COCH_2$), 28.4 (CH_2CH_3), 20.3 (PhCH_3), 10.4 (CH_2CH_3).

4.1.8. 3-{3-[(4-Methoxypheny)amino]pentanoyl}-1,3-oxazolidin-2-one (3h). Purified by column chromatography (ether/pentane=3:1, R_f 0.39) gave a w hite solid (Found: C, 61.5; H, 6.75; N, 9.5%; M^+, 292.1417. $C_{15}H_{20}N_2O_4$ requires C, 61.6; H, 6.9; N, 9.6%; M^+, 292.1423); mp 73–74 °C (from EtOAc/hexane); 9% ee (Chiral HPLC, *i*-PrOH/hexane=30:70, 1.0 mL/min, t_{major} 12.5 min, t_{minor} 18.6 min); $[\alpha]_D^{20}=-1.5$ ($c=0.020$ in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3355, 1778, 1682, 1514, 1408, 1241, 1039, 819; δ_H (360 MHz, $CDCl_3$) 6.75 (2H, d, $J=8.9$ Hz, Ph), 6.59 (2H, d, $J=8.9$ Hz, Ph), 4.22–4.33 (2H, m, OCH_2), 3.80–3.89 (3H, m, NCH_2 and NHC*H*), 3.73 (3H, s, OCH_3), 3.73 (1H, br s, PhNH), 3.29 (1H, dd, $J=8.2$, 15.0 Hz, $COCH_2$), 2.99 (1H, dd, $J=5.0$, 15.0 Hz, $COCH_2$), 1.58–1.66 (2H, m, CH_2CH_3), 0.98 (3H, t, $J=7.3$ Hz, CH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 172.1 (CO), 153.7 (CO), aromatic C [152.1, 141.5, 115.0, 114.8], 61.9 (OCH_2), 55.8 (OCH_3), 53.3 (NCH_2), 42.5 (CH), 39.5 ($COCH_2$), 28.3 (CH_2CH_3), 10.4 (CH_2CH_3).

4.1.9. 3-(3-Anilinohexanoyl)-1,3-oxazolidin-2-one (3i). Purified by column chromatography (ether, R_f 0.83) gave a white solid (Found: C, 65.3; H, 7.45; N, 10.2%; M^+, 276.1461. $C_{15}H_{20}N_2O_3$ requires C, 65.2; H, 7.3; N, 10.15%; M^+, 276.1474); mp 53–54 °C (from EtOAc/hexane); 50% ee (Chiral HPLC, *i*-PrOH/hexane=4:96, 1.0 mL/min, t_{major} 40.7 min, t_{minor} 37.9 min); $[\alpha]_D^{20}=-0.9$ ($c=0.015$ in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3360, 1770, 1688, 1601, 1404, 1119, 755, 692; δ_H (360 MHz, $CDCl_3$) 7.14 (2H, t, $J=$ 7.3 Hz, Ph), 6.66 (1H, t, $J=7.3$ Hz, Ph), 6.60 (2H, d, $J=$ 7.7 Hz, Ph), 4.17–4.31 (2H, m, OCH_2), 3.94–4.08 (1H, m, NHC*H*), 3.75–3.87 (2H, m, NCH_2), 3.72 (1H, br s, NH), 3.31 (1H, dd, $J=8.2$, 15.0 Hz, $COCH_2$), 3.01 (1H, dd, $J=$ 5.0, 15.0 Hz, $COCH_2$), 1.54–1.64 (2H, m, $CH_2CH_2CH_2$), 1.35–1.53 (2H, m, CH_2CH_3), 0.93 (3H, t, $J=7.7$ Hz, CH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 172.0 (CO), 153.7 (CO), aromatic C [147.4, 129.3, 117.3, 113.2], 61.9 (OCH_2), 50.5 (NCH_2), 42.5 (CH), 40.0 ($COCH_2$), 38.1 ($CH_2CH_2CH_2$), 19.3 (CH_2CH_3), 13.9 (CH_2CH_3).

4.1.10. 3-{3-[(4-Chlorophenyl)amino]hexanoyl}-1,3-oxazolidin-2-one (3j). Purified by column chromatography (*i*-PrOH/pet. ether=1:4, R_f 0.76) gave a white solid (Found: C, 58.2; H, 6.25; N, 8.8%; M^+, 310.1081. $C_{15}H_{19}ClN_2O_3$ requires C, 57.95; H, 6.15; N, 9.0%; M^+, 310.1084); mp 63–64 °C. 26% ee (Chiral HPLC, *i*-PrOH/hexane=8:92, 1.0 mL/min, t_{major} 35.5 min, t_{minor} 29.8 min); $[\alpha]_D^{20}=-3.1$ ($c=0.035$ in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3370, 1770, 1692, 1598, 1503, 1386, 819; δ_H (360 MHz, $CDCl_3$) 7.08 (2H, d, $J=8.9$ Hz, Ph), 6.52 (2H, d, $J=8.9$ Hz, Ph), 4.23–4.36 (2H, m, OCH_2), 3.95 (1H, br s, NHC*H*), 3.80–3.91 (2H, m, NCH_2), 3.75 (1H, br s, PhNH), 3.29 (1H, dd, $J=7.7$, 15.0 Hz, $COCH_2$), 2.99 (1H, dd, $J=5.5$, 15.0 Hz, $COCH_2$), 1.54–1.60 (2H, m, $CH_2CH_2CH_3$), 1.32–1.50 (2H, m, CH_2CH_3), 0.92 (3H, t, $J=7.3$ Hz, CH_2CH_3); δ_C (90.6 MHz, CDCl3) 171.8 (CO), 153.7 (CO), aromatic C [146.0, 129.1, 121.8, 114.3], 61.9 (OCH_2), 50.7 (NCH_2), 42.5 (CH), 39.8 ($COCH_2$), 37.9 ($CH_2CH_2CH_2$), 19.3 (CH_2CH_3), 13.9 (CH_2CH_3).

4.1.11. 3-{3-[(4-Methylphenyl)amino]hexanoyl}-1,3-oxazolidin-2-one (3k). Purified by column chromatography (ether, R_f 0.80) gave a white solid (Found: C, 66.0; H, 7.7; N, 9.4%; M^+, 290.1625. $C_{16}H_{22}N_2O_3$ requires C, 66.2; H, 7.65; N, 9.65%; M^+, 290.1630); mp 64–65 °C; 18% ee (Chiral HPLC, *i*-PrOH/hexane=3:97, 1.0 mL/min, t_{major} 44.9 min, t_{minor} 50.0 min); $[\alpha]_D^{20}=-1.8$ ($c=0.022$ in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1768, 1687, 1522, 1391, 1223, 807; δ_H (360 MHz, $CDCl_3$) 6.95 (2H, d, $J=8.2$ Hz, Ph), 6.53 (2H, d, $J=8.2$ Hz, Ph), 4.19–4.32 (2H, m, OCH_2), 3.93–4.00 (1H, m, NHC*H*), 3.77–3.89 (2H, m, NCH_2), 3.59 (1H, br s, PhNH), 3.29 (1H, dd, $J=7.7$, 15.0 Hz, $COCH_2$), 3.01 (1H, dd, $J=5.0$, 15.0 Hz, $COCH_2$), 2.21 (3H, s, $PhCH_3$), 1.52–1.63 (2H, m, $CH_2CH_2CH_2$), 1.34–1.50 (2H, m, CH_2CH_3), 0.92 (3H, t, $J=7.3$ Hz, CH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 172.1 (CO), 153.7 (CO), aromatic C [145.1, 129.7, 126.5, 113.5], 61.9 (OCH_2), 50.9 (NCH_2), 42.5 (CH), 39.9 ($COCH_2$), 38.0 ($CH_2CH_2CH_3$), 20.3 (CH_2CH_3), 19.3 ($PhCH_3$), 13.9 (CH_2CH_3).

4.1.12. 3-{3-[(4-Methoxyphenyl)amino]hexanoyl}-1,3-oxazolidin-2-one (3l). Purified by column chromatography (ether/pentane=1:1, R_f 0.19) gave a colourless oil (Found: C, 62.9; H, 7.1; N, 9.0%; M^+, 306.1574. $C_{15}H_{19}ClN_2O_3$ requires C, 62.7; H, 7.25; N, 9.15%; M^+, 306.1580). 10% ee (Chiral HPLC, *i*-PrOH/hexane=20:80, 1.0 mL/min, t_{major} 17.7 min, t_{minor} 20.3 min); $[\alpha]^{20}{}_D=+0.69$ ($c=0.026$ in $CHCl_3$); ν_{max} (thin film, NaCl plates)/cm^{-1} 1777, 1694, 1513, 1387, 1239, 1038, 822; δ_H (360 MHz, $CDCl_3$) 6.74 (2H, d, $J=9.1$ Hz, Ph), 6.58 (2H, d, $J=9.1$ Hz, Ph), 4.20–4.32 (2H, m, OCH_2), 3.87–3.94 (1H, m, NHC*H*), 3.80–3.86 (2H, m, NCH_2), 3.72 (3H, s, OCH_3), 3.45 (1H, br s, PhNH), 3.28 (1H, dd, $J=7.7$, 15.0 Hz, $COCH_2$), 2.98 (1H, dd, $J=$ 5.0, 15.0 Hz, $COCH_2$), 1.50–1.64 (2H, m, $CH_2CH_2CH_3$), 1.33–1.49 (2H, m, CH_2CH_3), 0.92 (3H, t, $J=7.3$ Hz, CH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 172.1 (CO), 153.7 (CO), aromatic C [152.0, 141.6, 114.9, 114.8], 61.9 (OCH_2), 55.7 (OCH_3), 51.7 (NCH_2), 42.4 (CH), 39.9 ($COCH_2$), 37.9 ($CH_2CH_2CH_3$), 19.3 (CH_2CH_3), 13.9 (CH_2CH_3).

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References and notes

1. Cheng, X. H.; Hii, K. K. *Tetrahedron* **2001**, *57*, 5445–5450.
2. Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Organomet. Chem.* **2003**, *665*, 250–257.
3. Li, K.; Hii, K. K. *Chem. Commun.* **2003**, 1132–1133.
4. Since, our original communication,[3] palladium-catalysed addition of amine salts to similar olefin substrates has been reported: Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, *6*, 1861–1864.
5. Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240–1241.
6. Due to the reversible process we were unable to isolate the product. In reference 4 the addition of benzylamine salts was reported to be slow, requiring a temperature of 40 °C and a reaction time of 60 h. The products were reported to be 'rather unstable' and were isolated as methyl esters.
7. Li, K.; Cheng, X. H.; Hii, K. K. *Eur. J. Org. Chem.* **2004**, 959–964.
8. Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gòmez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189.
9. Kunz, H.; Pees, K. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1168–1169.
10. Chow, H. F.; Mak, C. C. *J. Org. Chem.* **1997**, *62*, 5116–5127.
11. Soloshonok, V. A.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2000**, *65*, 6688–6696.
12. Wendt, O. F.; Kaiser, N. F. K.; Elding, L. I. *J. Chem. Soc., Dalton Trans.* **1997**, 4733–4738.

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Synthesis of C13–C22 of amphidinolide T2 via nickel-catalyzed reductive coupling of an alkyne and a terminal epoxide

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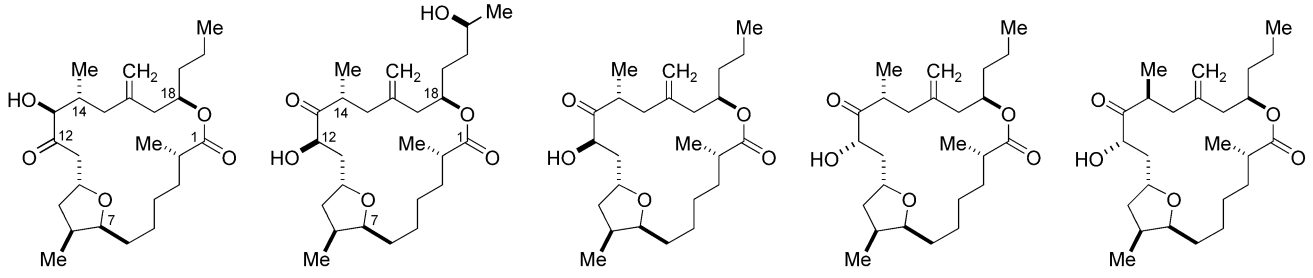
Abstract—Several stereoselective routes to the synthesis of (1*S*,3*R*)-*t*-butyldimethyl-(1-methyl-3-oxiranyl-propoxy)-silane (**13a**) were explored, and the use of Jacobsen's hydrolytic kinetic resolution to separate a mixture of diastereomeric epoxides was a key step in the shortest of these. As part of an approach to the total synthesis of amphidinolide T2 (**2**), this epoxide, corresponding to C17–C22 of the natural product, was successfully joined with an alkyne (C13–C16) by way of a nickel-catalyzed reductive coupling reaction.

1. Introduction

In the course of our recently reported total synthesis of amphidinolide T1 (**1**),[1–4] we utilized a nickel-catalyzed reductive coupling of an alkyne and an epoxide[5] as the last operation in the assembly of the C13–C21 region of the natural product. We have turned our attention to the other four naturally occurring amphidinolide T natural products, T2–T5 (**2–5**).[2]



1 amphidinolide T1 **2** amphidinolide T2 **3** amphidinolide T3 **4** amphidinolide T4 **5** amphidinolide T5

Using a similar approach to that in the T1 synthesis, only T2 (**2**) would require a different epoxide coupling partner (Scheme 1). That is, (*R*)-*n*-propyloxirane (**6**) could, in principle, be used for not only T1, but also T3–T5, whereas a six-carbon epoxide bearing an additional carbinol stereogenic center would be needed for T2, namely a suitably protected form of (2*S*,5*R*)-5-hexen-2-ol oxide (**7**). Compound **7** has been synthesized previously,[6] but as this starting material would likely be part of the longest linear sequence of our synthesis, we sought a route to this building block more expedient than the 6–10-step procedures reported in the literature. Herein, we detail several of the approaches that we have explored toward this end, each of which utilizes one or more stereoselective, catalyzed reactions.

2. Results and discussion

Initially, we focused our attention on the differentiation of the two termini of diepoxide **9a** via reductive ring opening to afford **7**.[6,7] Previously reported syntheses of **9a** entailed a lengthy reaction sequence from D-mannitol.[8] In contrast, we found that Jacobsen's (salen) Co(III)-catalyzed hydrolytic kinetic resolution (HKR)[9] of a stereorandom mixture 1,5-hexadiene diepoxides (**9**:*meso*-**9**:*ent*-**9**=1:2:1)[10] provided **9** with >99% ee in only two steps from 1,5-hexadiene (**10**)

Keywords: Nickel; Epoxide; Alkyne; Amphidinolide.
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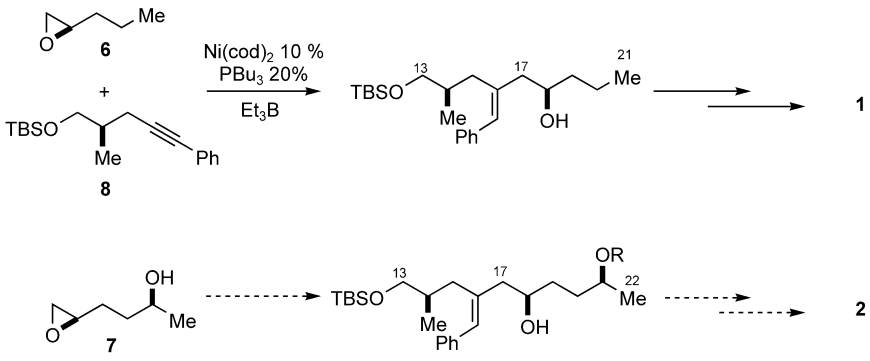
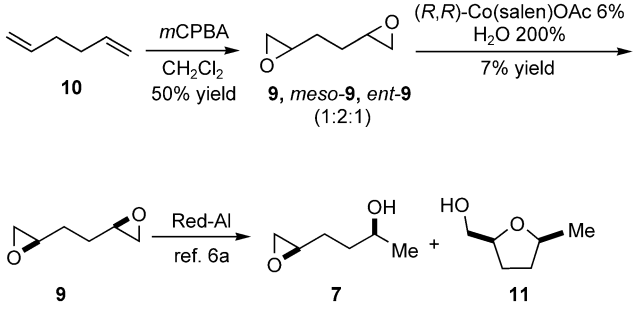


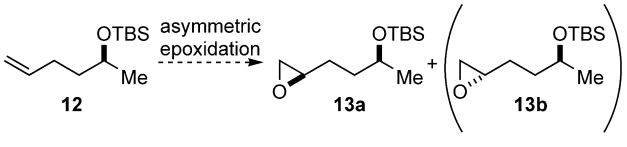
Scheme 1.

(Scheme 2). However, the subsequent reduction of **9** with both Red-Al and DIBAL-H resulted in a low yield of **7** due to rapid cyclization via attack of the hydroxyl group on the epoxide, giving undesired tetrahydrofuran **11**, and over-reduction of **9**.

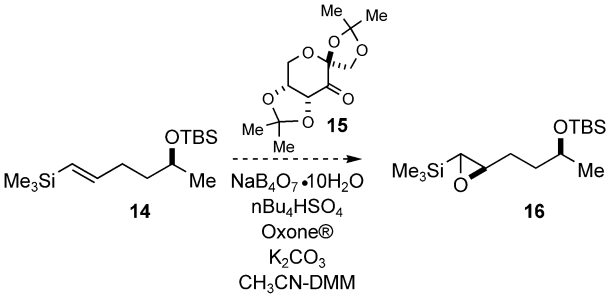


Scheme 2.

The unacceptable results in the selective epoxide-opening route to **7** shifted our interest to a sequence involving asymmetric epoxidation of a terminal alkene (e.g., **12**, Eq. 1). Asymmetric epoxidation of monosubstituted aliphatic alkenes is, however, a particularly challenging problem.[11] Sterically encumbered alkenes are the best substrates for this transformation. For example, 3,3-dimethylbutene can be epoxidized in >90% ee employing a metalloporphyrin complex in combination with iodosylbenzene.[12] 1-Cyclohexyl-1-ethene can be epoxidized in 71% ee using Shi's fructose-derived catalyst and Oxone®.[13] Straight-chain monosubstituted alkyl olefins are very poor substrates for all reported asymmetric epoxidations, producing the desired epoxides in <40% ee.[14] As no highly enantioselective method for the epoxidation of terminal, aliphatic alkenes currently exists, we sought to use Shi's asymmetric epoxidation of vinyl silanes to install the epoxide (Eq. 2).[13,15] Specifically, we predicted that vinyl silane **14** would undergo asymmetric epoxidation in the desired fashion, based on Shi's mode of asymmetric epoxidation of *trans* olefins catalyzed by fructose-derived ketone **15**. Subsequent protiodesilylation of **16** would afford the desired enantiomerically enriched epoxide **13a**.[15b]

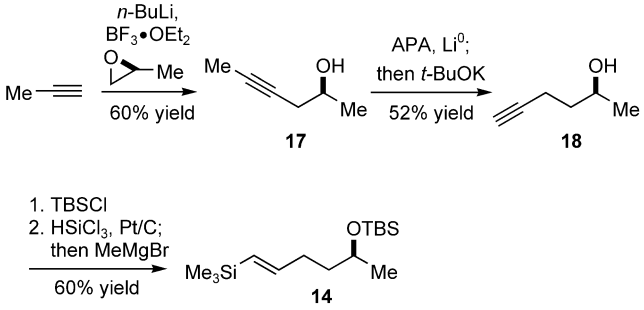


(1)



(2)

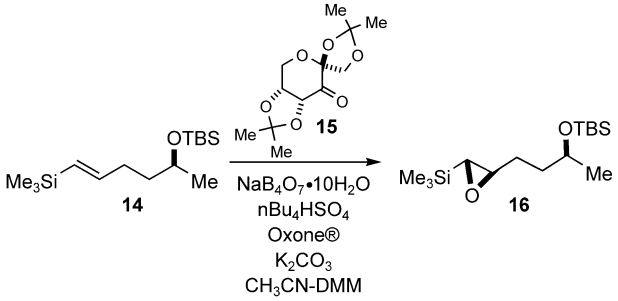
Our preparation of **14** began with selective opening of (*S*)-(−)-propylene oxide with prop-1-ynyl-lithium at the less hindered carbon affording alkynal **17**. Isomerization of **17** to the terminal alkyne **18** using potassium 3-aminopropylamide (KAPA),[16] protection of the alcohol, and platinum-catalyzed hydrosilylation[17] afforded **14** in 19% overall yield (four steps) (Scheme 3).



Scheme 3.

Exposure of **14** to Shi's epoxidation conditions[15] resulted in poor conversion and moderate diastereoselectivity. Disappointingly, a screen of reaction temperatures and ketone (**15**) concentration only improved the diastereoselectivity to 4.7:1 (entry 5, Table 1), with little improvement in conversion. Replacement of alkenylsilane **14** by monosubstituted alkene **12** and subsequent exposure to Shi's epoxidation conditions resulted in complete conversion to **13**, but proceeded non-selectively (1:1 dr, **13a**:**13b**, see Eq. 1). Finally, protiodesilylation of **16** failed to cleanly proceed to the desired terminal epoxide **13a**. For example, treatment with cesium fluoride in DMSO[18] was completely unsuccessful (only starting material was recovered), while treatment with TBAF[15b] promoted preferential cleavage of

Table 1. Epoxidation of silane **14**[a]

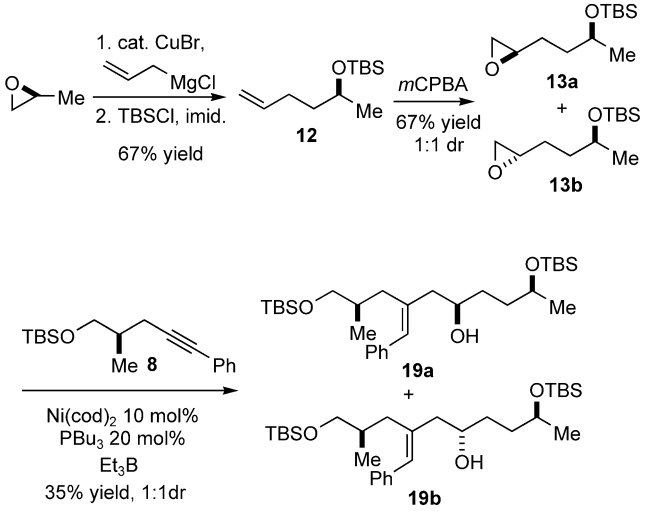


Entry	Stoichiometry[b]	Temperature (°C)	Addition time	Yield (%)[c]	dr[c]
1	**A**	0	2 h	<20	
2	**B**	0	2 h	<20	
3	**A**	23	20 min	<20	
4	**B**	23	2 h	22	3.8:1
5	**C**	23	2 h	33	4.7:1
6	**D**	23	2 h	29	3.5:1
7	**E**	23	2 h	26	4.5:1

[a] **14** was dissolved in CH_3CN–DMM (volume stated per mmol **14**) and the $Na_2B_4O_7$ buffer and nBu_4HSO_4 were added to this solution. Oxone and K_2CO_3 solutions were added simultaneously over the specified addition time.
[b] **A**: 52 mol% $Na_2B_2O_4$, 6 mol% nBu_4HSO_4, 67 mol% **15**, 143 mol% oxone, 600 mol% K_2CO_3, 15.5 mL CH_3CN–DMM. **B**: 104 mol% $Na_2B_2O_4$, 12 mol% $nBu_4HSO_4HSO_4$, 134 mol% **15**, 286 mol% oxone, 1200 mol% K_2CO_3, 31 mL CH_3CN–DMM. **C**: 120 mol% $Na_2B_2O_4$, 22 mol% nBu_4HSO_4, 234 mol% **15**, 463 mol% oxone, 1787 mol% K_2CO_3, 36 mL CH_3CN–DMM. **D**: 240 mol% $Na_2B_2O_4$, 44 mol% $nBuHSO_4$, 468 mol% **15**, 926 mol% oxone, 3573 mol% K_2CO_3, 72 mL CH_3CN–DMM. **E**: 480 mol% $Na_2B_2O_4$, 88 mol% $nBuHSO_4$, 936 mol% **15**, 1852 mol% oxone, 7.147 mol% K_2CO_3, 144 mL CH_3CN–DMM.
[c] Determined by intergration of ^1H NMR spectrum of the crude product mixture.

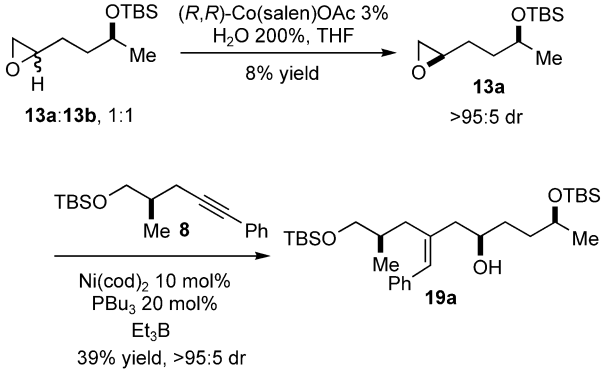
the oxygen–silicon bond over the carbon–silicon bond, followed by cyclization (see also Scheme 1).

Given the failure to obtain **7** through the Shi epoxidation route, we considered an approach that would use a mixture of diastereomeric epoxides, **13a** and **13b** (Scheme 4). That is, nickel-catalyzed reductive coupling of this mixture with enantiomerically enriched alkyne **8**[1] would give a mixture of diastereomers of homoallylic alcohols (**19a** and **19b**) that might be separable. As summarized in Scheme 4, addition of allyl magnesium chloride to (*S*)-propylene oxide followed by TBS protection[19] and epoxidation with *m*CPBA (1:1 dr) provided the desired mixture of epoxides **13a** and **13b** in 38% yield over the three steps. We were pleased to find that under our nickel-catalyzed alkyne-epoxide coupling conditions,[1,5] **8** and **13a/b** were indeed joined to afford alcohols **19a/b**. To our disappointment, however, the reaction proceeded in moderate yield, and the diastereomers were inseparable.



Scheme 4.

To circumvent the above problems, we utilized Jacobsen's HKR[9] in order to chemically separate the diastereomeric epoxide mixture of **13a/b** (Scheme 5). We were delighted to find that this method afforded **13a** in >98% diastereoselectivity, albeit in low yield. Diastereomer **13a** underwent reductive coupling with alkyne **8** to afford the desired alcohol **19a** in >95:5 dr and in 39% yield, representing rapid access to a significant fragment of amphidinolide T2.



Scheme 5.

3. Conclusions

Several stereoselective routes to the synthesis of epoxide **13a** were explored. Ultimately, we found Jacobsen's HKR of a mixture of diastereomers afforded the desired epoxide in the most efficient manner of those examined. As part of an approach to the total synthesis of amphidinolide T2 (**2**),

this epoxide, corresponding to C17–C22 of the natural product, was successfully joined with an alkyne (C13–C16) by way of a nickel-catalyzed reductive coupling reaction.

4. Experimental

4.1. General information

Unless otherwise noted, all reactions were carried out in an atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Tetrahydrofuran and diethyl ether were distilled from a blue solution of benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Toluene was distilled from sodium metal. Anhydrous dimethylformamide was used as purchased from Aldrich. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates and developed using UV light and 12-molybdophosphoric acid (PMA stain). Flash chromatography was with the indicated solvent system on silica gel (230–400 mesh) from Silicycle. NMR spectra were recorded on a Varian Inova 500 MHz spectrometer in $CDCl_3$. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesle Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Specific rotation ($[\alpha]_D$) values for chiral compounds were measured on a Perkin–Elmer 241 polarimeter at 589 nm.

4.1.1. (*R*)-1-(*t*-Butyldimethylsilanyloxy)-2-methyl-5-phenyl-4-pentyne (8). Synthesized according to a reported procedure.[1]

4.1.2. 1,2;5,6-Diepoxy-hexane (9, *meso*-9, *ent*-9). Synthesized as a mixture of diastereomers according to a reported procedure.[10]

4.1.3. (2*R*,5*R*)-1,2;5,6-Diepoxy-hexane (9). To a solution of (*R*,*R*)Co(II) (salen) complex (1.2 g, 1.8 mmol) in toluene (25 mL) was added AcOH (1.2 mL) and the mixture was stirred open to air for 30 min. After concentration, a solution of diepoxide (**9**, *meso*-**9**, *ent*-**9**; 3.4 g, 30 mmol) in THF (6 mL) was added. The solution was cooled to 0 °C and H_2O was added dropwise (1.1 mL). After stirring for 40 h at ambient temperature, the epoxide was purified via column chromatography (70:30, hexanes–EtOAc) to afford the title compound (120 mg, 7% yield out of 100%, >99% ee). Spectral data were consistent with reported.[8]

4.1.4. (*S*)-*t*-Butyldimethyl-(1-methyl-pent-4-enyloxy)-silane (12). Synthesized according to a reported procedure.[19a]

4.1.5. (1*S*)-*t*-Butyldimethyl-(1-methyl-3-oxiranyl-propoxy)-silane (13a/b). A solution of **12** (3.90 g, 18.2 mmol) in CH_2Cl_2 (74 mL) was cooled to 0 °C and *m*CPBA (8.30 g, 41 mmol) was added in three portions. The solution was stirred 30 min at 0 °C then warmed to ambient temperature and stirred 1 h. Saturated $NaHCO_3$ (50 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3×25 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified via gradient column chromatography (50:1, hexane–EtOAc, polarity gradually increased to 9:1) to afford an inseparable mixture of diastereomers as a clear, colorless oil (1.78 g, 42% yield, 1:1 dr). R_f (90:10, hexane–EtOAc)=0.59; IR (thin film/NaCl): 2930, 2858, 1473 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.90–3.78 (m, 2H), 2.95–2.90 (m, 2H), 2.75 (dd, J=5.2, 4.0 Hz, 2H), 2.50–2.46 (m, 2H), 1.72–1.45 (m, 8H), 1.15 (d, J=6.1 Hz, 3H), 1.14 (d, J=6.1 Hz, 3H), 0.89 (s, 18H), 0.058 (s, 6H), 0.053 (s, 3H), 0.047 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 68.4, 68.1, 52.7, 52.5, 47.4, 47.3, 36.0, 35.6, 29.2, 28.7, 26.1 (6C), 24.1, 23.9, 18.3 (2C), −4.1, −4.2, −4.6 (2C); HRMS (ESI) $[M+H]^+$: *m*/*z* calcd for $C_{12}H_{27}O_2Si$ 231.1780, obsd 231.1768.

4.1.6. (1*S*,3*R*)-*t*-Butyldimethyl-(1-methyl-3-oxiranyl-propoxy)-silane (13a). To a solution of (*R*,*R*)Co(II) (salen) complex (50 mg, 0.081 mmol) in CH_2Cl_2 (1.5 mL) was added AcOH (50 μL) and the mixture was stirred open to air for 30 min. After concentration, a solution of epoxide **13a/b** (0.62 g, 2.7 mmol) in THF (0.6 mL) was added. The solution was cooled to 0 °C and H_2O was added dropwise (0.1 mL). After stirring for 36 h at ambient temperature, the epoxide was purified via gradient column chromatography (50:1, hexanes–EtOAc, polarity gradually increased to 19:1) to afford the title compound (50 mg, 8% yield out of 100%, >95:5 dr). R_f (90:10, hexane–EtOAc)=0.59; IR (thin film/NaCl): 2930, 2858, 1473 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.90–3.83 (m, 1H), 2.95–2.92 (m, 1H), 2.76 (dd, J=4.4, 4.4 Hz, 1H), 2.49 (dd, J=4.4, 2.6 Hz, 1H), 1.72–1.45 (m, 4H), 1.14 (d, J=6.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 68.2, 52.5, 47.3, 35.6, 28.7, 26.1 (3C), 23.9, 18.3, −4.1, −4.5; HRMS (ESI) $[M+H]^+$: *m*/*z* calcd for $C_{12}H_{27}O_2Si$ 231.1780, obsd 231.1768.

4.1.7. (5*S*)-5-(*t*-Butyldimethylsilanyloxy)-1-trimethylsilanyl-hex-1-ene (14). Imidazole was dissolved (2.40 g, 35.3 mmol) in DMF (19 mL) and **18** (2.0 g, 19.2 mmol) and *t*-butyldimethylchlorosilane (4.83 g, 32.1 mmol) were then added sequentially. After stirring at ambient temperature for 14 h, the solution was partitioned between Et_2O (30 mL) and H_2O (30 mL). The organic layer was washed with H_2O (3×15 mL), then brine (3×15 mL). The solution was dried over $MgSO_4$, concentrated and purified via column chromatography (70:30, pentane–Et_2O). The product (3.0 g, 13.7 mmol) was then slowly added to a refluxing solution of $HSiCl_3$ (2.77 mL, 27.5 mmol) and 10% Pt/C (0.03 g, 0.14 mmol). The solution was refluxed for 2 h. After cooling to 0 °C, MeMgBr in Et_2O (27.5 mL, 82.4 mmol) was slowly added and the solution was heated to reflux, stirring 14 h. The solution was cooled to 0 °C and quenched by addition of NH_4Cl. The aqueous layer was extracted with Et_2O (3×15 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified via column chromatography (90:10, hexanes–EtOAc) to yield the title compound as a clear, colorless oil (2.62 g, 61% yield). R_f (90:10, hexane–EtOAc)=0.67; IR (thin film/NaCl): 2957, 2930, 2858, 1618, 1473 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.03 (dt, J=18.3, 6.3 Hz, 1H), 5.64 (dt, J=18.3, 1.5 Hz, 1H), 3.83–3.76 (m, 1H), 2.22–2.04 (m, 2H), 1.60–1.42 (m, 2H), 1.14 (d, J=6.1 Hz, 3H), 0.89

(s, 9H), 0.06 (s, 3H), 0.053 (s, 3H), 0.049 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.2, 129.9, 68.3, 38.9, 33.2, 26.2 (3C), 24.1, 18.4, −0.9 (3C), −4.1, −4.5; HRMS (ESI) $[M+H]^+$: *m/z* calcd for $C_{15}H_{34}ONaSi_2$ 309.2040, obsd 309.2032; $[\alpha]_D^{23}$ +1.2° (*c* 5.1, CH_2Cl_2).

4.1.8. (2*R*,3*S*)-2-[3-(*t*-Butyldimethylsilanyloxy)-butyl]-3-trimethylsilanyl-oxirane (16). Corresponding to entry 5 in Table 1. In a flask open to air, vinylsilane **14** (500 mg, 1.74 mmol) was dissolved in CH_3CN–DMM (63 mL, 1:2 v/v) followed by addition of buffer [42 mL, 0.05 M solution of $Na_2B_4O_7\cdot 10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA)], tetrabutylammonium hydrogen sulfate (139 mg, 0.38 mmol), and **14** (1.04 g, 4.05 mmol). Aqueous solutions of oxone (4.96 g, 8.06 mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 35 mL) and K_2CO_3 (0.89 M, 35 mL) were added via syringe pump over 2 h. After completion of the addition, the solution was stirred 1 h. The solution was diluted with H_2O (35 mL), extracted with hexane, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via column chromatography (90:10, hexanes–EtOAc) to afford the title compound as a colorless oil (110 mg, 21% yield, 4.7:1). R_f (90:10, hexane–EtOAc)=0.41; IR (thin film/NaCl): 2958, 2930, 2858, 1473 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.90–3.82 (m, 1H), 2.81–2.77 (m, 1H), 1.99 (d, J=3.7 Hz, 1H), 1.69–1.48 (m, 4H), 1.14 (d, J=6.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 9H), 0.058 (s, 3H), 0.054 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 68.2, 56.2, 51.9, 36.1, 30.3, 26.1 (3C), 23.9, −3.4 (3C), −4.2, −4.5; HRMS (ESI) $[M+H]^+$: *m/z* calcd for $C_{15}H_{35}O_2Si_2$ 303.2170, obsd 303.2162.

4.1.9. (*S*)-Hex-4-yn-2-ol (17). *n*-BuLi (41.1 mL, 2.5 M in hexanes, 103.4 mmol) was added to THF (150 mL) at −78 °C. Propyne was bubbled through the solution (1 min). To this solution was added $BF_3\cdot OEt_2$ (5.2 mL, 41.4 mmol) followed immediately by (*S*)-(−)-propylene oxide (4.0 mL, 51.7 mmol). The solution was stirred at −78 °C for 2 h, quenched with saturated $NaHCO_3$ and allowed to warm to ambient temperature. The solution was diluted with H_2O and the phases were separated. The aqueous phase was extracted with Et_2O (3×50 mL) and the combined organic phases were dried over $NaSO_4$, filtered, and concentrated. The crude product was purified via column chromatography (70:30, pentane–Et_2O) to afford the title compound as a clear, colorless oil (2.85 g, 53% yield). Spectral data were consistent with that reported.[20]

4.1.10. (*S*)-5-Hexyn-2-ol (18). To 1,3-diaminopropane (60 mL, 109.4 mmol) was added lithium wire (1.12 g, 161.4 mmol) cut into small pieces and stirred 45 min until the solution turned blue and the lithium was dissolved. The solution was heated at 70 °C for 3 h. After cooling to ambient temperature, *t*-BuOK was added (11.92 g, 109.4 mmol). After stirring for 20 min, **17** was added and the mixture was stirred for an additional 3 h. The reaction was quenched by pouring into 800 mL H_2O and neutralizing with 1.6 L 1 M HCl.CH_2Cl_2 (800 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×500 mL), washed with 1 M HCl (2×500 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified via column chromatography (70:30, pentane–Et_2O) to yield the title compound as a clear, colorless oil (1.48 g, 52% yield). Spectral data were consistent with that reported.[21]

4.1.11. (2*S*,5*R*,9*R*)-7-Benzylidene-2,10-bis-(*t*-butyldimethylsilanyloxy)-9-methyl-decan-5-ol (19a). In a glove box, Ni(cod)$_2$ (4 mg, 0.013 mmol) was placed in a 10 mL flask, which was then sealed with a rubber septum. The flask was removed from the glovebox and placed under Ar. To this flask was added tributylphosphine (4 μL, 0.026 mmol), **13a** (30 mg, 0.13 mmol in 0.7 mL Et_2O), triethylborane (0.40 μL, 0.26 mmol), and **8** (20 mg, 0.07 mmol). The resulting reddish-brown solution was stirred at ambient temperature 14 h, then opened to the air for 1 h. Volatile organics were evaporated, and the crude residue was purified via gradient column chromatography (50:1, hexane–EtOAc, polarity gradually increased to 9:1) to afford the title compound as a clear, colorless oil (14 mg, 39% yield, >95:5 dr by ^{1}H NMR). R_f (90:10, hexane–EtOAc)=0.24; IR (thin film/NaCl): 3428, 2955, 2929, 2857, 1600, 1472 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33–7.30 (m, 2H), 7.27–7.24 (m, 2H), 7.22–7.19 (m, 1H), 6.44 (s, 1H), 3.90–3.85 (m, 1H), 3.84–3.80 (m, 1H), 3.39 (dd, J=9.8, 5.8 Hz, 1H), 3.31 (dd, J=9.8, 6.1 Hz, 1H), 2.49 (dd, J=13.9, 6.3 Hz, 1H), 2.39 (dd, J=13.6, 4.1 Hz, 1H), 2.28 (dd, J=13.6, 8.5 Hz, 1H), 2.09–2.04 (m, 2H), 1.95–1.91 (m, 1H), 1.65–1.55 (m, 4H), 1.17 (d, J=5.8 Hz, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.83 (d, J=6.7 Hz, 3H), 0.08 (s, 6H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.1, 138.1, 129.5, 129.2 (2C), 128.4 (2C), 126.5, 69.5, 68.7, 68.3, 46.4, 35.5, 34.6, 34.3, 33.0, 26.19 (3C), 26.18 (3C), 23.9, 18.6, 18.4, 17.1, −4.1, −4.4, −5.15, −5.17; HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{30}H_{56}O_3NaSi_2$ 543.3660, obsd 543.3660; $[\alpha]_D^{23}$ +1.8° (*c* 2.8, CH_2Cl_2).

References and notes

1. Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998–999.
2. Isolation and structure determination of amphidinolides T1–T5: (a) Tsuda, M.; Endo, T.; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 1349–1352. (b) Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2001**, *66*, 134–142. (c) Kubota, T.; Endo, T.; Tsuda, M.; Shiro, M.; Kobayashi, J. *Tetrahedron* **2001**, *57*, 6175–6179.
3. Other syntheses of amphidinolide T natural products: (a) T1: Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374–2375. (b) T1: Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512–15520. (c) T4: Fürstner, A.; Aïssa, C.; Ragot, J. *J. Angew. Chem., Int. Ed.* **2002**, *41*, 4763–4766.
4. Authoritative review of the amphidinolides: Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77–93.
5. Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076–8077.
6. (a) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 841–844. (b) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 5739–5742.
7. Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9–17.
8. For the synthesis of **9**, see: (a) Machinaga, N.; Kibayashi, C.

Synthesis **1992**, 989–994. (b) Machinga, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 1386–1393. For syntheses of important intermediates in this synthesis, see: (c) Bladon, P.; Owen, L. N. *J. Chem. Soc.* **1950**, 598–603. (d) Tipson, R. S.; Cohen, R. *Carbohydr. Res.* **1965**, 338–340. (e) Baer, E. *J. Am. Chem. Soc.* **1945**, *67*, 338–339.

9. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.
10. Baylon, C.; Heck, M. P.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3354–3360.
11. Katsuki, T. Asymmetric epoxidation of unfunctionalized olefins and related reactions. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed. 2nd ed.; Wiley-VCH: New York, 2000; pp 287–325.
12. Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M. *J. Am. Chem. Soc.* **1999**, *121*, 460–461.
13. Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929–1931.
14. Using a copper–amino acid complex, 1-octene was epoxidized in 32% ee (a) Valodkar, V. B.; Tembe, G. L.; Ram, R. N.; Rama, H. S. *Catal. Lett.* **2003**, *90*, 91–94. Using a porphyrin-Ru catalyst and pyridine *N*-oxides, 1-octene was epoxidized in 28% ee (b) Berkessel, A.; Frauenkron, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, *1*, 2265–2266.
15. (a) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807. (b) Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675–7677. (c) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435–2446.
16. (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891–892. (b) Midland, M. M.; Halterman, R. L.; Brown, C. A.; Yamaichi, A. *Tetrahedron Lett.* **1981**, *22*, 4171–4172.
17. Chauhan, M.; Hauck, B. J.; Keller, L. P.; Boudjouk, P. *J. Organomet. Chem.* **2002**, *645*, 1–13.
18. Narula, A. S. *Tetrahedron Lett.* **1982**, *23*, 5579–5582.
19. (a) Toth, M.; Szocs, G.; Van Nieukerken, E. J.; Philipp, P.; Schmidt, F.; Francke, W. *J. Chem. Ecol.* **1995**, *21*, 13–26. (b) Schuda, A. D. C.; Mazzocchi, P. H.; Fritz, G.; Morgan, T. *Synthesis* **1986**, 309–312.
20. Fürstner, A.; Castanet, A. S.; Radkowski, K.; Lehmann, C. W. *J. Org. Chem.* **2003**, *68*, 1521–1528.
21. Fantin, G.; Fogagnolo, M.; Giovannini, P. P.; Medici, A.; Pedrini, P. *Tetrahedron: Asymmetry* **1995**, *6*, 3047–3053.

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Mechanism and scope of salen bifunctional catalysts in asymmetric aldehyde and α-ketoester alkylation

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Abstract—Metal complexes of C_2-symmetric Lewis acid/Lewis base salen ligands provide bifunctional activation resulting in rapid rates in the enantioselective addition of diethylzinc to aldehydes (up to 92% ee). Further experiments probed the reactivity of the individual Lewis acid and Lewis base components of the catalyst and established that both moieties are essential for asymmetric catalysis. These catalysts are also effective in the asymmetric addition of diethylzinc to α-ketoesters. This finding is significant because α-ketoesters alone serve as their own ligands to accelerate racemic 1,2-carbonyl addition of Et_2Zn and racemic carbonyl reduction. The latter proceeds via a metalloene pathway, and often accounts for the predominant product. Singular Lewis acid catalysts do not accelerate enantioselective 1,2-addition over these two competing paths. The bifunctional amino salen catalysts, however, rapidly provide enantioenriched 1,2-addition products in excellent yield, complete chemoselectivity, and good enantioselectivity (up to 88% ee). A library of the bifunctional amino salens was synthesized and evaluated in this reaction. The utility of the α-ketoester method has been demonstrated in the synthesis of an opiate antagonist.

1. Introduction

Recent studies have shown that bifunctional ligands possess useful characteristics for simultaneous substrate activation.[1] For example, ligands have been reported in which one portion engages a Lewis acid moiety that coordinates an electrophilic substrate while a separate basic portion coordinates to the nucleophilic substrate. The positioning of the two reactants in close proximity and with the correct relative geometry facilitates a reaction in a manner similar to that of some enzyme catalysts.[2] Seminal Lewis acid/Lewis base catalysts are the Corey oxazaborolidine **1** for ketone reduction[3] and the Noyori β-amino alcohol catalyst **2** for the addition of diethylzinc to aldehydes[4] (Fig. 1).

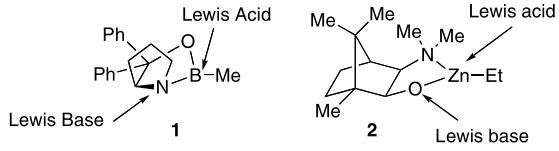

Figure 1. Interdependent Lewis acid/Lewis base bifunctional catalysts.

Catalysts **1** and **2** are examples of interdependent catalysts since the Lewis acid is directly coordinated to the Lewis base moiety. While the metal activates the electrophile as a Lewis acid, the heteroatom-containing moiety activates the nucleophile as a Lewis base. A bifunctional Lewis acid/base catalyst with electronically decoupled sites, however, would allow for separate activation of electrophilic and nucleophilic substrates. It would, therefore, be possible to tune each activation site independently. In particular, new catalysts can be envisioned with functional groups specifically tailored to activate the nucleophile and electrophile of a given reaction with the optimal spacing and orientation between groups. Such systems may provide better selectivity and turnover for reactions that have not been successful with either monofunctional or interdependent bifunctional catalysts.

The salen motif is one of several privileged ligands[5,6] for asymmetric catalysis that impart high levels of enantioselectivity in many diverse transformations.[7] In addition, salen–metal complexes have been demonstrated to function as chiral Lewis acid catalysts.[8] Salen ligands are readily available from inexpensive salicylaldehyde or phenol precursors and are typically air-stable crystalline solids. We therefore directed efforts toward the construction of catalyst systems with general structure **3** (Fig. 2), which

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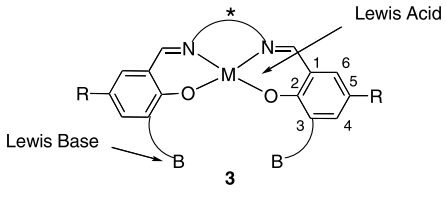


Figure 2. Bifunctional salen scaffold.

incorporates a basic moiety into a structurally well-defined and rigid salen complex.[9] Bifunctional salen complexes **3** would provide an accessible Lewis acid center for electrophile activation and a basic functional group for activation of the nucleophile. A survey of the chemical literature revealed few reports of chiral salens with secondary functional groups.[10,11]

An important structural consideration in the design of these bifunctional scaffolds was the nature of the tether connecting the salen to the basic functional group. This tether must be sufficiently short and/or rigid to prevent internal complexation of the Lewis base to the Lewis acid. Compounds **4** and **5** are inherently rigid by virtue of the biaryl bonds, whereas the short tether in compound **6** prevents self-complexation (Fig. 3). In spite of the simplified structure and ease of preparation of such ligands, chiral variants had not been explored as ligands for asymmetric catalysis previously.

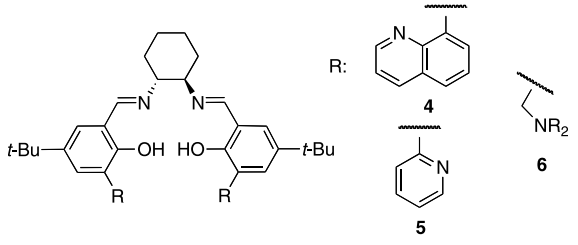


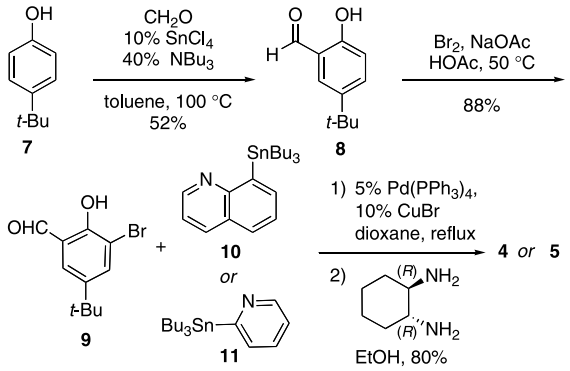
Figure 3. Bifunctional salen ligands.

In previous work, we showed that these amino-salen bifunctional catalysts catalyzed the rapid addition of diethylzinc to aldehydes.[12a] Having demonstrated the premise behind these catalysts in this well-understood, privileged reaction, they were also examined in the addition of diethylzinc to α-ketoesters, an unexplored reaction with a fast background rate and multiple reaction products.[12b,c] In this report, we describe the full structural and mechanistic details of these catalysts and their scope in these reactions.

2. Results and discussion

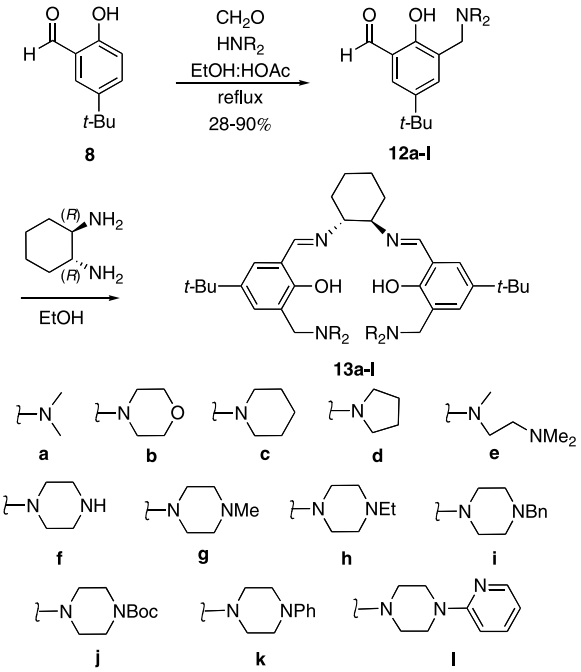
2.1. Ligand synthesis

Formylation of phenol **7**, followed by bromination of **8**, Stille coupling between **9** and **10**, and subsequent condensation with (*R*,*R*)-cyclohexanediamine provided quinoline salen **4** in four steps (Scheme 1). In a similar fashion, pyridinyl salen **5** was obtained using stannane **11** (Scheme 1).



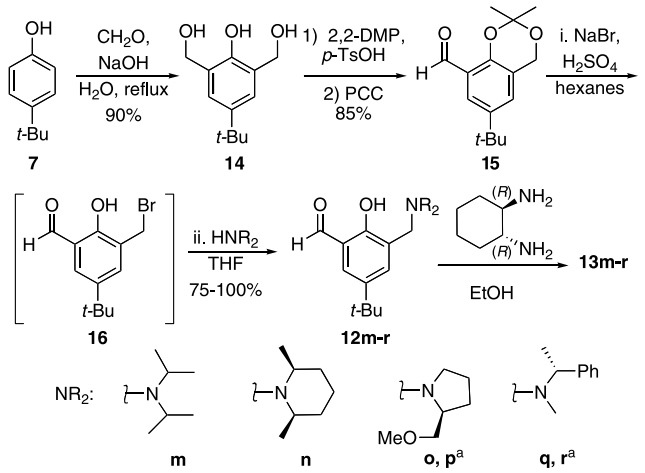
Scheme 1. Synthesis of quinoline and pyridyl salens.

Two expedient routes to chiral methylene-amine salens were devised. Method A, outlined in Scheme 2, allows for the rapid construction of amino salens in three simple steps from phenol **7**. A Mannich reaction of **8** with a secondary amine provides aldehyde **12**, which is then condensed with (*R*,*R*)-cyclohexanediamine to give methylene-tethered salen **13**. Although this route provides access to a number of amino salicylaldehydes, it is not without limitations. The aromatic Mannich reaction[13] to install the methylene-amine group is only effective with simple, unbranched secondary amines. It was, therefore, necessary to explore alternative synthetic routes to α-branched amino salicylaldehydes (Scheme 3).



Scheme 2. Synthesis of methylene tethered salens (Method A).

This alternate route began with acetonide **15** which was prepared in three steps from *tert*-butyl phenol **7** (Scheme 3). Treatment of this acetonide with anhydrous HBr, generated in situ, effected deprotection along with formation of benzyl bromide **16**. Direct addition of secondary amines afforded α-branched amino salicylaldehydes **13m–r**. The described methods provide a highly modular synthesis and easy access to numerous derivatives.



Scheme 3. Synthesis of amino salens (Method B). [a]Salen derived from (1*S*,2*S*)-cyclohexanediamine.

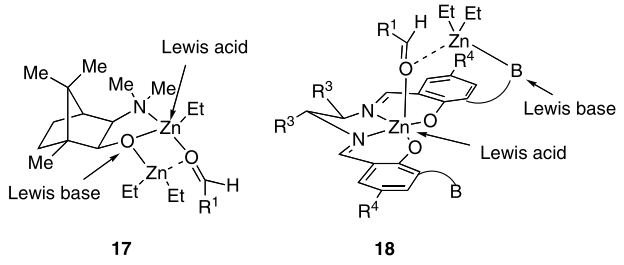
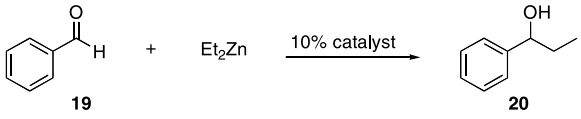


Figure 4. Transition state models for diethylzinc addition.

have been reported to catalyze the addition of diethylzinc to aldehydes with excellent enantioselectivity, these catalysts are generally less reactive than the titanium-based systems.[14a]

When a β-aminoalkoxy zinc catalyst is employed, the reaction proceeds by interdependent dual activation of the aldehyde electrophile and the diethylzinc nucleophile (Fig. 4, **17**).[16,17] With an independent bifunctional salen framework, an apical coordination site on the Lewis acidic metal center could activate the aldehyde[18] while the tethered base could independently activate the diethylzinc nucleophile (Fig. 4, **18**).[19]

The zinc complex of quinoline salen **4** proved to be very reactive in the aldehyde alkylation (Eq. 1, Table 1, entry 1) as 93% conversion was observed after 2 h at room temperature. In pyridyl salen **5**, the Lewis basic nitrogen is disposed closer to the zinc center. This arrangement allows for fast catalysis even at lower temperatures along with substantial enantiocontrol (Table 1, entry 2).



(1)

Pyridine salen derivatives, such as a *para*-dimethylamino pyridine salen, were pursued, but synthesis of such compounds was non-trivial. At this juncture pyridine salens were abandoned in order to pursue a class of amino-salen ligands that could be prepared and tested in a more rapid and efficient manner. Morpholine salen **13b** was selected (Scheme 2), on the basis of its highly crystalline nature, as the initial probe for the addition of diethylzinc to benzaldehyde. The screening process began with an evaluation of several Lewis acidic metal complexes of **13b** (Table 2, Eq. 1). While the Ni, Cu, Mg and Ti(O*i*-Pr)$_2$ complexes[20] with **13b** were effective catalysts, the Zn complex proved the most versatile giving high selectivities at lower temperatures (Table 2, entries 5–8).

Table 1. Biaryl salen ligands in the addition of Et_2Zn to PhCHO (Eq. 1)[a]

Entry	Catalyst	Solvent	*T* (°C)	Time (h)	Conv. (%)	ee (%)[b]
1	Zn-**4**	Toluene	25	2	93	10 (*R*)
2	Zn-**5**	Toluene	−50	20	97	78 (*S*)

[a] Addition of 2.0 equiv of Et_2Zn with 10 mol% catalyst.
[b] Determined by chiral GC (Cyclodexβ). Absolute configuration determined by comparison to literature.

2.2. The addition of diethylzinc to aldehydes

The addition of diethylzinc to aldehydes is a well-studied reaction and is used as a benchmark to measure the efficacy of new ligands. Titanium complexes of chiral diols and bis(sulfonamide) ligands have proven the most reactive and enantioselective to date.[14] One drawback of these systems, however, is the requirement for a stoichiometric amount of Ti(O*i*-Pr)$_4$.[15] Although various chiral aminoalcohol ligands

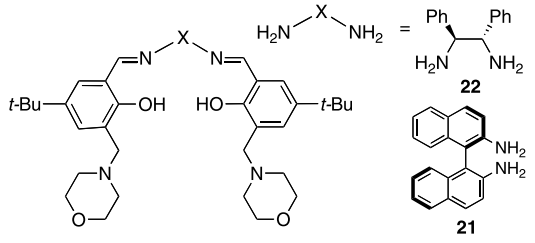


Figure 5. Salens comprised of other diamine backbones were inferior.

The effect of the chiral diamine backbone on the geometry and reactivity of the Zn-morpholine salen complexes was briefly examined. A significant loss of enantioselectivity was observed with the zinc complexes derived from (*R*)-BINAM (**21**) and (*S*,*S*)-1,2-diphenylethylenediamine (**22**) (Fig. 5, Table 2, entries 9–10).

In order to survey the role of the Lewis base component, zinc complexes of select amino salens and methyl ether salen **23** were examined (Table 3, Eq. 1). Reactions were conducted at −30 °C and quenched after 6 h for a direct comparison of catalyst reactivity.

Table 2. Lewis acid complexes of morpholine salens in the addition of Et_2Zn to PhCHO (Eq. 1)[a]

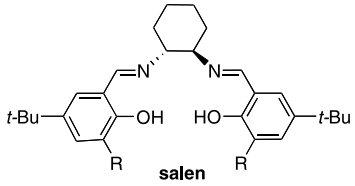
Entry	Catalyst	*T* (°C)	Time (h)	Conv. (%)[b]	ee (%)[b]
1	Ni-**13b**	25	2	99	32 (*R*)
2	Cu-**13b**	25	2	100	10 (*S*)
3	Mg-**13b**	25	2	99	3 (*S*)
4	Ti(O*i*-Pr)$_2$-**13b**	25	2	100	55 (*S*)
5	Zn-**13b**	25	2	100	54 (*S*)
6	Zn-**13b**	−30	12	98	80 (*S*)
7	Zn-**13b**	−35	15	98	87 (*S*)
8	Zn-**13b**	−70	24	46	83 (*S*)
9	Zn-**21**	25	2	95	19 (*S*)
10	Zn-**22**	25	2	84	23 (*S*)

[a] Reactions performed in toluene with 2.0 equiv Et_2Zn and 10 mol% catalyst.
[b] Determined by GC (Cyclodexβ). Absolute configuration assigned by comparison to the literature.

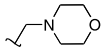
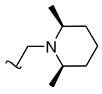
While the highest enantioselectivity was observed with morpholine salen **13b** (87% ee at −35 °C), an even more active catalyst was observed with the slightly more basic piperidyl salen **13c**, resulting in 90% conversion after 6 h at −30 °C (Table 3, entry 3). Surprisingly the less basic pyridyl derivative **5** provided the most reactive catalyst (Table 3, entries 5–6). Catalysts derived from salens **13m–n**, containing α-branched amines, were less reactive (Table 3, entries 7–10). With the methyl ether derivative **23**, a much less reactive complex was formed which was not catalytic at −30 °C (Table 3, entry 11). Indeed, significant conversion was only observed at higher temperatures (i.e., room temperature Table 3, entry 12).

A substantial loss of catalytic activity was observed with salens lacking secondary Lewis bases. For example, the catalyst derived from *tert*-butyl salen **24** provided only 2% conversion after 6 h at −30 °C (Table 3, entry 13) along with significant amounts of the reduced benzyl alcohol byproduct (15%). Zn-**24** requires 18 h at room temperature to achieve high conversion (90%). In order to rule out any steric effect from the larger *tert*-butyl groups in **24**, the zinc

Table 3. Zn-salen complexes in the addition of Et_2Zn to PhCHO (Eq. 1)[a]



salen

Entry	Salen	R	*T* (°C)	Time (h)	Conv. (%)[b,c]	ee (%)[b,d]	~pK_a (BH^+)[e]
1	**13b**		−30	6	72	77 (*S*)	6
2	**13b**		−35	15	98	87 (*S*)	6
3	**13c**		−30	6	90	76 (*S*)	9
4	**13c**		−40	15	82	85 (*S*)	9
5	**5**		−30	6	99	51 (*S*)	5
6	**5**		−50	20	97	78 (*S*)	5
7	**13m**		−30	6	5 (11)	52 (*S*)	9
8	**13m**		25	6	90 (5)	48 (*S*)	9
9	**13n**		−30	6	33	73 (*S*)	9
10	**13n**		−30	30	85	82 (*S*)	9
11	**23**		−30	6	8 (3)	18 (*R*)	−3
12	**23**		25	3	95	18 (*R*)	−3
13	**24**		−30	6	2 (15)	57 (*S*)	NA
14	**25**		−30	6	3 (7)	21 (*S*)	NA

[a] Reactions conducted in toluene with 10 mol% salen and 2.1 equiv Et_2Zn.
[b] Determined by chiral GC (Cyclodex-β).
[c] Values in parentheses refer to amount of benzyl alcohol side product.
[d] Absolute configuration assigned by comparison to the literature.
[e] Estimated from the pK_a(H_2O) values of *N*-methylmorpholine, *N*-methylpiperidine, benzylamine, methylamine, pyridine and dimethyl ether.

complex of cyclohexane salen **25**, which is an isosteric analog of **13b–c**, was examined. As expected, no catalysis was observed after 6 h at −30 °C with Zn-**25** (Table 3, entry 14).

2.3. Reaction mechanism

From the results collected in Table 3, a good Lewis base is required for an active catalyst. Furthermore, the electron pair donor/zinc-binding ability of this Lewis base can be correlated to catalyst reactivity. For the methylene-tethered Lewis base salens, a similar steric environment is expected in the vicinity of the sp^3 base. As such, the observed correlation between the conjugate acid (BH^+) pK_a values and reactivity of Zn-**13b**, Zn-**13c**, and Zn-**23** most likely reflects a difference in reactivity due to the inherent donor ability.[21] On the other hand, the most reactive pyridyl derivative Zn-**5** indicates that the less hindered pyridine with softer Lewis base character possesses superior donor/zinc-binding ability. The results with α-branched amine derivatives Zn-**13m** and Zn-**13n**, indicate that zinc-binding ability decreases with increasing steric hindrance.[22]

The above data support a direct role for the Lewis base in the course of the reaction. In addition, the enantiomeric excess of the reaction in Eq. 1 with the Zn-**13b** did not vary significantly as a function of conversion (Fig. 6) indicating that the composition of the catalytic species does not change over the course of the reaction. These results are in accord with our proposed transition state model (Fig. 4, **18**).

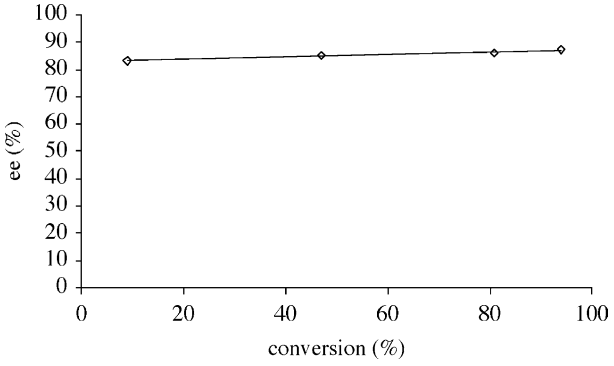


Figure 6. Conversion versus ee for Et_2Zn + PhCHO (Eq. 1) with Zn-**13b**.

To provide further evidence for this model, the reaction in Eq. 1 was examined for a nonlinear effect using the zinc complex derived from **13b**. A linear correlation was found between the product enantiomeric excess and the enantiomeric excess of **13b** (see Supporting information) consistent with a monomeric catalyst model **18**.

Interestingly, at temperatures above −20 °C the catalyst begins to deviate from Arrhenius behavior (Fig. 7), indicating the concurrent operation of different catalytic mechanisms.

A cooperative effects study was performed, using *tert*-butyl salen **24** in combination with *N*-methylmorpholine as an external Lewis base additive.[23] Neither Zn-**24** or *N*-methylmorpholine alone catalyzed the reaction. A combination of the Zn-**24** salen (10%) and *N*-methylmorpholine (20%) also

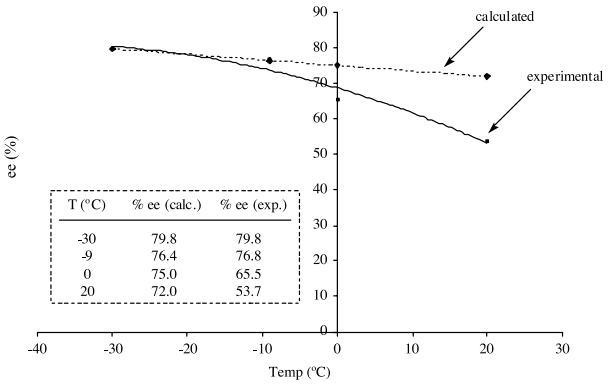


Figure 7. Non-Arrhenius behavior of catalyst Zn-**13b**.

failed to provide catalysis. The results of this study support a bifunctional activation model in which the Lewis acid and Lewis base portions in the same structure work together to promote a rapid asymmetric reaction.

Reaction rates for the reaction in Eq. 1 (1 equiv PhCHO + 10 equiv Et_2Zn) at 25 °C were also measured using a REACT-IR spectrometer. Rates were obtained at 4–20 mol% catalyst by monitoring the rate of disappearance of the aldehyde carbonyl stretching frequency over time. Using this data, the reaction was found to be first order in catalyst and first order in benzaldehyde, further supporting the proposed model **18** (Fig. 4).

2.4. Substrate scope

To demonstrate that the new catalyst system can accept different substrates, a number of other aldehydes were examined in the diethylzinc addition with Zn-**13b** (Eq. 2, Table 4). Similar levels of conversion and enantiomeric excess were obtained for aromatic aldehydes as well as aliphatic aldehydes.

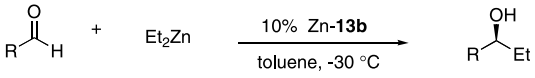


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Table 4. Zn-**13b** in the addition of Et_2Zn to RCHO (Eq. 2)[a]

Entry	R	Time (h)	Conv. (%)[b]	ee (%)[b]
1	Ph	12	98	87 (*S*)
2	*p*-MeO-C_6H_4	36	97	89 (*S*)
3	*p*-Cl-C_6H_4	10	92	83 (*S*)
4	*o*-Me-C_6H_4	36	99	69 (*S*)
5	Cy	24	78	75 (*S*)
6	$(CH_3CH_2)_2CH$	36	84	91 (*S*)

[a] Reactions were in $PhCH_3$ using 10 mol% ligand and 2.1 equiv Et_2Zn.
[b] Determined by chiral GC (Cyclodexβ). Absolute configuration assigned by comparison to the literature for entry 1. For all others, absolute configuration assigned by analogy.

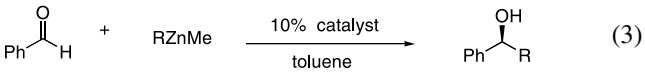
Metal complexes of morpholine salen **13b** and piperidine salen **13c** were also examined in the addition of other dialkylzinc nucleophiles to benzaldehyde (Eq. 3, Table 5). At −10 °C the addition of dimethylzinc to benzaldehyde proceeds to completion with modest enantioselectivity (Table 5, entry 2). The addition of phenylacetylide to benzaldehyde is very rapid at 0 °C with the zinc and titanium complexes of **13b–c** (Table 5, entries 5–6). When

Table 5. Addition of RZnMe to PhCHO (Eq. 3)[a]

Entry	R	Catalyst	T (°C)	Time (h)	Conv. (%)[b,c]	ee (%)[b]
1	Me	Zn-**13b**	25	2.5	99	44
2	Me	Zn-**13b**	−10	10	99	50
3	Me	Zn-**13b**	−30	20	42	50
4	CCPh	Zn-**13b**	−30	12	95 (88)	66 (*S*)
5	CCPh	Zn-**13b**	0	1	99 (96)	63 (*S*)
6	CCPh	Ti(O*i*-Pr)$_2$-**13c**	0	1	99	62 (*S*)
7	CCPh	Ti(O*i*-Pr)$_2$-**13c**	−20	20	100	73 (*S*)

[a] Reactions were in $PhCH_3$ using 10 mol% ligand and 2.1 equiv MeZnR.
[b] Determined by ^{1}H NMR and chiral GC (Cyclodexβ). Absolute configuration determined by comparison to the literature.
[c] Isolated yields in parentheses.

the temperature is lowered to −20 °C, the catalytic activity of Ti(O*i*-Pr)$_2$-**13c** is maintained and the enantioselectivity improves to 73% ee (Table 5, entry 7).



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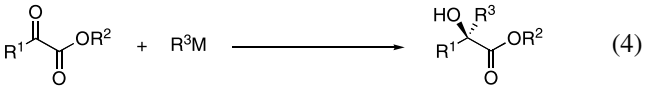
2.5. Addition of diethylzinc to α-ketoesters

The α-hydroxyester product of the addition of an organometallic to an α-ketoester contains a chiral quaternary center[24] and is a versatile synthetic precursor.[25] While a handful of methods are available for the catalytic asymmetric addition of soft nucleophiles to α-ketoesters,[26] relatively few methods exist for the enantioselective addition of hard nucleophiles.

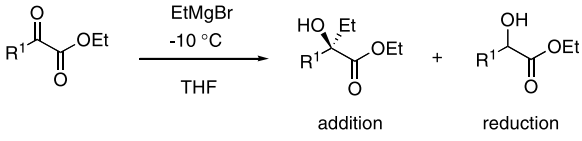


(4)

Diastereoselective additions of organometallics to chiral α-ketoesters have been studied extensively and many successful reports have been published.[27] Examples of the corresponding enantioselective addition are rare and most require the use of stoichiometric or excess chiral ligand.[28,29] For example, Seebach and Weber[29a] reported the enantioselective (68% ee) addition of octyl Grignard to methyl pyruvate in low yield (10%) in the presence of 1.1 equiv of TADDOL. Using excess (1.25–1.9 equiv) sparteine as a chiral mediator, Noyori et al.[29b] added EtMgBr and *n*-BuLi to ethylbenzoylformate with low selectivity (18%). In a third report, the asymmetric addition of a butyl group to methyl benzoylformate was accomplished in up to 43% ee, using a stoichiometric amount of a chiral lithium alkoxytributylaluminate.[29c] Recently, Shibasaki and co-workers have reported an enantioselective addition of dimethylzinc to α-ketoesters (59–96% ee) using a catalytic hydroxyproline derivative, but this method requires extensive reaction times (42 h) and does not tolerate more reactive alkylzinc reagents such as diethylzinc.[30]

Ketones and aldehydes are suitable electrophiles for Grignard reagents, however, they are generally inert toward dialkylzinc reagents and organozinc halides in the absence of catalyst. While many catalysts give rise to substantial ligand accelerated catalysis in[31] the asymmetric addition of alkyl zinc reagents to aldehydes, the corresponding ketone additions have been more difficult due to the greater steric hindrance of ketone carbonyls.[32] Assuming that the steric and electronic properties of α-ketoesters would confer a reactivity profile intermediate to that of aldehydes and ketones, we soon discovered that α-ketoesters react spontaneously and often uncontrollably with Grignard reagents, dialkylzinc reagents and organozinc halides. Furthermore, suppression of reactivity is minimal at low temperatures. Noyori and coworkers described similar enhanced reactivity with α-functionalized aldehydes and pyruvates, hypothesizing that bidentate coordination to the nucleophile facilitates the uncatalyzed achiral pathway.[33]

The development of a selective α-ketoester alkylation is further complicated due to competing reaction pathways. Two main products (addition and reduction) were encountered in the addition of ethylmagnesium bromide to α-ketoesters at −10 °C (Eq. 5, Table 6). We speculate that the reduction product arises via a metalloene pathway as illustrated in Scheme 4. Reduction is therefore possible with any organometallic that contains a β-hydrogen.[34]

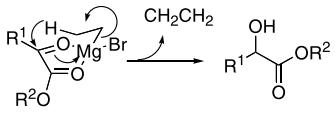


(5)

Table 6. Addition of EtMgBr to R^{1}COCO$_2$Et (Eq. 5)

Entry	R^1	Addition conv. (%)[a]	Reduction conv. (%)[a]
1	*p*-MeO-C$_6$H$_4$	81	16
2	*p*-Br-C$_6$H$_4$	69	22
3	Ph	60	19
4	*o*-Me-C$_6$H$_4$	38	19
5	β-Naphthyl	37	30
6	Me	38	52
7	Cy	31	54
8	*i*-Pr	21	48
9	*t*-Bu	21	63

[a] Determined by ^{1}H NMR spectroscopy



Scheme 4. Possible mechanism for reduction of α-ketoesters by EtMgBr.

Thus, several factors must be considered in developing enantioselective catalysts for the reaction in Eq. 6. First, the catalyst must accelerate asymmetric addition faster than the uncatalyzed, racemic addition. Second, the catalyst must accelerate addition to a greater degree than reduction. Prior

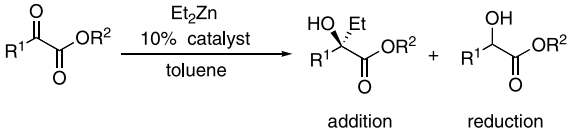
Table 7. M-**13c** in the addition of Et_2Zn to $PhC(O)CO_2Et$ (Eq. 6, $R^1=Ph$, $R^2=Et$)[a]

Entry	Catalyst	*T* (°C)	Time (h)	Redn (%)[b]	Addn (%)[b]	Addn ee (%)[b]
1	None	0	24	86	11	-
2	None	−40	2	45	23	-
3	Ni-**13c**	0	24	62	35	14 (*S*)
4	Cu-**13c**	0	24	12	75	18 (*R*)
5	Zn-**13c**	0	24	6	93	20 (*R*)
6	Zn-**13c**	−30	2	48	36	0
7	Mg-**13c**	−40	2	0	99	34 (*R*)
8[c]	Ti(O*i*-Pr)$_2$-**13c**	−30	48	8	68	52 (*R*)

[a] Reactions were in toluene with 10 mol% catalyst and 1.2 equiv Et_2Zn.
[b] Determined by chiral GC (Cyclodexβ column) and ^1H NMR spectroscopy. Absolute configuration determined by comparison to the literature.
[c] 1.32 equiv Et_2Zn.

to examining the salen catalysts in the additions of dialkylzincs to α-ketoesters, two control reactions were performed (Table 7, entries 1 and 2). Treatment of ethyl oxo(phenyl)acetate with Et_2Zn (Eq. 6, $R^1=Ph$, $R^2=Et$) revealed that reduction was the predominant pathway (86% at 0 °C, 45% at −40 °C) with lesser amounts of 1,2-addition (11% at 0 °C, 23% at −40 °C) occurring. From this result, it was clear that the rate of the 1,2-addition pathway was slow enough that the development of an asymmetric version by means of ligand-accelerated catalysis would be possible. The uncatalyzed reactions also revealed that suppression of the reduction pathway would be a major challenge in the development of this reaction. Recent related work of Shibasaki avoids this problem by using dimethylzinc; the lack of β-hydrogens precludes metalloene reduction.[30]

Our salen catalysts were found to be much more reactive in aldehyde alkylation compared to the Noyori type catalysts (Fig. 4). Believing that this higher reactivity profile would be useful, our investigation commenced with the piperidine salen metal complexes M-**13c**. In the absence of a catalyst, reduction is the principal pathway (86%) at 0 °C in the reaction of Et_2Zn with ethyl oxo(phenyl)acetate (Table 7, entry 1). In contrast, Zn-**13c** at 0 °C, affords 93% addition with very little reduction (Table 7, entry 5). This represents a 120-fold change in selectivity with respect to the uncatalyzed reaction, definitively indicating that the salen catalysts accelerate addition to a far greater degree than reduction. The Mg complex proved even more reactive, providing complete conversion to the addition product within 2 h at −40 °C (Table 7, entry 7). When the Ti(O*i*-Pr)$_2$ complex was examined, promising enantioselectivity (52%) was also observed at −30 °C (Table 7, entry 8). Encouraged by the improved enantioselectivity, we undertook a thorough examination of the reaction conditions with Ti(O*i*-Pr)$_2$-**13c**.



(6)

As expected, the reaction is optimal in nonpolar, noncoordinating solvents such as toluene, hexanes and pentane (Table 8). Further studies were undertaken with toluene due to incomplete catalyst solubility in hexanes or pentane.

Table 8. Solvent screening with Ti(O*i*-Pr)$_2$-**13c** in the addition of Et_2Zn to $PhC(O)CO_2Et$ (Eq. 6, $R^1=Ph$, $R^2=Et$)[a]

Entry	Solvent	Reduction Conv. (%)[b]	Addition Conv. (%)[b]	Addition ee (%)[b]
1	Toluene	8	68	52 (*R*)
2	Hexanes	0	88	62 (*R*)
3	Pentane	0	88	50 (*R*)
4	CH_2Cl_2	9	77	47 (*R*)
5	TBME	4	66	30 (*R*)
6	THF	7	12	17 (*R*)

[a] Reactions were at −30 °C with 10 mol% catalyst and 1.32 equiv Et_2Zn.
[b] Determined by chiral GC (Cyclodexβ) and ^1H NMR spectroscopy. Absolute configuration determined by comparison to the literature.

For the reactions in Tables 7 and 8 the Ti catalyst was generated in situ by treatment of the salen with Ti(O*i*-Pr)$_4$. The resultant solution was then treated with 1.32 equiv Et_2Zn followed by the substrate. As a result, the *i*-PrOH released upon metal complexation was converted into EtZn(O*i*-Pr) which may act as a catalyst or an inhibitor. To remove the EtZn(O*i*-Pr) from our analysis, the Ti complex was isolated by removal of all of the volatiles in vacuo. Under these conditions, the catalyst is freely soluble in $PhCH_3$ and was found to be much more reactive (99% conversion after 2 h vs 68% conversion after 48 h), more chemoselective (0% vs 8% reduction), and more

Table 9. M(O*i*-Pr)$_2$-**13c** catalysts in the addition of Et_2Zn to $PhC(O)CO_2Et$ (Eq. 6, $R^1=Ph$, $R^2=Et$)[a]

Entry	Catalyst	*T* (°C)	Time (h)	Redn (%)[b]	Addn (%)[b]	Addn ee (%)[b]
1	Ti(O*i*-Pr)$_4$	−40	2	46	30	–
2	Ti(O*i*-Pr)$_2$-**13c**	−40	2	0	99	62 (*R*)
3[c]	Al(O*i*-Pr)-**13c**	−40	2	0	92	21 (*R*)
4[c]	V(O)(O*i*-Pr)-**13c**	0	24	7	36	17 (*R*)
5	Zr(O*i*-Pr)$_2$-**13c**	−40	2	3	45	24 (*S*)

[a] Reactions were in toluene with 10 mol% catalyst and 1.2 equiv Et_2Zn.
[b] Determined by chiral GC (Cyclodexβ) and ^1H NMR spectroscopy. Absolute configuration determined by comparison to the literature.
[c] 1.32 equiv Et_2Zn.

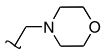
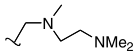
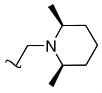
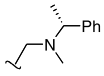
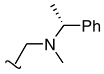
enantioselective (62% ee vs 52% ee). Even at low temperature this catalyst retained high reactivity (2 h, −40 °C, 99% conversion, 0% reduction, 62% ee). This improved protocol was used to screen further M(O*i*-Pr)$_n$ complexes for catalytic activity (Table 9).

Ti(O*i*-Pr)$_2$-**13c** outperformed all other M(O*i*-Pr)$_n$ complexes. Encouraged by the remarkable ligand acceleration (Table 9, entry 2 vs entry 1), we examined a number of other Lewis base functionalized salen ligands from our library as their titanium complexes (Table 10). This ligand screening confirmed the identification of Ti(O*i*-Pr)$_2$-**13c** as an optimal lead catalyst for further study and provided insight into the mechanism of catalysis.

2.6. Reaction mechanism

We propose that the piperidine group plays a critical role in this catalyst as a Lewis base activating group (Fig. 4, **18**, R^1=CO_2R, B=*N*-piperidine). In line with this hypothesis, the structurally similar complexes Ti(O*i*-Pr)$_2$-**13a–d** exhibited comparable reactivity and selectivity (Table 10, entries 1–4). More hindered amines are less effective for coordination of metal species (i.e., Et_2Zn) which is consistent with the decreased reactivity of 2,6-dimethylpiperidinyl Ti(O*i*-Pr)$_2$-**13n** (Table 10, entry 7). If the amine base is distant from the Ti center, bifunctional activation is less likely. This conjecture is supported by the lesser reactivity and selectivity of quinolinyl catalyst, Ti(O*i*-Pr)$_2$-**4** (Table 10, entry 12) compared to pyridinyl catalyst, Ti(O*i*-Pr)$_2$-**5** (Table 10, entry 6). Replacement of the amine with nonbasic groups should change the catalytic activity if this Lewis base causes activation. The lesser reactivity of the *tert*-butyl salen complex Ti(O*i*-Pr)$_2$-**24** (Table 10, entry 15) is consistent with this proposal. The use of chelating diamines (Table 10, entry 5), chiral diamines (Table 10, entries 8–11), or other activating groups (Table 10, entries 13–14) was not successful.

Table 10. Ti(O*i*-Pr)$_2$-salen in the addition of Et_2Zn to PhC(O)CO_2Et (Eq. 6, R^1=Ph, R^2=Et)[a]

Entry	Salen	Lewis base	Redn (%)[b]	Addn (%)[b]	Addn ee (%)[b]
1	**13a**		0	91	44 (*R*)
2	**13b**		9	72	54 (*R*)
3	**13c**		0	99	62 (*R*)
4	**13d**		3	94	54 (*R*)
5	**13e**		12	71	0
6	**5**		0	91	57 (*R*)
7	**13n**		10	84	20 (*S*)
8	**13o**		3	76	12 (*R*)
9	**13p**[c]		6	66	3 (*S*)
10	**13q**		0	98	15 (*R*)
11	**13r**[c]		1	98	50 (*S*)
12	**4**		5	57	7 (*S*)
13	**26**		2	66	5 (*S*)
14	**27**		15	63	0
15	**24**		20	56	4 (*S*)

[a] Reactions were in toluene with 10 mol% catalyst and 1.2 equiv Et_2Zn for 2 h.
[b] Determined by chiral GC (Cyclodexβ) and ^{1}H NMR spectroscopy. Absolute configuration determined by comparison to the literature.
[c] Salen derived from (1*S*,2*S*)-cyclohexanediamine.

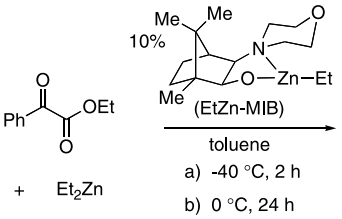
Although the *tert*-butyl salen is not a useful catalyst for this reaction alone, we investigated if asymmetric catalysis with Ti(O*i*-Pr)$_2$-**24** was possible under double activation conditions. *N*-Methylmorpholine (NMM)[23] was selected as a suitable Lewis base additive to be used in combination with this complex. The results of this experiment are collected in Table 11. In the absence of catalyst, reduction is the major reaction pathway (entry 1). The course of the reaction is not influenced by the presence of 20 mol% Lewis basic *N*-methylmorpholine (entry 2). Although some catalysis is observed with Lewis acidic Ti(O*i*-Pr)$_2$-**24** (Table 11, entry 3), the chemoselectivity and enantioselectivity are poor. When 2 equiv of *N*-methylmorpholine are added for every equiv of Ti(O*i*-Pr)$_2$-**24** (entry 4), similar results are observed as for Ti(O*i*-Pr)$_2$-**24** alone. Excess *N*-methylmorpholine relative to substrate with Ti(O*i*-Pr)$_2$-**24** diminishes reactivity and selectivity, showing that the amine is not simply deaggregrating the Et_2Zn (entry 5). The tethered Lewis acid and Lewis base clearly act in a cooperative manner as evidenced by the higher reactivity and enantioselectivity found in entry 6.

Table 11. Addition of Et_2Zn to $PhCOCO_2Et$ (Eq. 6, R^1=Ph, R^2=Et): Cooperative effects studies[a]

Entry	Catalyst	Redn. (%)	Addn. (%)[b]	Addn. ee (%)[b]
1	None	45	23	–
2	NMM	30	14	–
3	Ti(O*i*-Pr)$_2$-**24**	20	56	4 (*S*)
4	Ti(O*i*-Pr)$_2$-**24**+ NMM[c]	15	56	2 (*S*)
5	Ti(O*i*-Pr)$_2$-**24**+ NMM[d]	17	12	0
6	Ti(O*i*-Pr)$_2$-**13c**	0	99	62 (*R*)

[a] Addition of 1.2 equiv Et_2Zn with 10 mol% catalyst at −40 °C for 2 h.
[b] Determined by chiral GC (Cyclodexβ).
[c] 2.0 equiv (relative to Ti(O*i*-Pr)$_2$-**24**) of *N*-methylmorpholine added.
[d] 12 equiv (relative to Ti(O*i*-Pr)$_2$-**13c**) of *N*-methylmorpholine added.

Despite their success in aldehyde alkylation, we found that DAIB-type catalysts such as EtZn-MIB[35] performed poorly with α-ketoesters[36] (Eq. 7). This result serves to demonstrate the advantage of independent bifunctional activation.

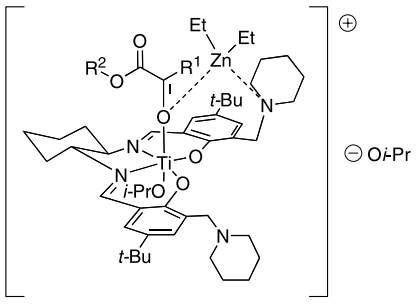


	Addition	Reduction
a) -40 °C, 2 h	25% conv, 5 % ee (*S*)	37% conv.
b) 0 °C, 24 h	30% conv, 0% ee	43% conv.

(7)

The data support a mechanism that involves ionization of an alkoxide group to provide a five-coordinate cationic Ti species (Fig. 8).[37] Unfortunately, attempts to promote the proposed ionization of isopropoxide with the addition of TMSOTf (5 mol% with 10 mol% Ti(O*i*-Pr)$_2$-**13c**) resulted in loss of catalytic activity (46% conv. addition, 0% ee; 15% conv. reduction after 2 h at −40 °C).

The lack of a nonlinear effect with enantio-impure **13c** in this reaction (Fig. 9) is also consistent with this proposed mechanism.



28

Figure 8. Proposed transition structure.

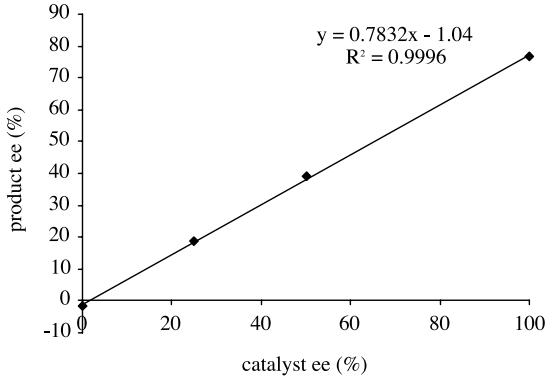


Figure 9. Linear relationship between catalyst ee and product ee (Et_2Zn + $PhCOCO_2Me$ using 10 mol% Ti(O*i*-Pr)$_2$-**13c** at −78 °C for 2 h).

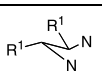
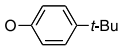
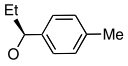
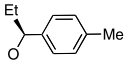
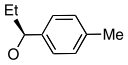
Also investigated was the effect of chiral product on enantioselectivity. When enantiopure 2-hydroxy-2-phenylbutyric acid ethyl ester was used as an apical ligand instead of *i*-PrO in **28** no significant enantiomeric excess was observed (7% ee (*R*)). This result suggests that the product, which can coordinate to titanium as an apical ligand, does not have a significant effect on the course of the reaction.

In the presence of 10 mol% Ti(O*i*-Pr)$_2$-**13c**, the reaction of methyl oxo(phenyl)acetate and diethylzinc is much faster than we originally estimated as judged by React-IR (reaction complete within 10 min at −40 °C). Although good catalytic activity is maintained at temperatures as low as −78 °C (reaction time=2 h), moderate enantioselectivity persists (74% ee). Unfortunately, this remarkable ligand-accelerated catalysis complicates kinetic measurements.

2.7. Diversity oriented synthesis of a ligand library

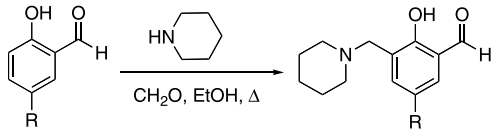
In an effort to increase enantioselectivity, we sought to extend our library of methylene tethered amino-salen ligands and their titanium complexes. Four segments of the amino-salen titanium complexes (Ti(L)$_2$-salen) can be altered easily. Modification of the diamine linker changes the stereochemical environment of the apical position or even the general shape of the salen structure. For example, BINAM allows the formation of salen metal complexes in which the metal ligands are not necessarily coplanar.[38] The Lewis acidity of the salen metal center can be altered by introduction of electron withdrawing or donating

Table 12. Addition of Et_2Zn to $PhCOCO_2Me$ (Eq. 6, R^1=Ph, R^2=Me): Screening the apical ligands (L) [$Ti(L)_2$-salen, R^2=*t*-Bu, NR^3_2=piperidine][a]

Entry	Catalyst	L		Redn. Conv. (%)[b]	Addn. Conv. (%)[b]	Addn. ee (%)[b]
1	$Ti(Oi\text{-}Pr)_2$-**13c**	O*i*-Pr		0	99	72 (*R*)
2[c]				0	99	72 (*R*)
3	$Ti(Ot\text{-}Bu)_2$-**13c**	O*t*-Bu		0	98	70 (*R*)
4	$TiCl_2$-**13c**	Cl		28	32	0
5[d]				9	63	0
6	$Ti(OAr)_2$-**13c**			0	92	81 (R)
7	$Ti(OR^*)_2$-**13c**			0	92	57 (*R*)
8	$Ti(OR^*)_2$-*ent***13c**			0	74	78 (*S*)
9	$Ti(OR^*)_2$-**13s**			0	60	18 (*S*)

[a] Reactions were in $PhCH_3$ at −40 °C for 2 h using 10 mol% catalyst.
[b] Determined by chiral GC (Cyclodex β). Absolute configuration determined by comparison to the literature.
[c] With 4 Å MS.
[d] In CH_2Cl_2.

C5-substituents (R^2) to the phenol ring. The basicity, hard/soft character, and the immediate stereochemical environment of the pendant amine base (NR^3_2) are also readily changed. Finally, the apical ligands (L) on the titanium center can be directly modified to provide complexes with different reactivity and substrate-binding profiles.



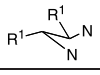
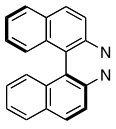
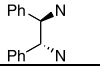
#	R	% yield	#	R	% yield	#	R	% yield
13c	t-Bu	70	**30**	NMe_2	37	**32**	Me	93
29	Cl	41	**31**	H	31	**33**	1-Ad	70

(8)

For each of the four variable segments, our selections were based on several factors, including commercial availability or ease of preparation. The elements examined provide a range of electronic and steric properties. Similarly, the various C5-substituted salens were easily prepared using the aromatic Mannich reaction (Scheme 2 and Eq. 8). The aminosalicylaldehyde precursors are either commercially available or prepared in one step.[39] In our early examination of the Lewis base moiety we discovered that the best catalysts contain the cyclic amines piperidine, morpholine and pyrrolidine (Table 10, entries 2–4). Since α-substituted piperidine derivatives are not useful (Table 10, entry 7) a number of commercially available substituted piperazines were investigated. Using a parallel synthesis strategy and a systematic screening approach, 30 of the 720 possible catalysts were prepared and tested in a rapid and efficient manner.

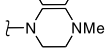
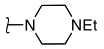
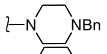
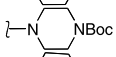
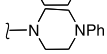
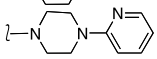
Beginning at the titanium center, various apical ligands were examined (Table 12). If our proposed mechanism

Table 13. Addition of Et_2Zn to $PhCOCO_2R$ (Eq. 6, R^1=Ph): Screening the diamine [$Ti(L)_2$-salen, L=O*i*-Pr, R^2=*t*-Bu, $NR^3{}_2$=piperidine][a]

Entry	Catalyst			Redn. (%)[b]	Addn. (%)[b]	Addn. ee (%)[b]
1	$Ti(Oi\text{-}Pr)_2$-**13c**		R=Me	0	99	72
2			R=Et	0	99	62
3	$Ti(Oi\text{-}Pr)_2$-**34**		R=Et	18	47	0
4	$Ti(Oi\text{-}Pr)_2$-**35**		R=Me	0	94	81
5			R=Et	0	92	65

[a] Reactions were in $PhCH_3$ at −40 °C for 2 h using 10 mol% catalyst.
[b] Determined by chiral GC (Cyclodex β).

Table 14. Addition of Et_2Zn to $PhCOCO_2R$ (Eq. 6, R^1 = Ph): Screening the amine Lewis base (NR^3_2) [$Ti(L)_2$-salen, L = O*i*-Pr, R^2 = *t*-Bu, diamine linker = (*R*,*R*)-1,2-cyclohexanediamine][a]

Entry	Catalyst	NR^3_2		Addn. (%)[b]	ee (%)[b]
1	Ti(O*i*-Pr)$_2$-**13c**		R = Me	99	72
2			R = Et	99	62
3	Ti(O*i*-Pr)$_2$-**13f**		R = Me	96	51
4	Ti(O*i*-Pr)$_2$-**13g**		R = Me	89	81
5			R = Et	78	72
6	Ti(O*i*-Pr)$_2$-**13h**		R = Me	97	76
7			R = Et	96	64
8	Ti(O*i*-Pr)$_2$-**13i**		R = Me	97	70
9	Ti(O*i*-Pr)$_2$-**13j**		R = Me	97	76
10	Ti(O*i*-Pr)$_2$-**13k**		R = Me	90	80
11	Ti(O*i*-Pr)$_2$-**13l**		R = Me	98	79

[a] Reactions were in $PhCH_3$ at −40 °C for 2 h using 10 mol% catalyst.
[b] Determined by chiral GC (Cyclodex β). Absolute configuration (*R*) determined by comparison to the literature. No reduction observed.

(Figure 8, **28**) is correct then the nature of the alkoxide ligands should not dramatically affect the selectivity as the remaining alkoxide ligand in **28** is distal from the site of stereochemical induction.[40] Indeed, similar results were obtained when Ti(O*t*-Bu)$_4$ was used in place of Ti(O*i*-Pr)$_4$ (Table 12, entry 1 vs 3). The $TiCl_2$-complex is partially insoluble and unreactive in toluene. Although soluble in CH_2Cl_2, $TiCl_2$-**13c** is a slow, nonselective catalyst (Table 12, entries 4–5).[41] When a chiral Ti-alkoxide is used to generate the salen complex, the influence of the alkoxide configuration on the enantioselectivity is relatively small (Table 12, entries 7–9 vs entry 1). An improvement in enantioselectivity was observed for the catalyst derived from *p*-(*t*-Bu)C_6H_4OH (entry 6).

We next examined various diamine linkers. The catalyst derived from (*R*,*R*)-1,2-diphenylethylenediamine is slightly more selective than that derived from cyclohexanediamine for both the methyl and ethyl oxo(phenyl)acetate (Table 13, entries 4–5 vs entries 1–2).

The catalysts derived from substituted piperazine salens are generally more enantioselective than the lead catalyst derived from piperidine salen **13c** (Table 14). A slight increase in enantioselectivity was observed for both the ethyl and methyl oxo(phenyl)acetate with the catalyst derived from *N*-methyl-piperazine (Table 14, entries 4–5 vs entries 1–2).

Finally we examined catalysts derived from various *para*-substituted amino salens (Table 15). The steric (Table 15, entries 6–7) and electronic (Table 15, entries 3, 8) of the *t*-Bu substituent were optimal.[42] Thus, only the *para*-adamantyl catalyst afforded comparable enantioselectivity to the *t*-Bu catalyst (Table 15, entries 4–5 vs entries 1–2).

New catalysts derived from various combinations of optimal structural elements were then examined (Table 16). Unfortunately, the ultimate combination of structural elements is elusive as their respective beneficial effects do not appear to be additive. To date we have identified seven highly reactive complexes that catalyze the addition of diethylzinc to methyl oxo(phenyl)acetate (Eq. 6, R^1 = Ph, R^2 = Me) in >90% conversion and >80% ee: Table 12, entry 6; Table 13, entry 4; Table 14, entries 4, 10; Table 16, entries 2, 3 and 7.

2.8. Substrate scope

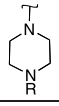
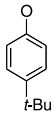
The scope of this reaction was examined with the easily prepared Ti(O*i*-Pr)$_2$-**13c** since it affords a good combination of reactivity and selectivity. In all cases, the catalyst greatly accelerates the addition pathway (Table 17) and provides a moderate degree of stereochemical control. Interestingly, we discovered a direct correlation between enantioselectivity and the steric size of the ester substituent

Table 15. Addition of Et_2Zn to $PhCOCO_2R$ (Eq. 6, R^1 = Ph): Screening the *para*-substituent (R^2) [$Ti(L)_2$-salen, L = O*i*-Pr, $NR^3{}_2$ = piperidine, diamine linker = (*R*,*R*)-1,2-cyclohexanediamine][a]

Entry	Catalyst	R^2		Addn. (%)[b]	Ee (%)[b]
1	Ti(O*i*-Pr)$_2$-**13c**	*t*-Bu	R = Me	99	72
2			R = Et	99	62
3	Ti(O*i*-Pr)$_2$-**36**	NMe_2	R = Et	94	46
4	Ti(O*i*-Pr)$_2$-**37**	1-adamantyl	R = Me	98	73
5			R = Et	92	61
6	Ti(O*i*-Pr)$_2$-**38**	Me	R = Et	81	25
7	Ti(O*i*-Pr)$_2$-**39**	H	R = Et	87	39
8	Ti(O*i*-Pr)$_2$-**40**	Cl	R = Et	74	16

[a] Reactions were in $PhCH_3$ at −40 °C for 2 h using 10 mol% catalyst.
[b] Determined by chiral GC (Cyclodex β). Absolute configuration (*R*) determined by comparison to the literature. No reduction observed.

Table 16. Addition of Et_2Zn to $PhCOCO_2Me$ (Eq. 6, R^1=Ph, R^2=Me): Combining optimal catalyst elements[a]

Entry	Catalyst	L		R^2		Addn. (%)[b]	ee (%)[b]
1	Ti(OAr)$_2$-**13g**			*t*-Bu	Me	77	43
2	Ti(OAr)$_2$-**41**			*t*-Bu	Me	97	80
3	Ti(O*i*-Pr)$_2$-**41**	O*i*-Pr		*t*-Bu	Me	93	83
4	Ti(O*i*-Pr)$_2$-**42**	O*i*-Pr		*t*-Bu	Et	98	57
5	Ti(O*i*-Pr)$_2$-**43**	O*i*-Pr		*t*-Bu	Boc	66	60
6	Ti(O*i*-Pr)$_2$-**44**	O*i*-Pr		*t*-Bu	Ph	99	68
7	Ti(O*i*-Pr)$_2$-**45**	O*i*-Pr		*t*-Bu	2-pyridine	88	81
8	Ti(O*i*-Pr)$_2$-**46**	O*i*-Pr			Me	91	61
9	Ti(O*i*-Pr)$_2$-**46**	O*i*-Pr			Me	91	74

[a] Reactions were in $PhCH_3$ at −40 °C for 2 h using 10 mol% catalyst.
[b] Determined by chiral GC (Cyclodex β). Absolute configuration (*R*) determined by comparison to the literature. No reduction observed.

Table 17. Addition of Et_2Zn to α-ketoesters (Eq. 6) using (*R*,*R*)-Ti(O*i*-Pr)$_2$-**13c**[a]

Entry	R^1	R^2	Yield (%)[b]	ee (%)[b]
1	Ph	Me	89	72 (*R*)
2	Ph	Et	78	62 (*R*)
3	Ph	Bn	100	50 (*R*)
4	Me	Me	90	16 (*S*)
5	Me	*i*-Pr	98	65 (*S*)

[a] Reactions were in $PhCH_3$ at −40 °C for 2 h using 10 mol% catalyst.
[b] Determined by chiral GC (Cyclodex β). Absolute configuration assigned by comparison to the literature for entries 1 and 2. For all others, absolute configuration assigned by analogy. No reduction observed.

Table 18. Addition of Et_2Zn to α-ketoesters (Eq. 6) using (*R*,*R*)-Ti(O*i*-Pr)$_2$-**13c** prepared with different amounts of Ti(O*i*-Pr)$_4$[a]

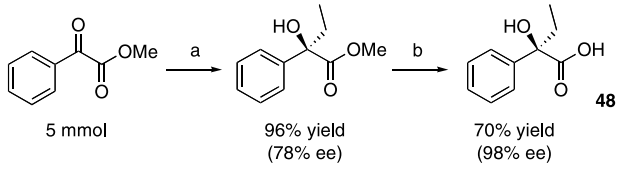
Entry	R^1	R^2	10% Ti(O*i*-Pr)$_4$ ee (%)[b]	70% Ti(O*i*-Pr)$_4$ ee (%)[b,c]
1	Ph	Me	72 (*R*)	88 (*R*)
2	Ph	Et	62 (*R*)	68 (*R*)
3	Ph	Bn	50 (*R*)	50 (*R*)
4	Fur	Me	72 (*R*)	72 (*R*)
5	*p*-MeO	Me	52 (*R*)	73 (*R*)
6	*p*-Br	Me	42 (*R*)	70 (*R*)
7	*o*-MeO	Me	72 (*R*)	85 (*R*)
8	*p*-NO_2	Me	39 (*R*)	65 (*R*)
9	*p*-CF_3	Me	73 (*R*)	83 (*R*)
10	PhCC	Me	53 (*R*)	80 (*R*)
11	PhCH=CH	Me	20 (*R*)	5 (*R*)
12	PhCCl=CH	Me	53 (*R*)	68 (*R*)
13	Cy	Me	24 (*R*)	75 (*R*)
14	*i*-Pr	Me	30 (*R*)	72 (*R*)
15	Me	Me	16 (*S*)	10 (*S*)
16	Me	*i*-Pr	65 (*S*)	50 (*S*)

[a] Reactions were in $PhCH_3$ at −40 °C for 2 h using 10 mol% catalyst. No reduction observed.
[b] Determined by chiral GC (Cyclodex).
[c] Determined by chiral HPLC (Chialpak AD). Absolute configuration assigned by comparison to the literature for entries 1 and 2. For all others, absolute configuration assigned by analogy.

(Eq. 6, R^2). For the benzoylformate ketoesters (R^1=Ph), higher enantioselectivity was observed with smaller ester substituents (Table 17, entries 1–3). This phenomenon is apparently general since the enantioselectivity is greater with the methyl ester (R^2=Me) than with the ethyl ester (R^2=Et) for a variety of α-ketoesters. One exception to this trend was observed with the pyruvate ketoesters (R^1=Me). With this series we observed higher enantioselectivity with larger ester substituents (Table 17, entries 4–5). The importance of steric differentiation about the keto carbonyl is interesting as it provides evidence for catalyst binding at the keto-carbonyl.

In a recent report by Wang and co-workers, it was shown that small variations in the ligand to Ti(O*i*-Pr)$_4$ ratio in the addition of zinc acetylides to aldehydes had a major impact on the enantioselectivity of the products.[43] Examining different amounts of piperidine salen and Ti(O*i*-Pr)$_4$ showed that an optimal ratio of 1–7 (ligand to Ti(O*i*-Pr)$_4$) increased the enantioselectivity in the addition of diethylzinc to methyl benzoylformate from 72 to 88% ee. Using these conditions, many substrates displayed marked increases (Table 18).

In order to demonstrate the utility of this method, the addition of diethylzinc to methyl oxo(phenyl)acetate (Table 18, entry 1) was performed on a 5 mmol scale using 5 mol% Ti(O*i*-Pr)$_2$-**13c** without additional Ti(O*i*-Pr)$_4$ (Scheme 5). The α-hydroxyester was isolated in 96% yield (99% conv.) with 78% ee. With added Ti(O*i*-Pr)$_4$ accordingly higher selectivity levels were obtained. After ester

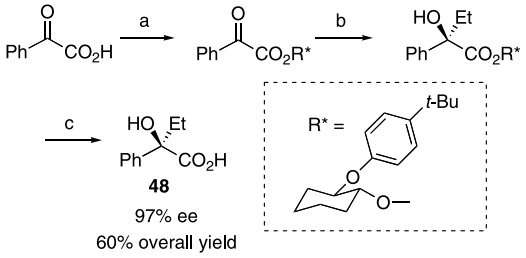


Scheme 5. Large scale synthesis and enrichment. (a) Et_2Zn, Ti(O*i*-Pr)$_2$-**13c**, $PhCH_3$, −40 °C, 2 h. (b) (i) EtOH, KOH. (ii) Recrystallize.

hydrolysis, the corresponding α-hydroxy acid **48** could be readily enriched to 98% ee by recrystallization. For this two-step sequence, a 70% yield of α-hydroxy acid **48** with 98% ee is obtained.

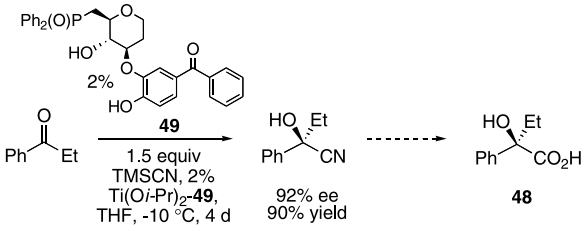
2.9. Comparison to known methods

We have developed a number of efficient catalysts for the enantioselective addition of diethylzinc to α-ketoesters. The catalysts are rapid, chemoselective and general. This method is superior to other established methods for the stereoselective synthesis of chiral quaternary hydroxy acids. One of the most practical diastereoselective alkylations of α-ketoesters utilizes a large excess of ethyl zinc chloride (5 equiv) prepared in situ from ethyl Grignard and $ZnCl_2$ (Scheme 6). Utilizing this method, 2-hydroxy-2-phenyl-butyric acid **48** can be prepared in 97% ee and 60% overall yield from oxo(phenyl)acetic acid.[44] In comparison, our method provides the product in greater overall yield.



Scheme 6. Diastereoselective synthesis of quaternary α-hydroxyesters. (a) (1*R*, 2*R*)-*R**OH, *p*-TsOH, benzene, △. (b) 5 equiv EtZnCl, −78 °C (3 h) to rt (1 h). (c) KOH, EtOH.

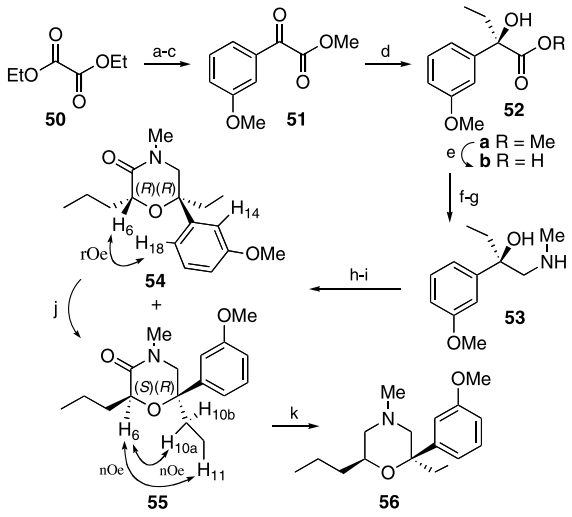
The best catalyst for the asymmetric addition of TMSCN to ketones[45] is the titanium complex of ligand **49** (Scheme 7).[46] However, the synthesis of ligand **49** is long (>9 steps in the longest linear sequence) and catalyst preparation is complex. While catalyst loadings between 1 and 2.5 mol% are generally sufficient, the reactions require 2–4 d between −10 and −50 °C. In contrast, the synthesis of chiral ligand **13c** requires only three steps (Schemes 1 and 2) and reaction of the α-ketoester with Ti(O*i*-Pr)$_2$-**13c** requires only 2 h at −40 °C (Scheme 5).



Scheme 7. Enantioselective synthesis of quaternary α-hydroxyesters.

2.10. Synthesis of a Wyeth pharmaceutical agent

The utility of this methodology has been highlighted in the enantioselective synthesis of a Wyeth pharmaceutical agent, 3-[(2*R*, 6*R*)-2-ethyl-4-methyl-6-*n*-propyl-2-morpholinyl] phenol, which possesses potent opiate antagonistic activity. The initial report of this compound described a racemic synthesis.[47] The synthesis commenced with Grignard addition of 3-methoxyphenyl magnesium bromide to ethyl oxalate, followed by saponification and methylation, to provide ketoester substrate **51** (Scheme 8). Ti(O*i*-Pr)$_2$-**13c** catalyzed alkylation, followed by saponification and recrystallization provided α-hydroxy acid **52b** in 99% ee and 78% yield. Conversion of the acid to the amide and subsequent reduction yielded amine **53**, which was cyclized by treatment with 2-chloro-pentanoyl chloride and base to provide heterocycles **54** and **55** as a 1:1 mixture of diastereomers which were assigned based on NOE and ROESY experiments. Conditions to convert diastereomer **54** to the required **55** were explored. Thermodynamic conditions (*tert*-butoxide in refluxing THF) gave a 5:1 ratio of **54** to **55**, whereas kinetic conditions (NaH in refluxing $PhCH_3$) gave a 1.6:1 ratio of **54** to **55**. Reduction of **55** with $LiAlH_4$ provided Wyeth compound **56**.



Scheme 8. Synthesis of a Wyeth pharmaceutical agent. Conditions: (a) 3-MeOPhMgBr. (b) KOH, MeOH. (c) MeI, DBU (74%, three steps). (d) Et_2Zn, Ti(O*i*-Pr)$_2$-**13c**. (e) KOH, MeOH, recrystalization (99% ee, 78%, two steps). (f) NH_2Me, $SOCl_2$ (82%). (g) $BH_3S(CH_3)_2$ (93%). (h) 2-Chloro-pentanoyl chloride, Et_3N. (i) KOH, *i*-PrOH. (j) NaH, three recycles (43%, three steps). (k) $LiAlH_4$ (90%).

3. Conclusions

These readily constructed bifunctional salen catalysts are among the most rapid for the addition of diethyl zinc to aldehydes, providing high enantioselectivities for both aromatic and aliphatic substrates. In addition, amino-salen titanium complexes rapidly alkylate α-ketoesters with excellent chemoselectivity and good enantioselectivity. Mechanistic studies have shown that a bifunctional mechanism is plausible for both of these reactions. Furthermore, an opiate antagonist has been synthesized enantioselectively using this methodology.

4. Experimental

4.1. General

Full details of the characterization of all new compounds and the mechanistic experiments can be found in Supporting information.

4.1.1. 5-*tert*-Butyl-2-hydroxy-3-piperidin-1-ylmethyl-benzaldehyde (12c). Piperidine (1.1 equiv) and paraformaldehyde (1.1 equiv) were combined in EtOH (0.3 M). The slurry was heated at 60 °C for 1–2 h (a clear solution usually results). Salicylaldehyde **8** (1.0 equiv) was added in one portion. After heating at reflux for 3 d, the EtOH was removed in vacuo. Chromatography afforded compound **12c** as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.65 (s, 1H), 7.26 (s, 1H), 3.71 (s, 2H), 2.03 (br s, 4H), 1.66 (m, 4H), 1.50 (br s, 2H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 159.9, 141.5, 132.3, 123.9, 122.8, 122.4, 61.3, 53.9, 34.1, 31.3, 25.7, 23.8. Compound **12c** has previously been synthesized by an alternative method.[48]

4.1.2. (−)-(*R*,*R*)-Cyclohexanediamine-(*p*-*t*-Bu)-(piperidin-1-ylmethyl)-salen (13c). Salicylaldehyde **12c** (2.0 equiv) in EtOH (1 mL/100 mg salicylaldehyde) was treated with the diamine (1.0 equiv) and was allowed to stir at room temperature for 24 h. After removal of the volatiles, **13c** was crystallized from EtOH as yellow clusters (90% yield): mp 88–94 °C; $[\alpha]_D^{20}$ −315 (*c* 0.5, $CHCl_3$); IR (film) 2933, 2857, 2791, 2756, 1629 (s), 1467, 1271 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.35 (br s, 2H), 8.29 (s, 2H) (HC=N), 7.36 (s, 2H), 7.06 (s, 2H), 3.58 (d, J=13.4 Hz, 2H), 3.50 (d, J=13.4 Hz, 2H) [AB], 3.29 (m, 2H), 2.43 (br s, 8H), 1.87 (m, 4H), 1.70– 1.36 (m, 16H), 1.24 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 164.8, 157.2, 140.4, 130.5, 126.4, 125.0, 117.9, 72.7, 57.0, 54.5, 33.8, 32.3, 31.4, 26.0, 24.4, 24.3; MS (ES) *m*/*z* 629 (MH^+); HRMS (ES) *m*/*z* calcd for $C_{40}H_{61}N_4O_2$ (MH^+) 629.4794, found 629.4786.

4.1.3. General procedure for addition of Et_2Zn and Me_2Zn to aldehydes. The salen (0.025 mmol) was introduced into a dry Schlenk flask, and the system was purged with N_2. After dissolution in $PhCH_3$ (1 mL), Et_2Zn (25 μL, 1.0 M in $PhCH_3$, 0.025 mmol) or Me_2Zn (12.5 μL, 2.0 M in $PhCH_3$, 0.025 mmol) was added. After stirring at rt for 1 h, the reaction was cooled to the indicated reaction temperature. Et_2Zn (500 μL, 1.0 M in $PhCH_3$, 0.500 mmol) or Me_2Zn (250 μL, 2.0 M in $PhCH_3$, 0.500 mmol) was added slowly. After 5 min, the aldehyde (0.25 mmol) was added dropwise. At the specified time, the reaction was quenched with 1 N HCl (aromatic aldehydes) or saturated NH_4Cl (aliphatic aldehydes), and then extracted with pentane. Spectral data for the addition of Et_2Zn to benzaldehyde is identical to that reported in literature.[49]

4.1.4. General procedure for formation of the metal salen complexes. The salen (0.030 mmol) was introduced into a dry Schlenk flask, and the system purged with N_2. After dissolution in $PhCH_3$ (1 mL), Ti(O*i*-Pr)$_4$ (18 μL, 1.4 M in hexanes, 0.025 mmol) was added. After stirring at room temperature for 1 h the $PhCH_3$, the volatiles were removed in vacuo. Fresh $PhCH_3$ (1 mL) was added to provide the catalyst solution.

4.1.5. General procedure for the addition of diethylzinc to α-ketoesters. After the catalyst solution (see above) was cooled to −40 °C, Et_2Zn (300 μL, 1.0 M in $PhCH_3$, 0.30 mmol) was added slowly. After 30 min, the α-ketoester (0.25 mmol) was added dropwise neat or as a 1 M solution in $PhCH_3$. After 2 h, the reaction was quenched by injection of 1 mL water, allowed to warm to room temperature, and then extracted with pentane or EtOAc. The extracts were dried over Na_2SO_4, and concentrated. Chromatography (10% EtOAc/hexanes) afforded pure α-hydroxy ester.

4.1.6. 2-Hydroxy-2-(3-methoxy-phenyl)-butyric acid methyl ester (52a). (93%): $[\alpha]_D^{20}$ −9.9 (*c* 0.015, CH_2Cl_2, 85% ee); IR (film) 3513, 2957, 2883, 2837, 1729, 1602 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J=10 Hz, 3H), 1.91–1.99 (m, 1H), 2.12–2.19 (m, 1H), 3.73 (s, 3H), 3.75 (s, 3H), 6.85–6.87 (m, 1H), 7.17–7.21 (m, 2H), 7.28–7.30 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ=8.5, 33.1, 53.6, 55.6, 79.2, 111.9, 113.4, 118.4, 129.6, 143.9, 160.0, 176.1; HRMS (ESI) calcd for $C_{12}H_{16}O_4$ (MNa^+) 247.0946, found 247.0930.

4.1.7. 2-Hydroxy-2-(3-methoxy-phenyl)-butyric acid (52b). The α-hydroxy ester (168 mg, 0.75 mmol) was stirred 5% KOH in EtOH (5 mL). After 1.5 h, the reaction was diluted with water and brought to pH 2 with HCl (10%). The mixture was extracted with EtOAc 2X, washed with brine, and dried (Na_2SO_4). Crystallization from CCl_4 yielded **52b** as a white solid (78% yield): mp 118–122 °C; $[\alpha]_D^{20}$ −26 (*c* 0.03, CH_2Cl_2, >99% ee); IR (film) 3428, 2972, 2941, 2841, 2629, 1718, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.97 (t, J=12 Hz, 3H), 2.02–2.14 (m, 1H), 2.23–2.34 (m, 1H), 3.83 (s, 3H), 6.84–6.88 (m, 1H), 7.19–7.22 (m, 2H), 7.27–7.32 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.4, 33.1, 55.7, 79.1, 112.0, 113.7, 118.4, 129.7, 143.1, 160.0, 179.6; HRMS (ESI) calcd for $C_{11}H_{14}O_4$ (M^+) 210.0892, found 210.0884.

4.1.8. 2-Hydroxy-2-(3-methoxy-phenyl)-*N*-methyl-butyramide. To a solution of **52b** (394 mg, 1.9 mmol) in $PhCH_3$ and THF (1:1) at −5 °C was added of $SOCl_2$ (164 μL, 2.3 mmol) followed by dropwise addition of methylamine (8 mL, 2 M in THF, 19 mmol). After completion, the mixture was washed with brine and back extracted with $PhCH_3$. The combined organic extracts were washed with brine and dried (Na_2SO_4). Chromatography (10% MeOH/CH_2Cl_2) afforded pure α-hydroxy amide as a white solid (82%); mp 98–104 °C; $[\alpha]_D^{20}$ −11.8 (*c* 0.0093, CH_2Cl_2, >99% ee); IR (film) 3381, 2968, 2883, 1652, 1602, 1536 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J=12.3 Hz, 3H), 2.07–2.12 (m, 1H), 2.20–2.30 (m, 1H), 2.80 (d, J=4.9 Hz, 3H), 3.82 (s, 3H), 6.82–6.86 (m, 1H), 7.14–7.16 (m, 2H), 7.29 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.0, 26.6, 32.6, 55.5, 79.3, 111.9, 113.3, 118.0, 129.7, 144.4, 160.0, 174.7; HRMS (ESI) calcd for $C_{12}H_{17}NO_3$ (M^+) 223.1202, found 223.1202.

4.1.9. 2-(3-Methoxy-phenyl)-1-methylamino-butan-2-ol (53). $BH_3 \cdot SMe_2$ (182 μL, 1.68 mmol) was added dropwise under N_2 to a stirred suspension of the α-hydroxy amide (150 mg, 0.67 mmol) in $PhCH_3$ at 0 °C. After heating at 105 °C for 2.5 h, the reaction was quenched with 10% aqueous Na_2CO_3 and extracted with $PhCH_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated. Kugelrohr distillation provided pure amine **53** as a yellow oil (93%); $[\alpha]_D^{20}$ +35 (*c* 0.033, CH_2Cl_2); IR (film) 3324, 3078, 2834, 2797, 2366, 2268, 2082, 1600, 1582 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (t, J=7.4 Hz, 3H), 1.65–1.70 (m, 2H), 2.28 (s, 3H), 2.58 (d, J=11.7 Hz, 1H), 2.95

(d, J=11.6 Hz, 1H), 3.74 (s, 3H), 6.79–6.81 (m, 1H), 6.98–6.99 (m, 1H), 7.04–7.05 (m, 1H), 7.38–7.40 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 7.4, 33.4, 36.5, 55.0, 61.5, 75.1, 111.4, 111.6, 111.7, 128.9, 158.0, 169.0; HRMS (ESI) calcd for $C_{12}H_{19}NO_2$ (MH^+) 210.1494, found 210.1504.

4.1.10. 6-Ethyl-6-(3-methoxy-phenyl)-4-methyl-2-propyl-morpholin-3-one (54). To a solution of of **53** (45 mg, 0.215 mmol) in CH_2Cl_2 at 0 °C under N_2 was added 2-chloro-pentanoyl chloride (37 mg, 1 M in CH_2Cl_2, 0.258 mmol). After 6 h, the reaction mixture was washed with 1 M HCl, dried ($MgSO_4$) and concentrated. After dissolution in *i*-PrOH (10 mL), aqueous NaOH (2 mL, 10 M) was added dropwise at 0 °C and the mixture warmed to rt and stirred overnight. After removal of the volatiles and dilution with H_2O, the reaction mixture was neutralized with 10% HCl, extracted with CH_2Cl_2, and dried ($MgSO_4$). Chromatography (60% EtOAc/hexanes) afforded a 1:1 mixture of diastereomers **54** and **55** as colorless oils. NOE experiments on diastereomer **55** found a strong NOE between H_6 and H_{10a} (absence of NOE for H_{10b}). A NOE was also present between H_6 and protons on C_{11}.

Diastereomer **54** was converted to **55** by refluxing in NaH (20 equiv) and THF. The reaction was quenched with H_2O and extracted with ether to yield diastereomer **55** after three recycles (43% yield, three steps): diastereomer **54**; $[\alpha]_D^{20}$+46 (c 0.0065, CH_2Cl_2); IR (film) 2961, 2870, 1656, 1582, 1488 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.66 (t, J=7.6 Hz, 3H), 0.88 (t, J=7.4 Hz, 3H), 1.20 (m, 2H), 1.73–1.79 (m, 4H), 2.94 (s, 3H), 3.58 (d, J=12.8 Hz, 1H), 3.68 (d, J=12.7 Hz, 1H), 3.75 (s, 3H), 3.83–3.86 (dd, J=3.62, 11.02 Hz, 1H), 6.74–6.69 (m, 2H), 7.19–7.23 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.2, 14.2, 18.7, 34.9, 35.7, 53.9, 55.5, 73.1, 77.1, 112.7, 113.2, 118.9, 129.9, 141.7, 160.2, 170.0; HRMS (ESI) calcd for $C_{17}H_{25}NO_3$ 292.1913 (MH^+), found 292.1925. Diastereomer **55**; $[\alpha]_D^{20}$−28 (c 0.005, CH_2Cl_2); IR (film) 2961, 2873, 2358, 1651, 1584, 1488 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.62 (t, J=7.3 Hz, 3H), 0.93 (t, J=7.4 Hz, 3H), 1.52 (sextet, J=7.5 Hz, 2H), 1.65–1.70 (m, 1H), 1.75–1.80 (m, 1H), 1.95–19.8 (m, 1H), 2.22 (sextet, J=7.3 Hz, 1H), 3.24–3.26 (d, J=12.3 Hz, 1H), 3.45–3.51 (d, J=12.3 Hz, 1H), 1.84 (s, 3H), 4.14–4.16 (dd, J=3.3, 11.3 Hz, 1H), 6.75–6.78 (m, 1H), 6.86–6.88 (m, 1H), 6.95–6.96 (m, 1H), 7.20–7.24 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 7.3, 14.2, 18.9, 26.9, 35.1, 35.1, 55.5, 58.5, 72.0, 111.8, 112.1, 117.2, 129.6, 144.6, 159.8, 169.9; HRMS (ESI) calcd for $C_{17}H_{25}NO_3$ (MH^+) 292.1915, found 292.1920.

4.1.11. 2-Ethyl-2-(3-methoxy-phenyl)-4-methyl-6-propyl-morpholine (56). After heating a suspension of $LiAlH_4$ (39 mg, 1.02 mmol) and **55** (14.8 mg, 0.051 mmol) in $PhCH_3$ (2 mL) at reflux for 2 h, the reaction mixture was quenched with H_2O, followed by NaOH, and H_2O. The mixture was extracted with $PhCH_3$, washed with brine, and dried (Na_2SO_4). Chromatography (10% MeOH/CH_2Cl_2) afforded **57** as a single diastereomer (90% yield). $[\alpha]_D^{20}$ −14.5 (c 0.0047, CH_2Cl_2); IR (film) 2934, 2873, 2792, 1610, 1583 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.62 (t, J=7.4 Hz, 3H), 0.98 (t, J=7.2, Hz, 3H), 1.43–1.46 (m, 2H), 1.46–1.67 (m, 5H), 1.94 (d, J=11.1 Hz, 1H), 2.28 (s, 3H), 2.66 (sextet, J=7.4 Hz, 1H), 2.78 (d, J=9.2 Hz, 1H), 2.96 (d, J=10.9 Hz, 1H), 3.82 (s, 3H), 3.78–3.85 (m, 1H), 6.77–6.79 (dd, J=2.6, 8.12 Hz, 1H), 6.94–6.97 (m, 1H), 7.04–7.05 (m, 1H), 7.23–7.28 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 7.1, 14.6, 19.0, 26.8, 30.0, 36.5, 46.6, 55.4, 60.7, 64.7, 68.7, 111.5, 111.8, 117.5, 117.5, 129.1, 159.7; HRMS (ESI) calcd for (MH^+) 278.2120, found 278.2119.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.117

References and notes

1. For reviews on bifunctional catalysis, see: (a) Hayashi, T. In *Organic synthesis: an interdisciplinary challenge*; Streith, J., Prinzbach, H., Schill, G., Eds.; Blackwell Scientific: Boston, 1985; p 35. (b) Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395–401. (c) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857–871. (d) van den Beuken, E. K.; Feringa, B. L. *Tetrahedron* **1998**, *54*, 12985–13011. (e) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865–1882. (f) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187–2210. (g) Cahard, D.; Ma, J. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4566.
2. (a) Dreyer, M. K.; Schulz, G. E. *J. Mol. Biol.* **1996**, *259*, 458–466. (b) Sugimoto, T.; Kaiser, E. T. *J. Am. Chem. Soc.* **1978**, *100*, 7750–7751. (c) Scrutton, M. C. In Eichhorn, G. L., Ed.; Inorganic biochemistry; Elsevier: Amsterdam, 1973; Vol. 1.
3. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
4. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69. (b) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832–4842.
5. Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691–1693.
6. Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Pure Appl. Chem.* **2001**, *73*, 325–329.
7. For reviews, see: (a) Katsuki, T. *Synlett* **2003**, 281–297. (b) Katsuki, T. *Adv. Synth. Catal.* **2003**, *344*, 133–147. (c) Ito, Y. N.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603–619. (d) Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85–93.
8. For selected examples see: Al: (a) Sammis, G. M.; Jacobsen,

E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442–4443. Cr: (b) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403–405. Mg: (c) Corazza, F.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Chem. Soc., Dalton Trans.* **1988**, 2341–2345. Ti: (d) Belokon, Y.; Caveda-Cepas, S.; Geen, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968–3973. V: (e) Belokon, Y. N.; North, M.; Parsons, T. *Org. Lett.* **2000**, 1617–1619. Zn: (f) Singer, A. L.; Atwood, D. A. *Inorg. Chim. Acta* **1998**, 157–162.

9. Dimauro, E. F.; Mamai, A.; Kozlowski, M. C. *Organometallics* **2003**, *22*, 850–855.
10. Lam, F.; Xu, J. X.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8414–8418.
11. For selected examples see: (a) Hu, Y.; Hu, H. *Synthesis* **1991**, 325–326. (b) Karunakaran, S.; Kandaswamy, M. *J. Chem. Soc., Dalton Trans.* **1995**, 1851–1855. (c) White, D. J.; Laing, N.; Miller, H.; Parsons, S.; Coles, S.; Tasker, P. A. *Chem. Commun.* **1999**, 2077–2078. (d) Miller, H. A.; Laing, N.; Parsons, S.; Parkin, A.; Tasker, P. A.; White, D. J. *J. Chem. Soc., Dalton Trans.* **2000**, 3773–3782. (e) Black, D.; Blake, A. J.; Finn, R. L.; Lindoy, L. F.; Nezhadali, A.; Rougnaghi, G.; Tasker, P. A.; Schroeder, M. *Chem. Commun.* **2002**, *4*, 340–341. (f) Coxall, R. A.; Lindoy, L. F.; Miller, H. A.; Parkin, A.; Parsons, S.; Tasker, P. A.; White, D. J. *J. Chem. Soc., Dalton Trans.* **2003**, 55–64.
12. (a) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 3053–3056. (b) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781–3784. (c) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668–12669.
13. For a review, see: Henry, H. In Trost, B. M., Ed.; Comprehensive organic synthesis; Pergamon: Oxford, 1991; Vol. 2, p 953.
14. (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321–1323. (b) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363–4384. (c) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron* **1998**, *30*, 7095–7098. (d) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691–5700. (e) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423–6424. (f) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92–138.
15. The method of Ohno et al. Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron* **1998**, *30*, 7095–7098. Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691–5700 makes use of a catalytic (30–60 mol%) amount of titanium..
16. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69. (b) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832–4842.
17. (a) Pu, L.; Yu, H. *Chem. Rev.* **2001**, *101*, 757–824. (b) Soai, K.; Shibata, T. In *Comprehensive asymmetric catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 911–922.
18. For previous applications of salen ligands as catalysts in the diethylzinc addition to aldehydes see Keller, F.; Rippert, A. J. *Helv. Chim. Acta* **1999**, *82*, 125–137. (b) Cozzi, P. G.; Papa, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 4613–4616.
19. Bifunctional catalysts have been proposed in the diethylzinc additions with binaphthyl-3,3′-dicarboxamides. See Ref. Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, 207–217.
20. Ni and Cu complexes of **13b** were prepared from the corresponding metal acetates while the Mg and Ti(O*i*-Pr)$_2$ complexes were generated in situ by treatment of **13b** with 1.0 equiv of $MgBu_2$ or Ti(O*i*-Pr)$_4$ for 1 h.
21. For an argument which correlates thermodynamic basicity (conjugate acid pK_a) and Lewis basicity, see: Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692–700.
22. For qualitative measurements of the electron-pair donating properties of solvent molecules toward different types of solutes and the deduced relative scales for Lewis basicity, see: Sandstroem, M.; Persson, I.; Persson, P. *Acta Chem. Scand.* **1990**, *44*, 653–675.
23. *N*-methylmorpholine (pK_a(HB$^+$)$\sim$7.5) was used as a Lewis base additive in all cooperative effects studies, since it is expected to exhibit electron-pair donor ability midway between morpholine salen **13b** (pK_a(HB$^+$)$\sim$6) and piperidine salen **13c** (pK_a(HB$^+$)$\sim$9).
24. For reviews of the enantioselective construction of quaternary centers see: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419–460. (b) Corey, E. J.; Guzman-Peresz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed* **2001**, *40*, 4591–4597. (d) Betancort, J. M.; García, C.; Walsh, P. J. *Synlett* **2004**, 749–760.
25. Coppola, G. M.; Schuster, H. F. *α-Hydroxy acids in enantioselective synthesis*; VCH: Weinhein, 1997.
26. Mukaiyama aldol: (a) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686–699. Isocyanoacetates: (b) Ito, Y.; Sawamura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 4681–4684. Self-aldol: (c) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Commun.* **2000**, 2211–2212.
27. For selected examples see: (a) Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *Chem. Commun.* **1983**, 802. (b) Basavaiah, D.; Bharathi, T. K. *Tetrahedron Lett.* **1991**, *32*, 3417–3420. (c) Tamai, Y.; Nakano, T.; Miyano, S. *Chem. Lett.* **1992**, 807–808. (d) Tamai, Y.; Nakano, T.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 439–445. (e) Basavaiah, D.; Pandiaraju, S.; Bakthadoss, M.; Mathukumaran, K. *Tetrahedron: Asymmetry* **1996**, *7*, 997–1000. (f) Loupy, A.; Monteux, D. A. *Tetrahedron* **2002**, *58*, 1541–1549 and references cited therein. (g) Wipf, P.; Stephenson, C. R. *J. Org. Lett.* **2003**, *5*, 2449–2452.
28. (a) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. Pure Appl. *Chem.* **1988**, *60*, 1597–1606. (b) Zadel, G.; Breitmaier, E. *Chem. Ber.* **1994**, *127*, 1323–1326. (c) Tan, L.; Chen, C.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, 711–713.
29. See (a) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117–6128. (b) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905–913. (c) Abenhaim, D.; Boireau, G.; Sabourault, B. *Tetrahedron Lett.* **1980**, *21*, 3043–3046.
30. Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int., Ed.* **2003**, *42*, 5489–5492.
31. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059–1070.
32. (a) Ph_2Zn: (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445–446. (b) Garcia, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641–3644. (c) Prieto, O.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955–1957. (d) Li, H. M.; Garcia, C.; Walsh, P. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5425–5427. dialkylzincs: (e) Ramón, D. J.; Yus, M. *Tetrahedron Lett.*

1998, *39*, 1239–1242. (f) Ramón, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651–5666. (g) Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970–10971. (h) Yus, M.; Ramon, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2002**, *13*, 2291–2293. (i) Jeon, S. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544–9545. (j) Yus, M.; Ramón, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2003**, *14*, 1103–1114. (k) Jeon, S. J.; Li, H. M.; Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448–455. vinyl zincs: (l) Li, H. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539. alkyl, aryl, vinyl zincs: (m) Betancort, J. M.; Garcia, C.; Walsh, P. J. *Synlett* **2004**, 749–760. (n) de Parrodi, C. A.; Walsh, P. J. *Synlett* **2004**, 2417–2420.

33. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69.
34. For other examples of this problem, see: Yong, K. H.; Chong, J. M. *Org. Lett.* **2002**, *4*, 3553–3556. Diastereoselective additions to α-ketoesters are often limited to MeMgX and ArMgX which do not contain β-hydrogens.
35. Nugent, W. *Chem. Commun.* **1999**, 1369–1370.
36. No enantioselection was seen in a prior DAIB α-ketoester alkylation: Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19–37.
37. (a) Jiang, Y.; Gong, L.; Feng, X.; Hu, W.; Pan, W.; Li, Z.; Mi, A. *Tetrahedron* **1997**, *53*, 14327–14338. (b) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710–1740.
38. Zhou, X-G. ; Che, C-M. *J. Chem. Soc., Dalton Trans.* **1999**, 3303–3309.
39. 5-*tert*-Butyl-2-hydroxy-benzaldehyde (**8**) was prepared as illustrated in Scheme 1 Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1862–1865. 5-Dimethylamino-2-hydroxy-benzaldehyde was prepared from 2-hydroxy-5-nitro-benzaldehyde by the established method: Ando, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2433–2434.2-Hydroxy-5-tricyclo[3.3.1.10.0] dec-1-yl-benzaldehyde was prepared from 4-adamantyl phenol in a manner analogous to the preparation of **8**.
40. Jiang, Y.; Gong, L.; Feng, X.; Hu, W.; Pan, W.; Li, Z.; Mi, A. *Tetrahedron* **1997**, *53*, 14327–14338.
41. The relative rates of ligand exchange from TiL_2-salen parallels the relative pK_a values of LH: see Chen, H.; White, P. S.; Gagné, M. R. *Organometallics* **1998**, *17*, 5358–5366. A similar lack of reactivity was observed by Belokon and North in their studies of the addition of TMSCN to RCHO with a $TiCl_2$-salen catalyst prepared in situ from $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ and salen: see Belokon, Y.; Flego, M.; Ikonnikov, N.; Margarita, M.; North, M.; Orizu, C.; Tararov, V.; Tasinazzo, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1293–1295.
42. These results are similar to those observed in the $Ti(O\textit{i}\text{-}Pr)_2$-salen catalyzed addition of trimethylsilylcyanide to aldehydes: see Jiang, Y.; Gong, L.; Feng, X.; Hu, W.; Pan, W.; Li, Z.; Mi, A. *Tetrahedron* **1997**, *53*, 14327–14338. and the MnCl-salen catalyzed epoxidation: (a) Jacobsen, E. N.; Zhang, W.; Gular, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703–6704.
43. Xu, Z.; Wang, R.; Xu, J.; Da, C.; Yan, W.; Chen, C. *Angew. Chem. Int., Ed.* **2003**, *42*, 5747–5749.
44. Basavaiah, D. Rama Krishna. *P. Tetrahedron* **1995**, *51*, 12169–12178.
45. For a review, see: North, M. *Tetrahedron: Asymmetry* **2003**, 147–176.
46. Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691–694.
47. White, A. C. (Wyeth) EP. 8405143, 8319372, 8061816.
48. Miller, H. A.; Laing, N.; Parsons, S.; Parkin, A.; Tasker, P. A.; White, D. J. *J. Chem. Soc., Dalton Trans.* **2000**, 3773–3782.
49. Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895–7898.

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Chiral β-diketonate ligands of 'pseudo planar chiral' topology: enantioselective synthesis and transition metal complexation

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Abstract—A practical enantioselective synthesis of chiral β-diketonate ligands **1a**–**1d**, which are of 'pseudo planar-chiral' topology, is described. Additionally, the first chiral bis(diketonates) **2a**–**2c**, ligands of C_2-symmetry that are isoelectronic with respect to related salen ligand systems, have been prepared. Protocols for the metallation of ligands **1a**–**1d**, **2b** and **2c** are reported.

1. Introduction

Since Knowles and Kagan reported that chiral phosphine ligands may serve as chiral inducing elements in transition metal catalyzed processes, the field of asymmetric catalysis has witnessed an explosion of activity leading to the development of numerous catalytic processes operating with high turnover and exceptional enantiomeric excess.[1] To date, the majority of chiral ligands employed in enantioselective catalysis incorporate structural features embodied by the archetypal ligand systems indicated in Figure 1. Although β-diketonate complexes are known for virtually every transition metal,[2] they are notably absent from this collection of 'privileged' structural motifs. Indeed, while numerous stereogenic β-diketonato(metal) catalyzed processes exist, few enantioselective β-diketonato(metal) catalyzed transformations are known. Moreover, to our knowledge, all reported examples of enantioselective β-diketonato(metal) catalyzed transformations employ camphor derived β-diketonates **3** (see Scheme 1). Indeed, the most successful application of metal-diketonates in asymmetric catalysis involves use of the oxovanadium complexes of camphor based β-diketonates **3**, which catalyze hetero-Diels–Alder cycloadditions in good enantiomeric excess (85% ee).[3]

The surprising paucity of chiral β-diketonato(metal) templates, coupled with their enhanced oxidative stability with respect to related *N*- and *P*-ligands, suggests the potential utility of such systems as chiral inducing elements in enantioselective transition metal catalyzed oxidations.[4] Here, we present a practical synthetic approach to chiral β-diketonate ligands **1a**–**1d** of 'pseudo planar-chiral' topology. Additionally, we report the first examples of chiral bis(diketonates) **2a**–**2c**, ligands of C_2-symmetry that are isoelectronic with respect to salen ligand systems (Fig. 1).

1.1. Design of pseudo-planar chiral β-diketone ligands

For camphor-based mono(diketonates) **3**, the diketonate enantiofaces are differentiated by virtue of the bridging ethano and (dimethyl)methano residues. Further accentuation of the steric bias between diketonate enantiofaces would potentially provide ligands with improved capabilities for asymmetric induction. Planar chirality represents the limiting case with regard to such enantiofacial differentiation. The utility of planar-chiral scaffolds in asymmetric catalysis is now widely recognized[5] and planar-chiral ferrocene-based ligands are employed industrially.[6] True planar-chiral diketonates, such as **4**, have been described.[7] However, cyclophane-based diketonates **4** only have been used as chiral auxiliaries or as precursors to salicylaldimine ligands.[8] The β-diketonate **1** embodies a 'pseudo planar-chiral' topology and may be envisioned to arise via desymmetrization of the readily accessible symmetric dione **5** (Scheme 1).[10–13]

Retrosynthetically, bis(diketonates) such as **2a** and **2b** should be accessible through dimerization of the 1,3-diketones **1e** and **1f**, respectively, using a Stille-type homocoupling reaction.[9] The 1,3-diketones **1e** and **1f** may be obtained through Claisen condensation of chiral

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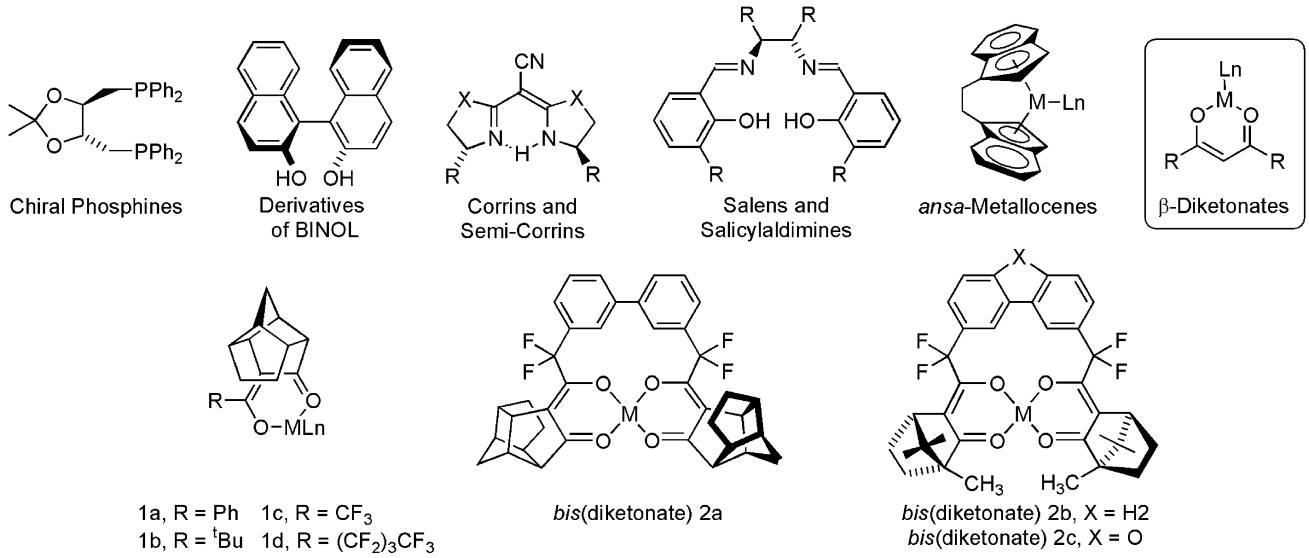
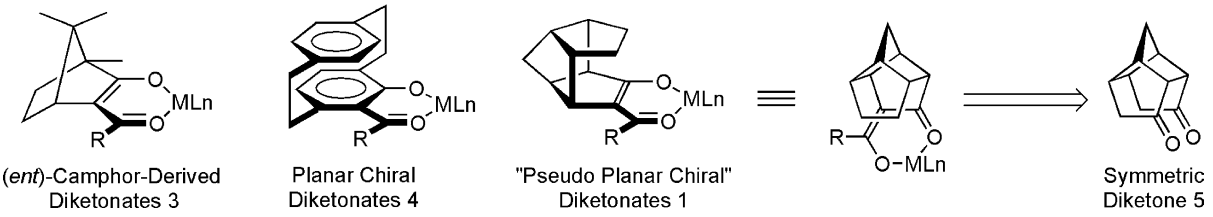


Figure 1. Pervasive structural motifs of chiral ligands used in enantioselective transition metal catalysis and new β-diketonate ligands prepared in our lab.



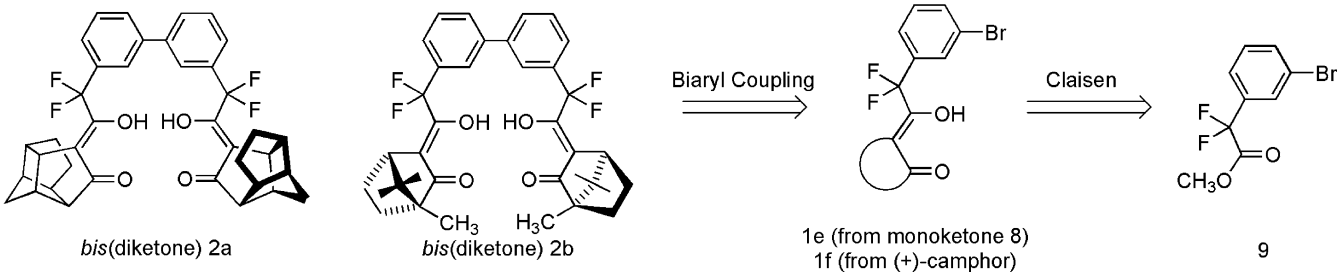
Scheme 1. Design and retrosynthetic analysis of a β-diketonate possessing 'pseudo planar-chiral' topology.

monoketone **8** or (+)-camphor, respectively, with the α-difluorinated phenylacetic ester **9** (Scheme 2).

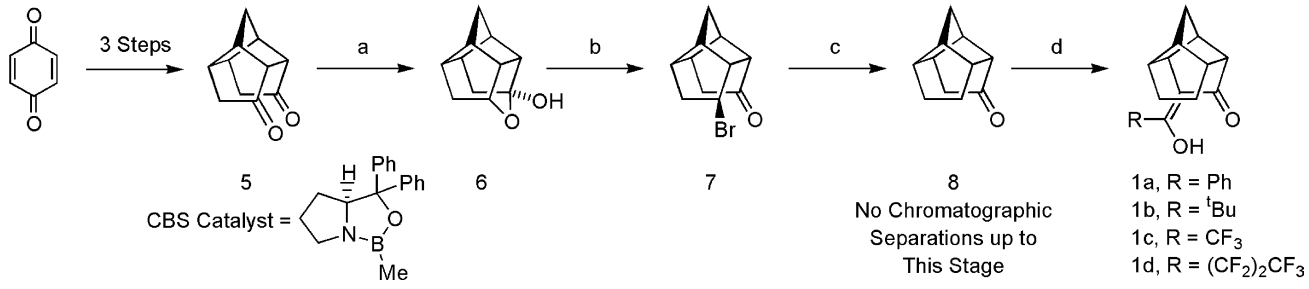
1.2. Synthesis of mono(diketonates) 1a–1d and bis(diketonates) 2a–2b

The synthesis of ligands **1a**–**1e** begins with the preparation of the previously reported diketone **5**, which is prepared in three steps from benzoquinone and cyclopentadiene.[10] Specifically, *endo*-Diels–Alder [4+2]cycloaddition of benzoquinone and cyclopentadiene is followed by photochemically promoted intramolecular [2+2]cycloaddition.[11] Zn-mediated reductive cleavage of the cyclobutane affords the dione **5**.[12,13] At each stage, the crude reaction products en route to **5** are purified via trituration or crystallization.

Elaboration of diketone **5** to the desired β-diketones **1a**–**1e** was envisioned to proceed via Claisen condensation of the optically enriched mono-ketone **8** with appropriate acyl transfer agents. A two-step procedure for the conversion of dione **5** to monoketone **8** is reported in the literature, which involves the conversion of **5** to the corresponding mono-(thioketal) followed by Raney Ni-mediated desulfurization.[14] To achieve an enantioselective synthesis of **8**, an alternative procedure was required. Desymmetrization of diketone **5** is achieved through Corey-Itsuno reduction using the commercially available (*S*)-2-methyl-CBS-oxazaborolidine as catalyst to provide the lactol **6**.[15,16] The enantioselectivity of this transformation could not be determined directly by chiral stationary phase HPLC analysis, as lactol **6** does not embody a sufficiently strong UV chromophore. However, exposure of the lactol to HBr/AcOH provides good yields of the corresponding bromoketone **7**,[17] which upon chiral stationary phase HPLC analysis reveals a 76% enantiomeric excess. Two recrystallizations from hexanes



Scheme 2. Retrosynthetic analysis of bis(diketones) **2a** and **2b**.



Scheme 3. Enantioselective synthesis of β-diketonates **1a**–**1d**. Reagents: (a) $BH_3 \cdot SMe_2$, THF, −15 °C, 5 mol% CBS catalyst, 92% (b) HBr, AcOH, 100 °C, 8 h, 87% yield, 76% ee. Twice recrystallized material is obtained in 45% yield, >99% ee (c) $HOP(OMe)_2$, $(PhCO_2)_2$, dioxane, reflux, 90% (d) LDA, THF, −78 °C and acylating agent (**1a**, acylating agent=*N*-benzoylbenzotriazole, 79%; **1b**, acylating agent=pivaloyl cyanide, 77%; **1c**, acylating agent=ethyl trifluoroacetate, 62%, **1d**, acylating agent=*N*-heptafluorobutyrylbenzotriazole, 60%).

provides bromoketone **7** as a single enantiomer, as determined by chiral stationary phase HPLC analysis. Single crystal X-ray diffraction analysis of bromoketone **7** corroborates the given structural assignment. However, absolute stereochemistry was not assigned, as X-ray diffraction analysis was performed on racemic material. Dimethyl phosphite mediated radical debromination of bromoketone **7** affords monoketone **8**.[18] Notably, all synthetic intermediates en route to monoketone **8** are subject to purification by trituration or recrystallization. The monoketone **8** itself requires purification by silica gel chromatography, and may be purified further by sublimation.

With optically pure monoketone **8** in hand, conditions for Claisen condensation were explored. Surprisingly, classical conditions for Claisen condensation involving exposure of **8** to sodium ethoxide in ethanol in the presence of ethyl benzoate proved ineffective. This may be due to the low kinetic and thermodynamic acidity of the caged ketone **8**. Eventually, it was found that treatment of **8** with lithium diisopropylamide (LDA) in THF solvent at −78 °C was the most efficient means of enolate generation. Due to competitive *O*-acylation, the choice of acyl transfer agent was highly case dependant. For preparation of the benzoyl derivative **1a**, the acyl benzotriazole proved most effective.[19] For the corresponding pivaloyl derivative **1b**, the acyl nitrile was the reagent of choice.[20] Finally, for derivatives **1c** and **1d**, which possess fluorinated side chains, ethyl trifluoroacetate and ethyl heptafluorobutyrate served best as acyl transfer agents (Scheme 3).[21]

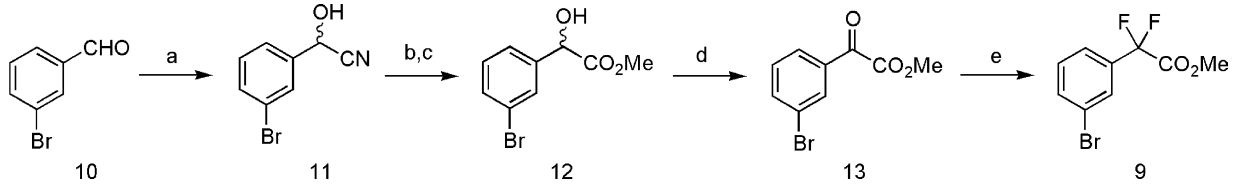
The synthesis of bis(diketones) **2a** and **2b** requires preparation of the α-difluorinated phenylacetic ester **9**, which begins with the preparation of conversion of commercially available *m*-bromobenzaldehyde **10** to its cyanohydrin **11** through intermediacy of the bisulfite.[22] Acidic hydrolysis of the cyanohydrin is followed by Fischer esterification provides the α-hydroxy methyl ester **12**, which is treated with activated MnO_2 to afford the aryloxoacetic ester **13**. Finally, exposure of oxoacetic ester **13** to (diethylamino)sulfur trifluoride (DAST) delivers the α-difluorinated phenylacetic ester **9** (Scheme 4).[23]

With ester **9** in hand, Claisen condensation with the chiral monoketone **8** and (+)-camphor was attempted. Here, it was found that ^{t}BuLi was the most effective base for generating the enolate derived from camphor. However, use of this base instead of LDA did not improve the isolated yield of the bis(diketonate) derived from **8**. Finally, palladium catalyzed homo-coupling of the aryl bromides **1e** and **1f** using $[(CH_3)_6Sn_2]$ provides the bis(diketones) **2a** and **2b**, respectively (Scheme 5).[24]

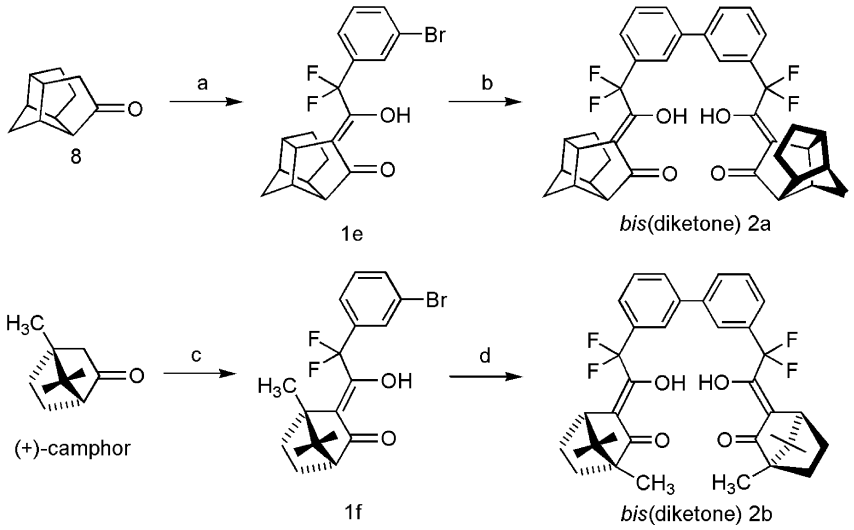
An alternative approach to bis(diketones) based on (+)-camphor begins with the Friedel–Craft acylation of benzofuran using ethyl chlorooxoacetate. Treatment of the resulting bis(oxoacetic) ester with (diethylamino)sulfur trifluoride (DAST) provides the corresponding bis(α-difluoroacetic ester) **14**. Clasien condensation of the diester **14** with (+)-camphor completes the synthesis bis(diketone) **2c** (Scheme 6).

1.3. Metallation of mono- and bis(diketonates)

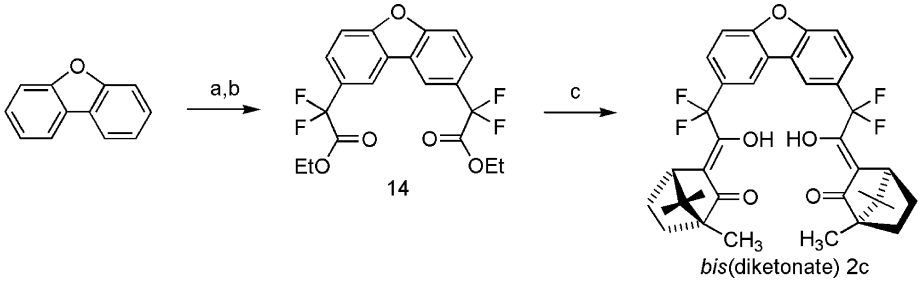
The general protocol for metallation of mono(diketones) **1a–d** involves preparation of an alcoholic or aqueous solution of the β-diketonate through acid–base reaction of the 1,3-diketone precursor with sodium hydroxide or ammonia. An aqueous solution of a transition metal salt is then combined with the β-diketonate solution, resulting in immediate precipitation of the insoluble metal complex, which is isolated by filtration, and dried in vacuo. This general approach has been applied to the preparation of



Scheme 4. Preparation of α-difluorinated phenylacetic ester **9**. Reagents: (a) $NaHSO_3$, H_2O, 25 °C, then KCN, H_2O, 0–25 °C, 100% over two steps (b) Conc. HCl (aq), 80 °C, (c) MeOH, H_2SO_4 (cat) reflux, 80% over two steps. (d) MnO_2, DCM, 25 °C, 76% (e) DAST (neat), 50 °C, 76%.



Scheme 5. Synthesis of bis(diketones) **2a** and **2b**. Reagents: (a) LDA, THF, −78 °C, then **9**, −78 to 25 °C, 59% (b) $[(CH_3)_3Sn]_2$, $(PPh_3)_4Pd$, $PhCH_3$, 100 °C, 45%. (c) ^{t}BuLi, THF, −78 °C, then **9**, −78 to 25 °C, 72% (d) $[(CH_3)_3Sn]_2$, $(PPh_3)_4Pd$, $PhCH_3$, 100 °C, 64%.



Scheme 6. Synthesis of the (+)-camphor based bis(diketone) **2c**. Reagents: (a) $ClCOCO_2Et$, $AlCl_3$, DCM, 0 °C, 40% (b) DAST (neat), DCM, 50 °C, 73% (c) (+)-camphor, ^{t}BuLi, THF, −78 to 25 °C, 44%.

related transition metal diketonates, and has been shown to provide analytically pure products.[25] For some oxo-vanadium(IV) complexes, an alternative approach involving ligand exchange is employed. Here, a mixture of the diketone and $VO(acac)_2$ in toluene is refluxed overnight. The metal complex was left behind after removal of the solvent, trituration, and drying of the residue in vacuo. Since it was possible to produce larger quantities of the bis(diketone) **2b** and **2c** derived from commercially available (+)-camphor, metallation studies focused solely

Table 1. Metallation of mono(diketones) **1a–1d** and bis(diketones) **2b** and **2c**[a]

Entry	Ligand	Metal salt	Complex	Isolated yield (%)	Formula	HRMS (Calcd, M+1)	HRMS (exp, M+1)
1	**1a**	$FeCl_3(H_2O)_6$	$Fe(1a)_3$	87	$C_{54}H_{51}FeO_6$	852.3113	852.3107
2	**1a**	$VOSO_4(H_2O)$	$VO(1a)_2$	50	$C_{36}H_{34}VO_5$	598.1924	598.1933
3	**1a**	$EuCl_3(H_2O)_6$	$Eu(1a)_3$	87	$C_{54}H_{51}EuO_6$	947.2962	947.2935
4	**1a**	$Cu(OAc)_2$	$Cu(1a)_2$	54	$C_{36}H_{34}CuO_4$	594.1831	594.1833
5	**1a**	$PdCl_2$	$Pd(1a)_2$	44	$C_{36}H_{34}PdO_4$	637.1570	637.1583
6	**1b**	$Co(NO_3)_2(H_2O)_6$	$Co(1b)_2$	56	$C_{32}H_{42}CoO_4$	550.2493	550.2488
7	**1b**	$FeCl_3(H_2O)_6$	$Fe(1b)_3$	79	$C_{48}H_{63}FeO_6$	792.4052	792.4045
8	**1c**	$Co(NO_3)_2(H_2O)_6$	$Co(1c)_2$	37	$C_{26}H_{24}CoFe_6O_4$	574.0989	574.9089
9	**1c**	$VOSO_4(H_2O)$	$VO(1c)_2$	64	$C_{26}H_{24}VF_6O_5$	582.1046	582.1043
10	**1c**	$EuCl_3(H_2O)_6$	$Eu(1c)_3$	83	$C_{39}H_{36}EuF_9O_6$	923.1645	923.1627
11	**1c**	$Zn(OAc)_2$	$Zn(1c)_2$	82	$C_{26}H_{24}ZnF_6O_4$	579.0948	579.0943
12	**1d**	$EuCl_3(H_2O)_6$	$Eu(1d)_3$	57	$C_{45}H_{36}EuF_{21}O_6$	1225.1467	1225.1455
13	**1d**	$VO(acac)_2$	$VO(1d)_2$	87	$C_{30}H_{24}VF_{14}O_5$	782.0918	782.0916
14	**2b**	$NiCl_2(H_2O)_6$	Ni(2b)	85	$C_{36}H_{36}NiF_4O_4$	667.1981	667.1991
15	**2b**	$CuCl_2(H_2O)_2$	Cu(2b)	88	$C_{36}H_{36}CuF_4O_4$	672.1924	672.1912
16	**2b**	$VO(acac)_2$	VO(2b)	92	$C_{36}H_{36}VF_4O_5$	676.2017	676.2028
17	**2c**	$NiCl_2(H_2O)_6$	Ni(2b)	72	$C_{36}H_{34}NiF_4O_4$	680.1695	680.1679
18	**2c**	$CuCl_2(H_2O)_2$	Cu(2b)	80	$C_{36}H_{34}CuF_4O_5$	685.1638	685.1648

[a] See Section 3 for metallation protocols.

on these bis(diketone) ligands. In all cases, formation of the desired metal complex was corroborated by high resolution mass spectrometric analysis (Table 1).

The Fe(III) complex of **1b**, which is highly crystalline, was prepared in racemic form in large scale. Single crystal X-ray diffraction analysis reveals the coordination of three diketonate ligands to the central iron atom, which exhibits octahedral geometry. The complex is of C_3 symmetry. However, dissociation of one ligand, a likely prerequisite for catalysis, would provide a C_2 symmetric complex. As C_2-symmetric transition metal complexes have found extensive use in enantioselective catalysis, the utility of these complexes in this capacity will comprise the basis of future study (Fig. 2).

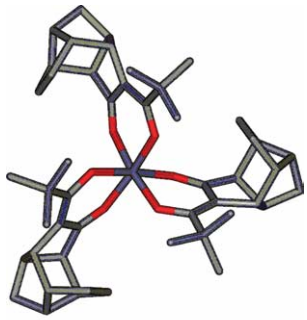


Figure 2. The structure of Fe(**1b**)$_3$ as determined by single crystal X-ray diffraction analysis.

2. Conclusion

In summary, although β-diketonate complexes are known for virtually all transition metals, the use of (β-diketonato)-metal complexes in enantioselective catalysis is highly underdeveloped. To broaden the availability of chiral (β-diketonato)metal templates, efficient protocols for the asymmetric synthesis of chiral β-diketonate ligands **1a**–**1d** and bis(diketonates) **2a**–**2c** are described. Future studies will focus on exploring the utility of these chiral (β-diketonato)metal complexes in enantioselective catalysis.

3. Experimental

3.1. General experimental considerations

All reactions were performed under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe, and degassed with argon prior to use. Flasks were flame-dried and cooled under a stream of nitrogen. Tetrahydrofuran (THF), 1,4-dioxane, and toluene were distilled from sodium/benzophenone ketyl. Dichloromethane (DCM) was distilled from calcium hydride. Other solvents and chemical reagents obtained from commercial sources were used without further purification, unless otherwise noted. The literature procedures used to prepare diketone **5** from benzoquinone and cyclopentadiene are described in Refs. 10–13.

Analytical thin-layer chromatography (TLC) was carried out by using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}, EMD Chemicals). Solvents for chromatography are listed as volume/volume ratios. Infrared spectra were recorded on a Perkin–Elmer 1420 spectrometer. Samples were prepared as films through evaporation from dichloromethane or chloroform solution on sodium chloride plates. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 by using chemical ionization in the positive ionization mode. Accurate masses are reported for the molecular ion (M+1) or a suitable fragment ion. Melting points were determined on a Thomas Hoover Uni-melt apparatus in open capillaries and are uncorrected. Enantiomeric purity was determined by chiral stationary phase HPLC analysis. Optical rotations were measured by using an Atago Polax-2L polarimeter. Concentrations are reported in units of g/100 mL.

Proton NMR (^{1}H NMR) spectra were recorded with a Varian Gemini (300 MHz) or Varian Gemini (400 MHz) spectrometer. Chemical shifts (δ) are expressed as ppm relative to trimethylsilane ($\delta=0.00$ ppm), referenced to the residual protic solvent. Coupling constants are reported in Hertz. Carbon-13 NMR (^{13}C NMR) spectra were recorded on a Varian Gemini 300 (75 MHz) or Varian Gemini 400 (100 MHz) spectrometer. Chemical shifts (δ) are expressed as ppm relative to trimethylsilane ($\delta=0.0$ ppm), referenced to the center of the triplet at $\delta=77.0$ ppm for deuteriochloroform. ^{13}C NMR analyses were run routinely with broadband decoupling. Fluorine-19 (^{19}F NMR) nuclear magnetic resonance spectra were recorded on a Varian Gemini 300 (282 MHz) spectrometer. Chemical shifts (δ) are expressed as ppm relative to $CFCl_3$ ($\delta=0.0$ ppm). Coupling constants are reported in Hertz.

3.2. Preparation of chiral monoketone 8 from diketone 5

3.2.1. Lactol 6. (*S*)-2-Methyl-CBS-oxazaborolidine catalyst (5.0 mL of a 1 M solution in toluene, 5.0 mmol, 5 mol%) was added to a solution of diketone **5** (17.6 g, 99.6 mmol, 100 mol%) in anhydrous THF (280 mL, 0.36 M). The mixture was stirred under nitrogen and cooled to −15 °C. A solution of $BH_3\cdot SMe_2$ (6.6 mL, 70 mmol, 70 mol%) in anhydrous THF (120 mL, 0.58 M) was added with stirring at a rate which maintained the temperature at −15 °C or lower. Total addition time was approximately 2 h. Upon completion of the addition, the reaction mixture was stirred at −15 °C for 1 h, and then allowed to warm to room temperature as it stirred for an additional 1 h. The reaction was quenched by slow addition of MeOH (150 mL), followed (after gas evolution slowed) by addition of aqueous 1 N HCl (300 mL). The quenched reaction mixture was transferred to a separatory funnel, and Et_2O (250 mL) and brine (50 mL) were added and the organic layer was separated. The aqueous solution was extracted with additional Et_2O (2×100 mL). The combined organic extracts were washed with H_2O (2×50 mL), aqueous 1 N HCl (2×50 mL), and brine (2×50 mL), and dried over Na_2SO_4. After filtration, evaporation, and drying of the residue in vacuo, lactol **6** (16.33 g, 91.61 mmol, 92% yield) was isolated as a white solid which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (t, $J=6.4$ Hz, 1H), 4.22 (s, 1H), 2.84 (m, 1H), 2.46 (s,

1H), 2.36 (m, 1H), 2.18 (s, 3H), 2.07 (d, $J=13.3$ Hz, 1H), 1.95 (dm, $J=13.3$ Hz, 1H), 1.83 (d, $J=14.2$ Hz, 1H), 1.77 (d, $J=10.6$ Hz, 1H), 1.64 (d, $J=10.6$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.6, 80.9, 58.5, 53.7, 49.2, 47.0, 43.6, 42.0, 41.2, 37.9, 37.7. IR (film): 3379, 2950, 2865, 1335, 1293, 1122, 1055, 984, 836 cm^{-1}. HRMS Calcd for $C_{11}H_{15}O$ [M+1] 179.1072, Found 179.1061.

3.2.2. Bromoketone 7. Two threaded pressure tubes equipped with magnetic stir bars were charged with **6** (Tube 1: 5.09 g, 28.6 mmol, 100 mol%; Tube 2: 5.08 g, 28.5 mmol, 100 mol%) and a 32% w/w solution of HBr/HOAc (Tube 1: 21.0 mL, 118 mmol HBr, 413 mol%; Tube 2: 21.0 mL, 118 mmol HBr, 414 mol%). The tubes were sealed, and the contents were heated to 100 °C with stirring for 8 h. After the stirring period, the reaction mixtures were cooled to room temperature, combined, and quenched by carefully pouring into a mixture of saturated aqueous $NaHCO_3$ (400 mL) and DCM (200 mL). The aqueous and organic layers were separated, and the aqueous solution was extracted with additional DCM (2×100 mL). The combined organic extracts were washed with H_2O (2×50 mL), saturated aqueous $NaHCO_3$ (2×50 mL) and brine (2×50 mL) and dried over Na_2SO_4. After filtration, evaporation, and drying of the residue in vacuo, crude **7** (12.0 g, 49.8 mmol, 87% yield, 76% ee) was isolated as a brown solid, which was purified to optical homogeneity by recrystallization from hexanes. After 2 recrystallizations, chiral HPLC (Daicel Chiralpak AD column, 85:15 hexanes/EtOH, $\lambda=254$ nm) showed the presence of only a single enantiomer. Twice recrystallized **7** (6.23 g, 25.8 mmol) was isolated 45% yield as a white, crystalline solid (needles); mp 185–186°C; $[\alpha]_D^{24}$ −70.8° ($c=1.06$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.29 (dd, $J=7.3$, 3.4 Hz, 1H), 3.01 (s, 1H), 2.75 (m, 1H), 2.66 (s, 1H), 2.46 (m, 4H), 2.30 (m, 1H) 2.16 (m, 2H), 1.80 (dd, $J=26.5$, 11.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.4, 58.6, 56.4, 51.6, 47.4, 42.2, 40.8, 40.2, 39.3, 32.5. IR (film): 2960, 2877, 1739, 1461, 1150, 915 cm^{-1}. HRMS: Calcd for $C_{11}H_{14}BrO$ [M+1] 241.0228, Found 241.0226.

3.2.3. Monoketone 8. Dimethyl phosphite (11.0 mL, 12.0 mmol, 997 mol%) was added to a solution of bromoketone **7** (2.904 g, 12.04 mmol, 100 mol%) in dioxane (100 mL, 0.12 M). The resulting solution was stirred under nitrogen and heated to reflux. In a separate vessel, a solution of benzoyl peroxide (5.82 g, 24.0 mmol, 200 mol%) in dry dioxane (32 mL, 0.75 M) was prepared. The initiator solution was added to the refluxing reaction mixture in 4 mL portions at 30 min increments. The reaction was monitored for disappearance of **7** by TLC (SiO_2: 4:1 hexanes/ethyl acetate). The reaction was complete after 2.5 h (100 mol% benzoyl peroxide had been added). The reaction mixture was cooled to room temperature and the majority of the dioxane solvent was removed via rotary evaporation. The concentrated solution was then partitioned between 5% aqueous Na_2CO_3 (100 mL) and Et_2O (100 mL). After separation of the aqueous and organic layers, the aqueous solution was extracted with additional Et_2O (2×100 mL). The combined organic extracts were washed with 5% aqueous Na_2CO_3 (2×50 mL), H_2O (1×50 mL), and brine (1×50 mL), and dried over Na_2SO_4. After filtration, evaporation, and drying of the residue in vacuo, the crude product was isolated as an oily yellow-white solid. The crude product was purified by flash chromatography (SiO_2, 2.5:97.5 Et_2O/hexanes) to obtain a white solid which was further purified by sublimation (72–74 °C; 0.1 Torr). Monoketone **8** (1.758 g, 10.84 mmol, 90% yield) was isolated as a white solid. $[\alpha]_D^{25}$ +27.3° ($c=1.13$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (s, 1H), 2.45 (m, 1H), 2.36 (m, 4H), 2.26 (m, 1H), 2.04 (m, 1H), 1.71 (m, 4H), 1.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 223.2, 55.8, 49.7, 47.0, 46.4, 42.4, 40.6, 39.2, 33.0, 27.0, 26.1. IR (neat): 2951, 2871, 1737 cm^{-1}. HRMS: Calcd for $C_{11}H_{15}O$ [M+1] 163.1123, Found 163.1124.

3.3. Preparation of mono(1,3-diketones) 1a–1d

General procedure for Claisen condensation. A solution of diisopropylamine (200 mol%) in anhydrous THF (0.15 M) was cooled to −78 °C while stirring under a nitrogen atmosphere. A solution of *n*-butyllithium (1.6 M in hexanes, 195 mol%) was added dropwise with stirring over a period of 30 min, and the solution was allowed to stir at −78°C for 1 h. A solution of monoketone **8** (100 mol%) in anhydrous THF (0.3 M) was added dropwise over a period of 30 min and the mixture was allowed to stir at −78 °C for 1 h. Subsequently, a solution of the acylating agent in anhydrous THF (1.5 M) was added over a period of 20 min. The reaction mixture was left to stir overnight and was allowed to slowly warm to room temperature. The reaction was poured into H_2O (100 mL), and acidified by addition of 10% aqueous H_2SO_4 (50 mL). The aqueous solution was extracted with Et_2O (3×100 mL), and the combined organic extracts were washed with H_2O (2×50 mL), 10% aqueous H_2SO_4 (2×50 mL), and brine (2×50 mL), and were dried (Na_2SO_4). After filtration, evaporation, and further drying of the residue in vacuo, the crude product was isolated and purified by flash chromatography on a silica gel column.

3.3.1. Mono(diketone) 1a. Monoketone **8** (1.50 g, 9.26 mmol, 100 mol%) and *N*-benzoylbenzotriazole (2.13 g, 9.13 mmol, 99 mol%) were reacted according to the general procedure described above. The crude product was isolated as a yellow oil, which was purified by flash chromatography (SiO_2: 2.5:97.5 Et_2O/hexanes) to yield a mixture of keto- and enol-tautomers of **1a** (1.19 g, 4.47 mmol, 48% isolated yield) as a very pale tan, viscous oil. The overall yield based on recovered **8** (580 mg, 3.57 mmol) was 79%. $[\alpha]_D^{28}$ −242.6° ($c=1.01$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.35 (s, 1H), 7.61 (m, 2H), 7.43 (m, 3H), 3.12 (m, 1H), 2.65 (s, 1H), 2.56 (s, 4H), 1.77 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.0, 164.1, 133.9, 130.6, 128.3, 127.5, 113.9, 55.9, 50.5, 48.9, 46.6, 45.5, 45.1, 33.4, 28.2, 27.6. IR (film): 3431, 2953, 1653, 1597 cm^{-1}. HRMS: Calcd for $C_{18}H_{19}O_2$ [M+1] 267.1385, Found 267.1382.

3.3.2. Mono(diketone) 1b. Monoketone **8** (1.58 g, 9.70 mmol, 100 mol%) and pivaloyl cyanide (2.5 mL, 20 mmol, 210 mol%) were reacted according to the general procedure. The crude product was isolated as an orange oil, which was purified by flash chromatography (SiO_2: 2.5/97.5 Et_2O/hexanes) to yield a mixture of keto- and enol-tautomers of **1b** (1.74 g, 7.07 mmol, 73% isolated yield)

as a colorless viscous oil. The overall yield based on recovered **8** (88 mg, 0.54 mmol) was 77%. $[\alpha]_D^{27}$ −45.0° ($c=1.11$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 14.08 (s, 1H), 3.79 (s, 1H), 3.02 (s, 1H), 2.42 (s, 2H), 2.36 (s, 3H), 1.71 (m, 4H), 1.48 (m, 1H), 1.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.9, 213.1, 56.8, 56.7, 49.1, 46.7, 45.0, 44.9, 43.2, 32.8, 28.0, 26.9, 26.6, 26.1. IR (film): 2956, 2873, 1743, 1695, 1476, 1154, 1065 cm^{-1}. HRMS: Calcd for $C_{16}H_{23}O_2$ [M+1] 247.1698, Found 247.1693.

3.3.3. Mono(diketone) 1c. Monoketone **8** (1.62 g, 10.0 mmol, 100 mol%) and ethyl trifluoroacetate (3.6 mL, 30 mmol, 150 mol%) were reacted according to the general procedure. The crude product was isolated as an orange-brown oil, which was purified by flash chromatography (SiO_2: 2.5:97.5 Et_2O/hexanes) to yield a mixture of keto- and enol-tautomers of **1c** (1.375 g, 5.32 mmol, 53% isolated yield) as a dark purple, viscous oil. The overall yield based on recovered **8** (233 mg, 1.44 mmol) was 62%. $[\alpha]_D^{28}$ +23.4° ($c=1.28$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 12.26 (s, 1H), 3.17 (m, 1H), 2.69 (s, 1H), 2.52 (m, 3H), 2.42 (m, 1H), 1.77 (m, 4H), 1.43 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.5, 151.0 (q, $J=36.6$ Hz), 119.2 (q, $J=276.2$ Hz), 116.3, 55.9, 49.9, 47.4, 47.3, 45.1, 43.7, 33.5, 27.7, 27.2. IR (film): 3461, 2960, 1686, 1640 cm^{-1}. HRMS: Calcd for $C_{13}H_{14}F_2O_2$ [M+1] 259.0946, Found 259.0937.

3.3.4. Mono(diketone) 1d. Monoketone **8** (1.49 g, 9.21 mmol) and *N*-heptafluorobutyrylbenzotriazole (3.42 g, 10.86 mmol, 118 mol%) were reacted according to the general procedure. The crude product was isolated as a yellow oil, which was purified by flash chromatography (SiO_2, 2.5:97.5 Et_2O/hexanes) to yield a mixture of keto and enol tautomers of **1d** (1.67 g, 4.66 mmol, 51% isolated yield) as a dark purple, viscous oil. The overall yield based on recovered **8** (230 mg, 3.57 mmol) was 60%. $[\alpha]_D^{28}$ −73.1° ($c=0.14$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 12.58 (s, 1H), 3.16 (m, 1H), 2.69 (s, 1H), 2.58 (s, 2H), 2.50 (s, 1H), 2.42 (m, 1H), 1.75 (m, 4H), 1.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.4, 151.3, 119.0, 55.7, 49.9, 47.7, 47.3, 45.5, 44.1, 33.5, 27.7, 27.1; ^{19}F NMR (282 MHz, $CDCl_3$): δ −81.1 (t, $J=8.0$ Hz, 3F), −118.8 (m, 2F), −127.7 (m, 2F). IR (film): 3452, 2089, 1654 cm^{-1}. HRMS: Calcd for $C_{15}H_{14}F_7O_2$ [M+1] 359.0882, Found 359.0872.

3.4. Preparation of phenylacetic ester 9

3.4.1. Cyanohydrin 11. *m*-Bromobenzaldehyde (30 mL, 257 mmol, 100 mol%) was added over 45 min to a stirred solution of $NaHSO_3$ (54 g, 520 mmol, 202 mol%) in H_2O (185 mL, 2.81 M) at ambient temperature to afford a white precipitate. The mixture was allowed to stir at room temp for 2.5 h once addition was complete, at which point the mixture was cooled to 0 °C and a solution of KCN (33.8 g, 519 mmol, 202 mol%) in H_2O (125 mL, 4.15 M) was added over a period of 45 min. Once the addition was complete, the mixture was allowed to stir for 2 h as it warmed to room temperature. The precipitate gradually disappeared. The reaction mixture was extracted with Et_2O (3×100 mL). The combined organic extracts were washed with brine (1× 50 mL) and were dried (Na_2SO_4). After filtration, evaporation, and further drying of the residue in vacuo, the title compound (54.5 g, 257 mmol) was isolated in 100% yield as an orange oil which appeared pure by ^1H NMR analysis. This material was used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (m, 1H), 7.54 (dm, $J=7.8$ Hz, 1H), 7.43 (dm, $J=7.8$ Hz, 1H), 7.30 (t, $J=7.8$ Hz, 1H), 5.50 (s, 1H), 4.68 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.3, 132.7, 130.6, 129.5, 125.0, 122.9, 118.5, 62.4.

3.4.2. α-Hydroxy ester 12. A mixture of compound **11** (54.5 g, 257 mmol) and concentrated aqueous HCl (350 mL) was heated to 80 °C for 6 h, at which point the reaction mixture was allowed to cool to ambient temperature. The mixture was rendered basic through the careful addition of KOH pellets and the basic solution was extracted with Et_2O (3×250 mL). The aqueous solution was then rendered acidic by careful addition of 10% aqueous H_2SO_4 and the acidic solution was extracted with Et_2O (3× 250 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to afford the carboxylic acid (53.43 g, 231 mmol) as a yellow solid, which was carried into the next step without further purification. A solution of the carboxylic acid and concentrated aqueous H_2SO_4 (12.5 mL) in methanol (250 mL, 0.92 M) was heated to reflux for a 2 h period, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was rendered basic by the addition of 5% aqueous Na_2CO_3 (300 mL). A white precipitate formed, which dissolved in the organic layer upon addition of Et_2O (200 mL). After separation of the aqueous and organic layers, the aqueous solution was extracted with additional Et_2O (2×100 mL). The combined organic extracts were washed with brine (1×50 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by flash chromatography (SiO_2: 1:1 Et_2O/hexanes) provides methyl ester **12** (50.4 g, 206 mmol) in 80% yield over 2 steps as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (m, 1H), 7.46 (dm, $J=7.8$ Hz, 1H), 7.35 (dm, $J=7.8$ Hz, 1H), 7.24 (t, $J=$ 7.8 Hz, 1H), 5.16 (s, 1H), 3.78 (s, 3H), 3.72 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 140.3, 131.5, 130.0, 129.6, 125.2, 122.6, 72.1, 53.2.

3.4.3. Phenyloxoacetic ester 13. Activated MnO_2 (5 μm, 75.1 g, 863 mmol, 1500 mol%) was added to a solution of **12** (14.1 g, 57.5 mmol, 100 mol%) in DCM (500 mL, 0.12 M) and the reaction mixture was allowed to stir at ambient temperature until **12** was completely consumed. The reaction mixture was filtered through Celite and the filtrate was then concentrated in vacuo to provide **13** (10.6 g, 43.8 mmol) in 76% yield as a yellow solid, which appeared pure by ^1H NMR analysis. This material was used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$): δ 8.19 (m, 1H), 7.98 (dm, $J=7.9$ Hz, 1H), 7.80 (dm, $J=7.9$ Hz, 1H), 7.42 (t, $J=7.9$ Hz, 1H), 4.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.2, 163.0, 137.6, 134.0, 132.6, 130.3, 128.6, 122.9, 52.8.

3.4.4. Phenylacetic ester 9. A flame-dried 100 mL round bottom flask equipped with a Teflon-coated magnetic stir bar was charged with **13** (10.40 g, 42.79 mmol, 100 mol%). The flask was capped with a rubber septum and purged with argon. (Diethylamino)sulfur trifluoride (10.0 mL, 75.7 mmol, 177 mol%) was added by syringe. The mixture was heated to 50°C and was allowed to stir vigorously for

3 h. After cooling to room temperature, the reaction was carefully poured into ice water (150 mL) and the resulting mixture was extracted with DCM (3×50 mL). The combined organic extracts were washed with brine (1× 50 mL) and dried (Na_2SO_4). After filtration, removal of the volatiles in vacuo, the crude product was isolated as a dark orange oil. Purification by flash chromatography (SiO_2: 2.5:97.5 Et_2O/hexanes) afford the α-difluorinated phenylacetic ester **9** (8.626 g, 32.54 mmol, 76% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.64 (d, J=7.9 Hz, 1H), 7.56 (d, J=7.9 Hz, 1H), 7.35 (t, J= 7.9 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 134.6, 134.2, 130.3, 128.6, 124.2, 122.7, 112.4, 53.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.3 (s). IR (film): 2959, 1767, 1425, 1302, 1252, 1112, 1076, 1017, 818, 796, 728 cm^{-1}. HRMS: Calcd for $C_9H_8BrF_2O_2$ [M+1] 264.9676, Found 264.9679.

3.5. Preparation of bis(1,3-diketones) 2a–2c

3.5.1. Mono(diketone) 1e. A solution of LDA in anhydrous THF was prepared as described above. Monoketone **8** (1.51 g, 9.30 mmol, 100 mol%) and **9** (3.746 g, 14.13 mmol, 152 mol%) were then reacted according to the general acylation procedure. The crude product was isolated as an orange-brown oil, which was purified by flash chromatography (SiO_2: 1:4 DCM/hexanes) to yield a mixture of keto- and enol-tautomers of **1e** (1.16 g, 2.93 mmol) in 32% yield as a dark purple, viscous oil. The overall yield based on recovered **8** (707 mg, 4.36 mmol) was 59%. $[\alpha]_D^{26}$ +22.1° (c=1.13, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.78 (s, 1H), 7.73 (s, 1H), 7.62 (d, J=7.9 Hz, 1H), 7.53 (d, J=7.9 Hz, 1H), 7.34 (t, J= 7.9 Hz, 1H), 3.26 (m, 1H), 2.67 (s, 1H), 2.50 (m, 3H), 2.42 (m, 1H), 1.76 (m, 4H), 1.44 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.7, 158.4, 136.4, 133.7, 130.1, 128.7, 124.2, 122.5, 115.4, 114.8, 55.6, 50.0, 47.5, 47.4, 45.1, 44.0, 33.4, 27.9, 27.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −100.9 (d, J= 4.0 Hz). IR (film): 3446, 2955, 1680, 1635 cm^{-1}. HRMS: Calcd for $C_{19}H_{18}BrF_2O_2$ [M+1] 395.0458, Found 395.0454.

3.5.2. Bis(diketone) 2a. Compound **1e** (530 mg, 1.34 mmol, 100 mol%) and hexamethylditin (255 mg, 0.78 mmol, 58 mol%) were dissolved in dry toluene (10 mL, 0.13 M with respect to **1e**). The reaction vessel was sealed with a rubber septum, and the solution was sparged with argon for 1 min, at which point $Pd(PPh_3)_4$ (73 mg, 0.063 mmol, 5 mol%) was added. The mixture was heated to 100 °C with stirring under argon for 17 h. The reaction mixture was evaporated onto silica gel. Purification by flash chromatography (SiO_2: 1:4 DCM/hexanes) provides **2a** (0.189 g, 0.30 mmol) in 45% yield as a pale purple oily solid. $[\alpha]_D^{28}$ −94.4° (c=0.90, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.82 (s, 2H), 7.80 (s, 2H), 7.72 (m, 2H), 7.57 (m, 4H), 3.31 (m, 2H), 2.68 (s, 2H), 2.51 (m, 8H), 1.73 (m, 8H), 1.48 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 217.7, 159.0, 140.7, 135.2, 130.4, 130.3, 129.4, 129.2, 124.6, 114.7, 55.7, 50.0, 47.6, 47.4, 45.2, 44.1, 33.4, 28.0, 27.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −100.6 (s, 2F), −100.8 (s, 2F). IR (film): 2926, 2872, 2854, 1680, 1624 cm^{-1}. HRMS: Calcd for $C_{38}H_{34}F_4O_4$ [M+1] 630.2393, Found 630.2399.

3.5.3. Mono(diketone) 1f. A solution of (+)-camphor (5.02 g, 33.0 mmol, 200 mol%) in anhydrous THF (100 mL) was cooled to −78 °C. *tert*-Butyllithium (1.7 M solution in pentane, 20 mL, 34 mmol, 207 mol%) was added dropwise over a period of 15 min. The mixture was stirred at −78°C for 1 h, at which point the ester **9** (4.35 g, 16.4 mmol, 100 mol%) was added. Notwithstanding these deviations, the general procedure for Claisen condensation was followed as described above. The crude product was isolated as a yellow oil, which was purified by flash chromatography (SiO_2: 2.5:97.5 ethyl acetate/hexanes) to yield a mixture of keto and enol tautomers of **14** (4.54 g, 11.8 mmol) in 72% yield as a pale purple oil. $[\alpha]_D^{27}$ +72.6° (c=1.13, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.80 (s, 1H), 7.71 (s, 1H), 7.60 (d, J=8.1 Hz, 1H), 7.50 (d, J= 8.1 Hz, 1H), 7.32 (t, J=8.1 Hz, 1H), 2.99 (m, 1H), 2.08 (m, 1H), 1.73 (m, 1H), 1.43 (m, 2H), 0.99 (s, 3H), 0.96 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.4, 155.3, 136.7, 133.7, 130.1, 128.6, 124.1, 122.6, 116.4, 115.7, 57.8, 49.1, 47.3, 30.2, 26.9, 20.4, 18.4, 8.6. IR (film): 3456, 2967, 1680, 1640 cm^{-1}. HRMS: Calcd for $C_{18}H_{20}BrF_2O_2$ [M+1] 385.0615, Found 385.0614.

3.5.4. Bis(diketone) 2b. Compound **1f** (0.504 g, 1.31 mmol, 100 mol%) and hexamethylditin (0.219 g, 0.670 mmol, 58 mol%) were dissolved in dry toluene (10 mL, 0.13 M with respect to **1f**). The reaction vessel was sealed with a rubber septum, and the solution was sparged with argon for 1 min, at which point $Pd(PPh_3)_4$ (100 mg, 0.09 mmol, 7 mol%) was added. The mixture was heated to 100 °C with stirring under argon for 17 h. The reaction mixture was evaporated onto silica gel. Purification by flash chromatography (SiO_2: SiO_2; 20:80 ethyl acetate/hexanes) provides **2b** (0.256 g, 0.419 mmol) in 45% yield as a pale purple solid. Mp 187–189°C. $[\alpha]_D^{27}$ +10.2° (c=0.98, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.85 (s, 2H), 7.77 (s, 2H), 7.57 (m, 4H), 3.01 (m, 2H), 2.08 (m, 2H), 1.75 (m, 2H), 1.45 (m, 4H), 0.99 (s, 6H), 0.96 (s, 6H), 0.83 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.4, 155.3, 136.7, 133.7, 130.1, 128.6, 124.1, 122.6, 116.4, 116.4, 57.8, 49.1, 47.4, 30.2, 26.9, 20.4, 18.4, 8.6; IR (film): 3460, 2975, 1675, 1635 cm^{-1}. HRMS: Calcd for $C_{36}H_{39}F_4O_4$ [M+1] 611.2784, Found 611.2793.

3.5.5. Friedel–Craft acylation of dibenzofuran. To a solution of dibenzofuran (172 mg, 1.02 mmol, 100 mol%) in DCM (5.20 mL, 0.20 M) at 0 °C was added $AlCl_3$ (1.67 g, 12.5 mmol, 1250 mol%) followed by ethyl chlorooxoacetate (670 μL, 6.0 mmol, 600 mol%). The reaction mixture was allowed to stir for 2 h and was allowed to reach ambient temperature, at which point ice water (10 mL) was added to reaction mixture. The reaction mixture was transferred to a separatory funnel and the aqueous layer was extracted with DCM (3×10 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and evaporated to afford the crude reaction product as a yellow oil. Purification by flash chromatography (SiO_2: 1:4 EtOAc/hexanes) provides the bis(oxoacetic) ester (150 mg, 0.41 mmol) in 40% yield as a yellow solid. Mp 97–99 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.71 (d, J=1.5 Hz, 1H), 8.25 (dd, J=8.7, 1.8 Hz, 2H), 7.70 (d, J=8.7 Hz, 2H), 4.54 (q, J=7.2 Hz, 4H), 1.49 (t, J= 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 185.0, 163.6,

160.4, 130.5, 128.5, 124.2, 124.0, 112.6, 62.6, 14.1. IR (film): 1734, 1685, 1594, 1194, 1018 cm^{-1}. HRMS: Calcd for $C_{20}H_{16}O_7$ [M+1] 369.097, Found 369.095.

3.5.6. Bis(α-difluoroacetic ester) 14. To a solution of bis(oxoacetic) ester (1.99 g, 5.41 mmol, 100 mol%) in DCM (55 mL, 0.1 M) at ambient temperature under an argon atmosphere was added (diethylamino)sulfur trifluoride (3.60 mL, 27.2 mmol, 500 mol%) dropwise via syringe. Once the addition of (diethylamino)sulfur trifluoride was complete, the reaction vessel was placed in a heating bath and was allowed to stir at 50 °C for 6 h, at which point the reaction mixture was removed from the heating bath and allowed to reach ambient temperature. Ice water (50 mL) was added slowly to the reaction mixture and the reaction mixture was transferred to a separatory funnel and the aqueous layer was extracted with DCM (3×10 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and evaporated to afford the crude reaction product as a yellow oil. Purification by flash chromatography (SiO_2: 1:4 EtOAc/hexanes) provides the title compound (1.63g, 3.95 mmol) in 73% yield as a yellow solid; mp 55–57 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.26 (d, J=1.4 Hz, 2H), 7.76 (dd, J=8.5, 1.7 Hz, 2H), 7.65 (m, 2H), 4.33 (q, J=7.2 Hz, 4H), 1.32 (t, J=7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.2 (t, 35.4 Hz), 157.9, 128.2 (t, 25.4 Hz), 125.3, 123.8, 118.8, 113.5, 112.2, 63.3, 13.9. IR (film): 1765, 1302, 1253, 1098, 1015 cm^{-1}. HRMS: Calcd for $C_{20}H_{16}F_4O_5$ [M+1] 412.0933, Found 412.0936.

3.5.7. Bis(diketone) 2c. To a solution of (+)-camphor (3.80 g, 25.0 mmol, 325 mol%) in anhydrous THF (50 mL, 0.5 M) at −78 °C under an argon atmosphere was added *tert*-butyllithium (1.7 M in pentane, 14.7 mL, 25.0 mmol, 325 mol%) dropwise via addition funnel over a period of 30 min. Once the addition of *tert*-butyllithium was complete, a solution bis(α-difluoroacetic ester) **14** (3.18 g, 7.70 mmol, 100 mol%) in anhydrous THF (10 mL, 0.77 M) was added dropwise via syringe and the cooling bath was removed. The reaction mixture was allowed to stir at ambient temperature for 16 h, at which point saturated aqueous NH_4Cl (100 mL) was added and reaction mixture was transferred to a separatory funnel, and the aqueous layer was extracted with DCM (3×10 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and evaporated to afford the crude reaction product as a yellow solid. Recrystallization of the crude residue from hexanes provides bis(diketone) **2c** (2.12 g, 3.40 mmol) in 44% yield as a pink solid. Mp 125 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 11.9 (bs, 2H), 8.20 (s, 2H), 7.69 (dd, J=8.6, 1.4 Hz, 2H), 7.66 (dd, J=22.2, 8.6 Hz, 2H), 3.02 (m, 2H), 2.07 (m, 2H), 1.74 (m, 2H), 1.44 (m, 4H), 0.97 (s, 6H), 0.95 (s, 6H), 0.81 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 214.5, 157.6, 155.9 (t, 32.9 Hz), 129.9 (t, 26.8 Hz), 125.2, 123.8, 118.6, 118.5, 116.2, 112.1, 57.8, 49.2, 47.4, 30.3, 26.9, 20.5, 18.4, 8.6. IR (film): 3389, 1691, 1633, 1253, 1160, 1071 cm^{-1}. HRMS: Calcd for $C_{36}H_{36}O_5F_4$ [M+1] 625.157, Found 625.258.

3.6. General procedures for ligand metallation

3.6.1. Cobalt(II) complexes. To a solution of diketone **1** (100 mol%) in 50% aqueous ethanol (0.25–0.35 M) at ambient temperature was added solid $Co(NO_3)_2 \cdot 6H_2O$ (50 mol%). The reaction mixture was sparged with argon and placed under an argon atmosphere. Concentrated aqueous NH_3 (500 mol%) was added dropwise to the reaction mixture via syringe. The mixture was allowed to stir for 1 h, at which point an orange-red precipitate was isolated by filtration, washed with H_2O, and dried in vacuo.

3.6.2. Iron(III) complexes. To a solution of diketone **1** (100 mol%) in ethanol (0.30–0.40 M) at ambient temperature was added a solution of $FeCl_3 \cdot 6H_2O$ (33 mol%) and KOAc (500 mol%) in H_2O (0.10–0.15 M with respect to the iron salt) dropwise via syringe. The mixture was allowed to stir for 1 h, at which point the purple-red precipitate was isolated by filtration and dried in vacuo.

3.6.3. Oxovanadium(IV) complexes. To a solution of diketone **1** (100 mol%) in EtOH (0.16 M) at ambient temperature was added a solution of NaOH in 50% aqueous MeOH (0.50 M solution, 100 mol%) dropwise via syringe. After the addition of NaOH was complete, a solution of $VOSO_4 \cdot H_2O$ (50 mol%) in H_2O (0.16 M) was added to the reaction mixture dropwise via syringe. The reaction mixture was allowed to stir for 1 h, at which point the dark green precipitate was isolated by filtration and dried in vacuo. In the event that a precipitate was not formed, the reaction mixture was extracted with pentane and the organic layer was dried (Na_2SO_4), filtered and evaporated and the resulting dark green film was dried in vacuo.

3.6.4. Oxovanadium(IV) complexes (ligand exchange method). To a solution of diketone **1** (100 mol%) in toluene (0.23 M) at ambient temperature was added $VO(acac)_2$ (50 mol%). The mixture was placed in a heating bath at 110 °C and the reaction mixture was allowed to reflux for 24 h, at which point solvent was removed by rotary evaporation, and the dark green residue was dried in vacuo. For the metallation of bis(diketones) **2**, an analogous procedure employing equimolar quantities of ligand, base and $VO(acac)_2$ was applied.

3.6.5. Europium(III) complexes. To a solution of diketone **1** (100 mol%) in EtOH (0.15–0.20 M) at ambient temperature was added a solution of NaOH (100 mol%) in 50% aqueous MeOH (0.50 M) dropwise via syringe. After the addition of NaOH was complete, a solution of $EuCl_3 \cdot 6H_2O$ in MeOH (0.10–0.15 M) was added to the reaction mixture dropwise via syringe. The reaction mixture was allowed to stir for 1 h, at which point the yellow precipitate was isolated by filtration and dried in vacuo.

3.6.6. Zinc(II) complexes. To a solution diketone **1** (100 mol%) in EtOH (0.16 M) at ambient temperature was added a solution of NaOH in 50% aqueous MeOH (0.50 M) dropwise via syringe. After the addition of NaOH was complete, a solution of $Zn(OAc)_2 \cdot 2H_2O$ (50 mol%) in H_2O (0.17 M) was added to the reaction mixture dropwise via syringe. The reaction mixture was allowed to stir for 1 h, at which point the white precipitate was isolated by filtration and dried in vacuo.

3.6.7. Copper(II) complexes. To a solution diketone **1**

(100 mol%) in EtOH (0.56 M) at ambient temperature was added a solution of KOAc (100 mol%) and $Cu(OAc)_2$ or $CuCl_2$ (50 mol%) in H_2O (0.22 M) dropwise via syringe. The reaction mixture was allowed to stir for 1 h, at which point the yellow-brown was isolated by filtration and dried in vacuo. For the metallation of bis(diketones) **2**, an analogous procedure employing equimolar quantities of ligand, base and $Cu(OAc)_2$ was applied.

3.6.8. Palladium(II) complexes. To a solution diketone **1** (100 mol%) in EtOH (0.36 M) at ambient temperature was added a solution of NaOH (100 mol%) in 50% aqueous MeOH (0.50 M) dropwise via syringe. After the addition of NaOH was complete, a solution of $PdCl_2$ (50 mol%) in warm H_2O (0.07 M) was added dropwise via syringe. The reaction mixture was allowed to stir for 2 h, at which point the yellow-brown was isolated by filtration and dried in vacuo.

3.6.9. Nickel(II) complexes. To a suspension of diketone **2** (100 mol%) in MeOH (0.3 M) at ambient temperature was added a solution of NaOH (100 mol%) in H_20 (1.0 M) dropwise via syringe. After the addition of NaOH was complete, a solution of $NiCl_2 \cdot 6H_2O$ (100 mol%) in H_2O (0.5 M) was added dropwise via syringe. The green precipitate was immediately isolated by filtration and dried in vacuo.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.118

This comprises scanned images of ^1H NMR and ^{13}C NMR spectra. X-ray crystallographic data for compounds **7** and $Fe(\mathbf{1b})_3$.

References and notes

1. For a compilation of reviews, see: *Comprehensive asymmetric catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999.
2. For reviews, see: (a) Mehrotra, R. C. *Pure Appl. Chem.* **1988**, *60*, 1349. (b) Toscano, P. J.; Dettelbacher, C.; Waechter, J.; Pavri, N. P.; Hunt, D. H.; Eisenbraun, E. T.; Zheng, B.; Kaloyeros, A. E. *J. Coord. Chem.* **1996**, *38*, 319.
3. (a) Togni, A.; Rist, G.; Rihs, G.; Schweiger, A. *J. Am. Chem. Soc.* **1993**, *115*, 1908. (b) Togni, A. *Organometallics* **1990**, *9*, 3106.
4. *Asymmetric oxidation reactions*; Katsuki, T., Ed.; Oxford University Press: New York, 2001.
5. For a review, see: Dai, L.-X.; Hou, X.-L.; Deng, W.-P.; You, S.-L.; Zhou, Y.-G. *Pure Appl. Chem.* **1999**, *71*, 1401.
6. See references in: Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Yu, Y. H.; Xia, W. *Chem. Commun.* **2000**, 285.
7. (a) Hopf, H.; Barrett, D. G. *Liebigs Ann.* **1995**, 449. (b) Rozenberg, V.; Kharitonov, V.; Antonov, D.; Sergeeva, E.; Aleshkin, A.; Ikonnikov, N.; Orlova, S.; Belokon, Y. *Angew. Chem., Int. Ed.* **1994**, *33*, 91.
8. For Schiff-base derivatives of **3**, see: Vetter, A. H.; Berkessel, A. *Tetrahedron Lett.* **1998**, *39*, 1741.
9. (a) Corriu, R. J. P.; Geng, B.; Moreau, J. J. E. *J. Org. Chem.* **1993**, *58*, 1443. (b) Levin, J. I. *Tetrahedron Lett.* **1993**, *34*, 6211.
10. Oda, M.; Kawase, T.; Okada, T.; Enomoto, T. *Org. Synth.* **1996**, *73*, 253.
11. Marchand, A. P.; Allen, R. W. *J. Org. Chem.* **1974**, *39*, 1596.
12. Wenkert, E.; Yoder, J. E. *J. Org. Chem.* **1970**, *35*, 2986.
13. Cookson, R. C.; Crundwell, E.; Hudec, J. *Chem. Ind.* **1958**, 1003.
14. Lerman, B. M.; Galin, F. Z.; Umanskaya, L. A.; Tolstikov, G. A. *J. Org. Chem. U.S.S.R. (Engl. Trans.)* **1978**, *14*, 2336.
15. For a review, see: Corey, E. J.; Helal, C. *J. Angew. Chem.* **1998**, *37*, 1986.
16. For an excellent experimental procedure, see: Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mather, D. J.; Sohar, P.; Turner-Jones, E. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763.
17. Eaton, P. E.; Hudson, R. A.; Giordano, C. *J. Chem. Soc. Chem. Commun.* **1974**, 978.
18. Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838.
19. For a review, see: Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.
20. (a) Ferrer, L. O.; Margaretha, P. *J. Chem. Res.* **1999**, 204. (b) Howard, A. S.; Meerholz, C. A.; Michael, J. P. *Tetrahedron Lett.* **1979**, 1339.
21. Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210.
22. Young, S. D.; Buse, C. T.; Heathcock, C. H. *Org. Synth.* **1985**, *67*, 79.
23. Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883.
24. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.
25. Berg, E. W.; Herrera, N. M. *Anal. Chim. Acta* **1972**, *60*, 117.

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A highly diastereoselective synthesis of 3-carbethoxy-2,5-disubstituted-3-pyrrolines by phosphine catalysis

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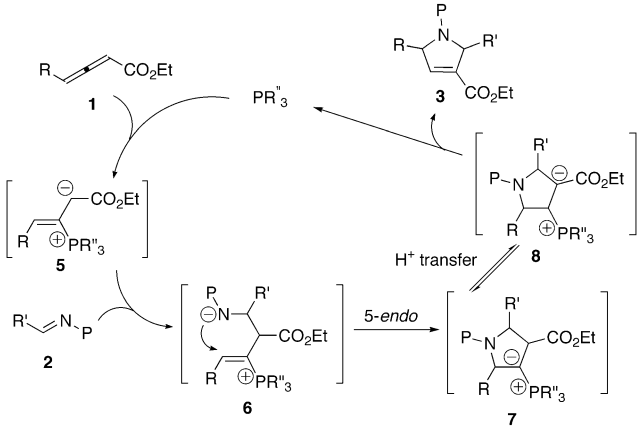
Abstract—Tributylphosphine was used as catalyst to facilitate a [3+2] cycloaddition between γ-substituted allenoates and *N*-sulfonylimines. The resulting adducts, 3-carbethoxy-2,5-disubstituted-3-pyrrolines, were formed in excellent yields with high diastereoselectivity. The reaction went to completion in several hours at room temperature, and the starting materials were easily prepared with one step from commercially available compounds via known procedures.

1. Introduction

Synthesis of 3-pyrrolines has been largely inspired by the structural relationship of this heterocycle to the ubiquitous pyrrolidine and pyrrole.[1,2] 3-Pyrrolines are often used as intermediates for the synthesis of five-membered nitrogen containing heterocyclic natural products and other compounds of pharmaceutical interest.[3] Recently, there has been considerable interest in developing a strategy for diversity oriented synthesis of pyrrolidines.[4] Development of a general procedure for the synthesis of highly substituted and functionalized 3-pyrrolines provides an expedient entry point into the synthesis of related compounds, highly substituted pyrrolidines and pyrroles.

1,3-Dipolar cycloaddition reactions provide the most versatile method for the formation of five-membered ring heterocycles.[5] One such example is the formal 1,3-dipolar cycloaddition of a zwitterionic intermediate derived from the addition of a phosphine to ethyl 2,3-butadienoate with imines to form pyrroline derivatives.[6] As part of a program to synthesize a library of heterocycles, we became interested in employing Lu's [3+2] reaction. To maximize the diversity in the pyrroline products, we decided to employ various 2,3-butadienoates. The mechanism of the reaction indicated that 4-substituted 2,3-butadienoates **1** would be ideal to synthesize 5-substituted dihydropyrroles **3** (Scheme 1). In the proposed mechanism, zwitterionic intermediate **5** adds to imine **2** to produce amide **6**. Intramolecular addition of the amide anion to the vinylphosphonium brings about the ylide **7**. Proton transfer generates the final intermediate **8** that dissociates to 3-pyrroline **3** and phosphine catalyst. Instead of exploring this option for the synthesis of 2,5-disubstituted-3-pyrrolines, Lu employed substituted 2-alkynoates. His approach provided 5-alkyl-2-aryl-2,5-dihydropyrrole 3-carboxylates in 33–75% yields.[7] Herein, we report our utilization of γ-substituted allenoates in the synthesis of 3-carbethoxy-2,5-disubstituted-3-pyrrolines in excellent yields with high diastereoselectivity.



Scheme 1. Mechanistic rationale for the formation of pyrroline **3**.

Keywords: [3+2] Cycloaddition; Organocatalysis; Phosphine; Pyrrolines.
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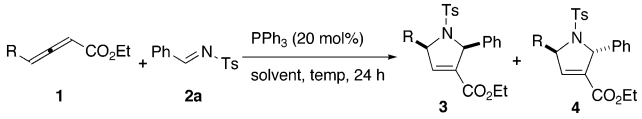
Table 1. Effect of reaction variables on the formation of pyrrolines **3** and **4**[a]



Entry	R	Solvent	Temp.	Yield (%)[b]	**3/4**[c]
1	Ethyl (**1b**)	Benzene	RT	44	15:1
2	*tert*-Butyl (**1e**)	Benzene	RT	0	N/A
3	Ethyl (**1b**)	$CHCl_3$	RT	32	9:1
4	Ethyl (**1b**)	EtOAc	RT	51	17:1
5	Ethyl (**1b**)	DME	RT	58	34:1
6	Ethyl (**1b**)	THF	RT	64	39:1
7	Ethyl (**1b**)	1,4-Dioxane	RT	65	23:1
8	Ethyl (**1b**)	Et_2O	RT	68	25:1
9	Ethyl (**1b**)	2-MeTHF	RT	69	39:1
10	Ethyl (**1b**)	THF	0 °C	55	9:1
11	Ethyl (**1b**)	THF	84 °C	31	**3** only

[a] See Section 4 for a detailed procedure.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.

2. Results and discussion

Ethyl γ-substituted allenoates were easily prepared[8] and subjected to Lu's original reaction conditions for the formation of 2-aryl-2,5-dihydropyrrole 3-carboxylates. When ethyl 2,3-hexadienoate (**1b**) (1.2 mmol) was mixed with *N*-tosyl benzaldimine (**2a**) (1.0 mmol) in the presence of PPh_3 (0.2 mmol) in benzene at room temperature, 44% yield of 5-ethyl-2-phenyl-3-pyrroline 3-ethylcarboxylate **3b** and **4b** were obtained as a 15:1 mixture of diastereomers (Table 1, entry 1). The assignment of *cis* stereochemistry of the major diastereomer **3b** was secured by X-ray crystallographic analysis (Fig. 1).[9] When a sterically more demanding substrate, ethyl γ-(*t*-butyl) allenoate (**1e**), was subjected to the same conditions, no cycloaddition product was formed (Table 1, entry 2). For this reaction to be employed in the synthesis of a library of pyrrolines, we needed more robust reaction conditions to provide a near quantitative yield with almost exclusive diastereoselectivity. To improve the reaction yield and diastereoselectivity seven additional common organic solvents were tested, and 2-methyltetrahydrofuran and tetrahydrofuran emerged as the best solvents in terms of yield and diastereoselectivity (Table 1, entries 3–9). Variation in the reaction temperature only brought inferior results (Table 1, entries 10 and 11).

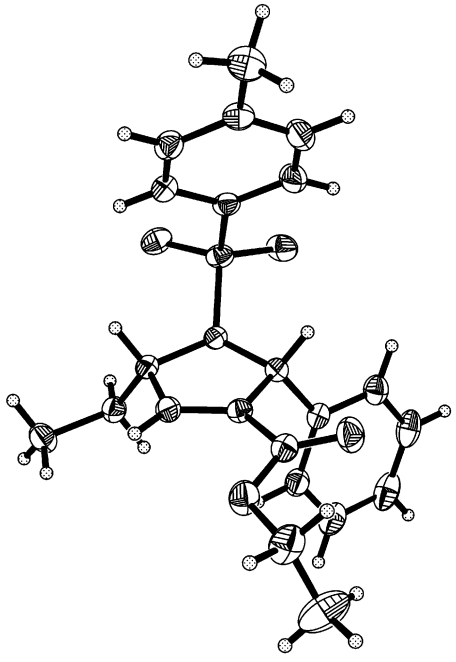
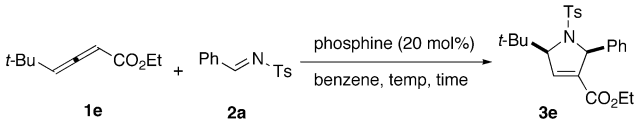


Figure 1. ORTEP representation of compound **3b**.

A dramatic increase in the efficiency of the reaction came from the usage of more nucleophilic phosphines. When the most sterically demanding γ-(*t*-butyl)-allenoate was employed as a test substrate, the triphenylphosphine catalyst did not facilitate any product formation even after elongated reaction time or at an elevated reaction temperature (Table 2, entries 1 and 2). Sterically demanding, yet more nucleophilic tricyclopentylphosphine furnished the desired product in 86% yield as a single diastereomer (Table 2, entry 3). Quantitative yield was obtained when less bulky trialkylphosphines or dimethylphenylphosphine was used (Table 2, entries 4–7). With trimethylphosphine, the reaction was fast and went to completion in 2 h (Table 2, entry 7).

Under the optimized reaction conditions a variety of γ-alkyl

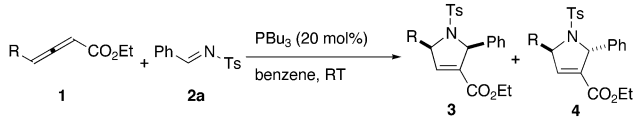
Table 2. Effect of phosphine catalysts on the formation of pyrroline **3e**[a]



Entry	Phosphine	Temp.	Time (h)	Yield (%)[b]
1	PPh_3	RT	98	0
2	PPh_3	80 °C	48	0
3	$PCyp_3$	RT	24	86
4	$PPhMe_2$	RT	24	99
5	PBu_3	RT	24	99
6	PBu_3	RT	8	99
7	PMe_3	RT	2	99

[a] See Section 4 for a detailed procedure.
[b] Isolated yield.

Table 3. Synthesis of 3-pyrrolines **3/4** under the optimized conditions[a]



Entry	R	Time (h)	Product	Yield (%)[b]	**3/4**[c]
1	Methyl (**1a**)	2	**3a/4a**	89	91:9
2	Ethyl (**1b**)	5	**3b/4b**	99	95:5
3	Propyl (**1c**)	5	**3c/4c**	98	96:4
4	Isopropyl (**1d**)	5	**3d**	99	100:0
5	*tert*-Butyl (**1e**)	8	**3e**	99	100:0
6	Phenyl (**1f**)	1.5	**3f**	99	100:0

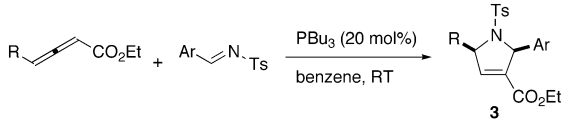
[a] See Section 4 for a detailed procedure.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.

and γ-aryl allenoates provided the 2,5-disubstituted products in excellent yields (Table 3). Diastereoselectivities ranged from high (91:9 for γ-methyl, Table 3, entry 1) to exclusive (Table 3, entries 4–6) with the *cis* product as the major isomer. γ-(*n*-Propyl) allenoate afforded the desired product in 98% yield (Table 4, entry 3), facilitating a direct comparison to the reactivity of the tautomeric 2-butynoate that furnished the same 3-pyrroline in 63% yield.[7]

To further establish the scope of the reaction, a variety of *N*-tosyl imines were prepared and reacted with several γ-substituted allenoates. Various aryl imines furnished 95–97% yield of the desired 3-pyrrolines when γ-isopropyl allenoate was used (Table 4, entries 1–4). Reaction yields remained quantitative for all aromatic imines tested when γ-phenyl and γ-(*tert*-butyl) allenoate were employed (Table 4, entries 5–16).

For this reaction to be utilized in the synthesis of pyrroles, it would be ideal to have a protecting group on nitrogen that can be cleaved in the presence of an α,β-unsaturated ester. Dissolving metal reduction conditions required for the tosyl deprotection are not compatible with the α,β-unsaturated ester functionality. The nosyl (Ns) group[10] and 2-trimethylsilylethanesulfonyl (SES) group[11] can be easily removed under milder conditions. We have tested the [3+2] reaction on the *N*-(*p*-Ns) imine and *N*-SES imine. *N*-SES benzaldimine provided the desired product **3w** in a nearly quantitative yield (Table 5, entry 1). However, *N*-(*p*-Ns) benzaldimine provided 3-pyrrole product **3x** in 93% yield, which is in accordance with our observation on the phosphine-catalyzed [4+2] annulation.[12] *N*-Nosyl imines, in general, underwent phosphine catalysis more sluggishly and provided diminished product yields compared to their *N*-tosyl counterparts. The removal of the SES group in pyrroline **3w** was facilitated by tetrabutylammonium fluoride (TBAF). Concomitant aromatization,[13] under the influence of TBAF, provided pyrrole **9** in 78% yield (Scheme 2).

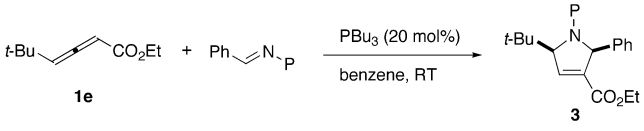
Table 4. Imine scope in the synthesis of 3-pyrrolines **3**[a]



Entry	R	Ar	Product	Yield (%)[b]
1	Isopropyl (**1d**)	2-FC_6H_4	**3 g**	97
2	Isopropyl (**1d**)	3-BrC_6H_4	**3 h**	95
3	Isopropyl (**1d**)	4-$CF_3C_6H_4$	**3i**	96
4	Isopropyl (**1d**)	4-(*i*-Pr)C_6H_4	**3j**	96
5	Phenyl (**1f**)	2-ClC_6H_4	**3k**	99
6	Phenyl (**1f**)	3-ClC_6H_4	**3 l**	99
7	Phenyl (**1f**)	4-FC_6H_4	**3m**	99
8	Phenyl (**1f**)	4-$MeOC_6H_4$	**3n**	99
9	*tert*-Butyl (**1e**)	2-ClC_6H_4	**3o**	> 99
10	*tert*-Butyl (**1e**)	3-ClC_6H_4	**3p**	> 99
11	*tert*-Butyl (**1e**)	3,4-$Cl_2C_6H_4$	**3q**	> 99
12	*tert*-Butyl (**1e**)	4-CNC_6H_4	**3r**	> 99
13	*tert*-Butyl (**1e**)	4-FC_6H_4	**3 s**	> 99
14	*tert*-Butyl (**1e**)	4-MeC_6H_4	**3t**	> 99
15	*tert*-butyl (**1e**)	4-$MeOC_6H_4$	**3u**	> 99
16	*tert*-Butyl (**1e**)	1-Naphthyl	**3v**	> 99

[a] See Section 4 for a detailed procedure.
[b] Isolated yield.

Table 5. Effect of *N*-sulfonyl groups of imines on the synthesis of 3-pyrrolines **3**[a]



Entry	P	Product	Yield (%)[b]	*cis*/*trans*[c]
1	SES	**3w**	100	100:0
2	*p*-Ns	**3x**	93	100:0

[a] See Section 4 for a detailed procedure.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.

Scheme 2. Synthesis of pyrrole **9**.

3. Conclusion

We have disclosed a formal [3+2] cycloaddition between γ-substituted allenoates and *N*-sulfonylimines. In this reaction, tributylphosphine was used as a nucleophilic

catalyst to facilitate the formation of 3-carbethoxy-2,5-disubstituted-3-pyrrolines in excellent yields with high diastereoselectivity. Reaction efficiency and selectivity are of paramount importance when performing reactions with hundreds of differentially functionalized complex substrates, as in the diversity-oriented synthesis (DOS). Despite the seemingly advanced state of modern organic synthesis, such reactions are scarce. The reaction reported herein meets the high standard of DOS in its efficiency and selectivity. The method also has many advantages, such as short reaction time at room temperature and easy non-aqueous work-up. The reactants were easily prepared in one step from commercially available materials via known procedures.[13] Efforts to perform the annulations to synthesize a library of heterocycles on solid support in a split-and-pool format are underway, and the results will be reported in due course.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. THF and diethyl ether were distilled over sodium/benzophenone ketyl; dichloromethane and benzene were freshly distilled from CaH_2. All other anhydrous solvents were packaged in Sure/Seal™ bottles and were used as received from Aldrich Company; chloroform was stabilized with amylenes. All the phosphines are commercially available and purchased from Aldrich Company or Strem Chemicals, Inc. All other reagents were used as received from commercial sources. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) and visualized by UV or permanganate staining. Flash column chromatography was performed using E. Merck silica gel 60 (230–400 mesh) using compressed air. IR spectra were recorded on a Perkin–Elmer pargon 1600 FT-IR spectrometer. NMR spectra were obtained on Bruker Avance-500, ARX-500 or ARX-400 instruments as indicated and calibrated using residual undeuterated chloroform as an internal reference (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, sept=septet, m=multiplet, br=broad, app=apparent. High-resolution EI mass spectra were recorded by rapid thermal vaporization of samples deposited on desorption ionization filament that was directly inserted into the electron ionization (EI, 70 eV, 200 °C) source of a triple sector high resolution instrument (VG/Micromass Autospec.) tuned to 8000 static resolution (M/DM, 10% valley) using perflourinated kerosene (formula weight 705, Lancaster Synthesis, Inc., NH) as internal calibrant. High resolution electrospray ionization (ESI) mass spectra were recorded by flow injection of chloroform solutions into an ESI source attached to a 7.5 T FTMS (Ion Spec Ultima, Irvine, CA) instrument. Data were analyzed using instrument-supplied software. X-ray crystallographic data were collected using a Bruker SMART CCD based diffractometer equipped with a low-temperature apparatus operating at 100 K.

4.2. General procedure for the synthesis of pyrrolines 3

Imine (1.0 mmol) was weighed in a 25-mL round-bottom flask, which was subsequently flushed with argon. Distilled benzene (10 mL) was added via syringe. Tributylphosphine was added via microsyringe (0.2 mmol.) Lastly allenoate (1.2 mmol) was added dropwise to the stirred solution. After several seconds a slight color change was visible: clear changing to light yellow. The reaction was monitored by TLC analysis. Upon completion, the solvent was evaporated under reduced pressure and the product was purified by flash column chromatography.

The spectral data for new 3-pyrrolines synthesized in Tables 3–5 are provided.

4.2.1. 5-Methyl-2-phenyl-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3a). IR (film) ν_{max} 2962, 1719, 1348, 1234, 1164, 1089 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, J=7.1 Hz, 3H), 1.59 (d, J=6.7 Hz, 3H), 2.42 (s, 3H), 4.01–4.09 (m, 2H), 4.82–4.83 (m, 1H), 5.71–5.73 (m, 1H), 6.68–6.69 (m, 1H), 7.23 (d, J=8.1 Hz, 2H), 7.29–7.36 (m, 5H), 7.60 (d, J=8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 21.4, 22.3, 60.7, 62.8, 69.7, 127.4, 127.8, 128.0, 128.2, 129.5, 133.8, 135.6, 140.0, 140.6, 143.4, 162.0; HRMS (EI) calcd for $C_{21}H_{24}NO_4S$ [(M+H)$^+$]: 366.1700, found: 366.1711.

4.2.2. 5-Ethyl-2-phenyl-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3b). IR (film) ν_{max} 2973, 1718, 1348, 1164, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, J=7.5 Hz, 3H), 1.06 (t, J=7.1 Hz, 3H), 1.74–1.76 (m, 1H), 2.04–2.06 (m, 1H), 2.36 (s, 3H), 3.94–4.05 (m, 2H), 4.56 (br s, 1H), 5.67 (br s, 1H), 6.75 (br s, 1H), 7.17 (d, J=8.01 Hz, 2H), 7.23–7.27 (m, 3H), 7.31 (d, J=8.2 Hz, 2H), 7.54 (d, J=8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.3, 13.7, 21.4, 29.7, 60.6, 68.7, 69.4, 127.4, 127.7, 127.9, 128.1, 129.5, 134.1, 135.3, 139.3, 139.9, 143.4, 162.0; HRMS (EI) calcd for $C_{22}H_{26}NO_4S$ [(M+H)$^+$]: 400.1583, found: 400.1597.

4.2.3. 5-Isopropyl-2-phenyl-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3d). IR (film) ν_{max} 2978, 1719, 1350, 1164, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, J=6.8 Hz, 3H), 1.02–1.05 (m, 6H), 2.07–2.09 (m, 1H), 2.36 (s, 3H), 3.95–4.04 (m, 2H), 4.45–4.47 (br s, 1H), 5.71–5.73 (br s, 1H), 6.73–6.75 (m, 1H), 7.18 (d, J=8.1 Hz, 2H), 7.24–7.28 (m, 3H), 7.36 (d, J=8.0 Hz, 2H), 7.53 (d, J=8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 19.1, 21.4, 27.2, 29.7, 53.4, 60.6, 119.5, 125.9, 127.2, 128.3, 129.1, 137.2, 138.0, 139.4, 142.9, 149.4, 166.8; HRMS (EI) calcd for $C_{23}H_{28}NO_4S$ [(M+H)$^+$]: 414.1694, found: 414.1760.

4.2.4. 5-(*tert*-Butyl)-2-phenyl-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3e). IR (film) ν_{max} 2971, 1722, 1346, 1259, 1166, 1090 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (s, 9H), 1.19 (t, J=7.1 Hz, 3H), 2.45 (s, 3H), 4.14–4.19 (m, 2H), 4.41 (br s, 1H), 5.94 (br s, 1H), 6.77–6.78 (m, 1H),

7.29–7.36 (m, 5H), 7.47 (d, J=7.5 Hz, 2H), 7.76 (d, J=8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.5, 27.9, 35.9, 53.4, 60.8, 68.4, 77.9, 127.5, 128.0, 128.1, 129.6, 134.1, 134.2, 139.7, 141.2, 143.8, 162.7; HRMS (EI) calcd for $C_{24}H_{29}NO_4S$ [$(M)^+$]: 427.1817, found: 427.1820.

4.2.5. 5-Phenyl-2-phenyl-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3f). IR (film) ν_{max} 2980, 1718, 1351, 1164, 1033 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, J=7.12 Hz, 3H), 2.35 (s, 3H), 4.02–4.13 (m, 2H), 5.91–5.93 (m, 1H), 5.97–5.99 (m, 1H), 6.80–6.81 (m, 1H), 7.05 (d, J=8.2 Hz, 2H), 7.25 (d, J=8.2 Hz, 2H), 7.34–7.43 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 21.4, 60.8, 69.5, 69.8, 127.2, 127.6, 128.0, 128.10, 128.13, 128.4, 128.5 129.1, 133.9, 135.9, 138.2, 139.2, 139.3, 143.2, 162.7 HRMS (EI) calcd for $C_{26}H_{25}NO_4S$ [$(M)^+$]: 448.1538, found: 448.1522.

4.2.6. 5-Isopropyl-2-(*o*-fluorophenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3g). IR (film) ν_{max} 2965, 1720, 1491, 1349, 1261, 1166, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J=7.1 Hz, 3H), 1.08 (d, J=6.6 Hz, 3H), 1.11 (d, J=7.1 Hz, 3H), 2.39 (s, 3H), 2.44–2.50 (m, 1H), 3.89–4.01 (m, 2H), 4.46 (br s, 1H), 5.92 (br s, 1H), 6.74 (m, 1H), 7.00–7.08 (m, 2H), 7.21–7.25 (m, 3H), 7.35–7.37 (m, 1H), 7.70 (d, J=8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 17.6, 20.3, 21.5, 32.7, 60.7, 61.3 (J_{CF}=3.9 Hz), 73.1, 115.3 (d, J_{CF}=22.5 Hz), 124.1 (J_{CF}=3.0 Hz), 127.9, 128.0, 128.2, 129.2, 129.7, (J_{CF}=6.8 Hz), 129.8, 133.9 (J_{CF}=28.5 Hz), 138.1, 143.9, 160.8, (J_{CF}=247.2 Hz) 161.7; HRMS (EI) calcd for $C_{23}H_{25}FNO_4S$ [$(M\text{-}H)^+$]: 430.1488, found: 430.1474.

4.2.7. 5-Isopropyl-2-(*m*-bromophenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3h). IR (film) ν_{max} 2964, 1719, 1346, 1261, 1164, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, J=6.8, Hz, 3H), 1.04–1.07 (m, 6H), 2.09–2.17 (m, 1H), 2.36 (s, 3H), 3.92–4.08 (m, 2H), 4.45–4.48 (m, 1H), 5.62 (br s, 1H), 6.74–6.76 (m, 1H), 7.12 (app t, J=7.83 Hz, 1H), 7.20 (d, J=8.1 Hz, 2H), 7.29 (dm, J=7.7 Hz, 1H), 7.35 (dm, J=7.9 Hz, 1H), 7.42–7.43 (m, 1H), 7.55 (d, J=8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 17.9, 20.1, 21.4, 32.8, 60.8, 68.6, 73.2, 122.0, 126.8, 127.6, 129.6, 130.9, 131.3, 133.9, 134.7, 139.2, 142.1, 143.8, 161.8; HRMS (EI) calcd for $C_{23}H_{26}BrNO_4S$ [$(M)^+$]: 491.0766, found: 491.0710.

4.2.8. 5-Isopropyl-2-(*p*-trifluoromethylphenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3i). IR (film) ν_{max} 3059, 2968, 1723, 1389, 1266, 1117, 1307 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J=7.1 Hz, 3H), 1.14 (d, J=7.1 Hz, 3H) 1.17 (d, J=6.8 Hz, 3H), 2.39 (s, 3H), 2.64 (sept, J=6.8 Hz, 1H), 3.86–3.95 (m, 2H), 4.39 (br s, 1H), 6.07 (br s, 1H), 6.77 (br s, 1H), 7.27 (d, J=7.7 Hz, 2H), 7.35–7.37 (m, 2H), 7.44–7.61 (m, 2H), 7.66 (d, J=7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 17.9, 20.4, 21.5, 32.1, 60.8, 64.8, 72.4, 128.0, 128.4, 129.1, 129.7, 131.6, 133.7, 134.8, 138.4, 139.8, 143.9, 161.6; HRMS (EI) calcd for $C_{24}H_{25}F_3NO_4S$ [$(M-H)^+$]: 480.1456, found: 480.1435.

4.2.9. 5-Isopropyl-2-(*p*-isopropylphenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3j). IR (film) ν_{max} 2962, 1720, 1343, 1164, 1092, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J=6.9 Hz, 3H), 1.06–1.13 (m, 6H), 1.26 (d, J=7.0 Hz, 6H), 2.14–2.21 (m, 1H), 2.38 (s, 3H), 2.91 (sept, J=6.9 Hz, 1H), 3.96–4.03 (m, 1H), 4.06–4.12 (m, 1H), 4.53–4.55 (m, 1H), 5.76 (br s, 1H), 6.77–6.79 (m, 1H), 7.16 (d, J=8.1 Hz, 2H), 7.20 (d, J=8.1 Hz, 2H), 7.32 (d, J=8.2 Hz, 2H), 7.56 (d, J=8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 17.9, 20.1, 21.3, 32.7, 33.6, 60.5, 69.0, 73.1, 126.0, 127.4, 128.1, 129.3, 134.5, 135.3, 137.0, 138.2, 143.3, 148.3, 162.1; HRMS (EI) calcd for $C_{26}H_{34}NO_4S$ [$(M+H)^+$]: 456.2209, found: 456.2193.

4.2.10. 5-Phenyl-2-(*o*-chlorophenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3k). IR (film) ν_{max} 2985, 1724, 1355, 1262, 1164, 1089, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J=7.1 Hz, 3H), 2.36 (s, 3H), 3.92–4.01 (m, 2H), 5.82 (br s, 1H), 6.37 (br s, 1H), 6.78 (d, J=2.2 Hz, 1H), 7.15–7.17 (m, 4H), 7.23 (d, J=8.2 Hz, 2H), 7.33–7.40 (m, 4H), 7.53–7.56 (m, 3H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.5, 60.1, 65.2, 69.8, 126.9, 127.4, 127.9, 128.2, 128.7, 129.0, 129.1, 129.4, 129.6, 134.1, 134.5, 137.7, 138.7, 139.7, 143.8, 161.7; HRMS (EI) calcd for $C_{26}H_{24}ClNO_4S$ [$(M)^+$]: 481.1115, found: 481.1113.

4.2.11. 5-Phenyl-2-(*m*-chlorophenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3l). IR (film) ν_{max} 2981, 1720, 1341, 1164, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, J=7.1 Hz, 3H), 2.31 (s, 3H), 3.96–4.12 (m, 2H), 5.86 (br s, 1H), 5.89 (br s, 1H), 6.77–6.79 (m, 1H), 7.04 (d, J=8.0 Hz, 2H), 7.18–7.40 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.4, 61.1, 69.0, 69.9, 126.9, 127.5, 128.0, 128.3, 128.6, 128.8, 128.9, 129.4, 129.6, 133.9, 134.2, 135.6, 138.2, 139.7, 141.3, 143.7, 161.9; HRMS (EI) calcd for $C_{26}H_{24}ClNO_4S$ [$(M)^+$]: 481.1115, found: 481.1104.

4.2.12. 5-Phenyl-2-(*p*-fluorophenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3m). IR (film) ν_{max} 3065, 1720, 1509, 1342, 1254, 1165, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, J=7.13 Hz, 3H), 2.32 (s, 3H), 3.98–4.09 (m, 2H), 5.85 (br s, 1H), 5.91 (br s, 1H), 6.76 (br s, 1H), 6.93–6.98 (m, 3H), 7.04 (d, J=8.1 Hz, 2H), 7.24 (d, J=8.3 Hz, 2H), 7.30–7.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.4, 61.0, 68.8, 69.8, 115.1, (d, J_{CF}=21.6 Hz), 127.3, 127.6, 128.3, 129.3, 130.2, 133.8, 135.4, 135.8, 138.3, 139.5, 143.5, 161.3, 162.0, 163.7; HRMS (EI) calcd for $C_{26}H_{24}FNO_4S$ [$(M)^+$]: 465.1410, found: 465.1405.

4.2.13. 5-Phenyl-2-(*p*-methoxyphenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3n). IR (film) ν_{max} 2983, 1720, 1351, 1250, 1164, 1033 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, J=7.1 Hz, 3H), 2.40 (s, 3H), 3.78 (s, 3H), 4.00–4.07 (m, 2H), 5.84 (br s, 1H), 5.90 (br s, 1H), 6.72–6.74 (m, 1H), 6.80 (d, J=8.7 Hz, 2H), 7.03 (d, J=8.1 Hz, 2H), 7.23–7.37 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.4, 55.3, 60.9, 69.1, 69.8, 113.6, 127.3, 127.6, 128.1, 129.1, 129.2, 129.7, 131.7, 134.0, 136.0, 138.4, 139.1, 143.2, 159.4, 165.2; HRMS (EI) calcd for $C_{27}H_{27}NO_4S$ [$(M)^+$]: 477.1610, found: 477.1614.

4.2.14. 5-(*tert*-Butyl)-2-(*o*-chlorophenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3o). IR (film) ν_{max} 2967, 1721, 1355, 1267, 1168, 1022 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, J=7.1 Hz, 3H), 1.15 (s, 9H), 2.34 (s, 3H), 3.89–3.99 (m, 2H), 4.61–4.62 (m, 1H), 6.29–6.30 (m, 1H), 6.77–6.78 (m, 1H), 7.12–7.17 (m, 2H), 7.20 (d, J=8.2 Hz,

2H), 7.28 (dm, $J=7.8$ Hz, 1H), 7.58 (dm, $J=7.7$ Hz, 1H), 7.69 (d, $J=8.3$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 21.4, 28.8, 36.7, 60.7, 67.0, 76.6, 126.5, 128.1, 128.9, 129.3 129.4, 129.5, 133.5, 134.3, 134.7, 137.8, 139.5, 143.7, 161.7; HRMS (EI) calcd for $C_{24}H_{29}ClNO_4S$ [$(M+H)^+$]: 462.1506, found: 462.1494.

4.2.15. 5-(*tert*-Butyl)-2-(*m*-chlorophenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3p). IR (film) ν_{max} 2961, 1717, 1346, 1260, 1233, 1164, 1089 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (s, 9H), 1.14 (t, $J=7.1$ Hz, 3H), 2.40 (s, 3H), 4.08–4.14 (m, 2H), 4.35 (dm, $J=2.7$ Hz, 1H), 5.80 (s, 1H), 6.74 (dm, $J=2.7$ Hz, 1H), 7.20–7.23 (m, 2H), 7.26 (d, 2H), 7.29–7.31 (m, 1H), 7.34 (br s, 1H), 7.69 (d, $J=8.3$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.5, 27.9, 36.0, 61.0, 68.0, 77.9, 83.0, 126.3, 127.8, 128.1, 128.3, 129.3, 129.7, 133.7, 133.8, 133.9, 141.7, 141.9, 144.1; HRMS (EI) calcd for $C_{24}H_{29}ClNO_4S$ [$(M+H)^+$]: 462.1506, found: 462.1498.

4.2.16. 5-(*tert*-Butyl)-2-(3,4-dichlorophenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3q). IR (film) ν_{max} 2965, 1718, 1472, 1352, 1260, 1165, 1089 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (s, 9H), 1.14 (t, $J=7.1$ Hz, 3H), 2.38 (s, 3H), 4.07–4.14 (m, 2H), 4.33 (d, $J=2.4$ Hz, 1H), 5.75, (s, 1H), 6.73–6.74 (m, 1H), 7.24–7.27 (m, 3H), 7.33–7.35 (m, 1H), 7.45–7.46 (m, 1H), 7.68 (d, $J=8.2$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.5, 27.9, 35.9, 61.1, 67.4, 77.8, 127.5, 128.0, 129.7, 129.9, 130.2, 131.7, 132.1, 133.2, 133.5, 140.0, 142.2, 144.3, 162.2; HRMS (EI) calcd for $C_{24}H_{28}Cl_2NO_4S$ [$(M+H)^+$]: 496.1116, found: 496.1111.

4.2.17. 5-(*tert*-Butyl)-2-(*p*-cyanophenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3r). IR (film) ν_{max} 2967, 2229, 1718, 1347, 1165, 1089 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (s, 9H), 1.23 (t, $J=7.1$ Hz, 3H), 2.38 (s, 3H), 4.06–4.12 (m, 2H), 4.32 (d, $J=2.4$, Hz, 1H), 5.81 (s, 1H), 6.73 (d, $J=2.4$ Hz, 1H), 7.26 (d, $J=8.1$ Hz, 2H), 7.54–7.59 (m, 4H), 7.68 (d, $J=8.2$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.5, 27.7, 35.8, 61.1, 67.8, 78.0, 111.4, 118.6, 127.9, 128.8, 129.7, 131.8, 133.1, 133.3, 142.3, 144.3, 144.9, 162.2; HRMS (EI) calcd for $C_{25}H_{29}N_2O_4S$ [$(M+H)^+$]: 453.1848, found: 453.1852.

4.2.18. 5-(*tert*-Butyl)-2-(*p*-fluorophenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3s). IR (film) ν_{max} 3054, 2986, 1718, 1421, 1266, 1165, 896 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (s, 9H), 1.18 (t, $J=7.1$ Hz, 3H), 2.44 (s, 3H), 4.15 (br q, $J=7.1$ Hz, 2H), 4.38 (d, $J=2.3$ Hz, 1H), 5.88 (s, 2H), 6.78 (br s, 1H), 7.02 (app t, $J=8.6$ Hz, 2H), 7.31 (d, $J=8.0$ Hz, 2H), 7.45 (dd, $J=8.4$, 5.4 Hz, 2H), 7.75 (d, $J=8.1$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.4, 27.8, 35.9, 60.9, 67.8, 77.8, 114.7, 114.9, 127.9, 129.8 (d, $J_{CF}=8.3$ Hz), 133.9 (d, $J_{CF}=7.9$ Hz), 135.5 (d, $J_{CF}=3.0$ Hz), 141.5, 144.0, 161.1, 162.5, 163.1; HRMS (EI) calcd for $C_{24}H_{29}FNO_4S$ [$(M+H)^+$]: 446.1801, found: 446.1782.

4.2.19. 5-(*tert*-Butyl)-2-(*p*-tolyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3t). IR (film) ν_{max} 2963, 1719, 1513, 1347, 1254, 1164 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (s, 9H), 1.03 (t, $J=7.1$ Hz, 3H), 2.20 (s, 3H), 2.28 (s, 3H), 3.96–4.03 (m, 2H), 4.24 (d, $J=2.5$ Hz, 1H), 5.74 (s, 1H), 6.61 (dm, $J=2.5$ Hz, 1H), 6.98 (d, $J=8.0$ Hz, 2H), 7.15 (d, $J=8.1$ Hz, 2H), 7.19 (d, $J=8.1$ Hz, 2H), 7.60 (d, $J=8.1$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.0, 21.4, 27.9, 35.8, 60.7, 68.2, 77.7, 127.90, 127.93, 128.6, 129.5, 134.1, 134.3, 136.6, 137.1, 140.9, 143.7, 162.7; HRMS (EI) calcd for $C_{25}H_{32}NO_4S$ [$(M+H)^+$]: 442.2052, found: 442.2039.

4.2.20. 5-(*tert*-Butyl)-2-(*p*-methoxyphenyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3u). IR (film) ν_{max} 2962, 1719, 1348, 1260, 1234, 1164, 1089 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78 (s, 9H), 1.10 (t, $J=7.1$ Hz, 3H), 2.35 (s, 3H), 3.74 (s, 3H), 4.05–4.10 (m, 2H), 4.31 (d, $J=2.3$ Hz, 1H), 5.81 (s, 1H), 6.68 (dm, $J=2.3$ Hz, 1H), 6.80 (d, $J=6.9$ Hz, 2H), 7.22 (d, $J=8.0$ Hz, 2H), 7.31 (d, $J=8.7$ Hz, 2H), 7.68 (d, $J=8.3$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.4, 27.8, 35.8, 55.0, 60.7, 68.0, 77.6, 113.2, 127.9, 129.2, 129.5, 131.7, 134.0, 134.2, 140.9, 143.7, 158.8, 162.6; HRMS (EI) calcd for $C_{25}H_{32}NO_5S$ [$(M+H)^+$]: 458.2001, found: 458.1996.

4.2.21. 5-(*tert*-Butyl)-2-(1-napthyl)-*N*-tosyl-3-pyrroline-3-ethylcarboxylate (3v). IR (film) ν_{max} 2966, 1721, 1346, 1236, 1166, 1091, 1021, 988 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, $J=7.1$ Hz, 3H), 1.06 (s, 9H), 2.20 (s, 3H), 3.85–3.92 (m, 2H), 4.91–4.93 (m, 1H), 6.87–6.90 (m, 3H), 6.92 (app t, $J=2.1$ Hz, 1H), 7.35–7.38 (m, 3H), 7.40–7.42 (m, 1H), 7.42–7.44 (m, 1H), 7.55 (dm, $J=7.3$ Hz, 1H), 7.76 (app t, 7.4 Hz, 2H), 8.57 (d, $J=8.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 21.2, 28.8, 36.8, 60.6, 65.6, 76.7, 124.2, 124.4, 125.4, 125.9, 126.5, 127.3, 128.1, 128.8, 128.9, 131.9, 133.5, 134.7, 136.1, 136.1, 139.1, 143.0, 162.2; HRMS (EI) calcd for $C_{28}H_{32}NO_4S$ [$(M+H)^+$]: 478.2052, found: 478.2048.

4.2.22. 5-(*tert*-Butyl)-2-phenyl-*N*-SES-3-pyrroline-3-ethylcarboxylate (3w). IR (film) ν_{max} 2986, 1717, 1266, 1165, 1064, 976, 896 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.14 (s, 9H), 0.81 (s, 9H), 0.87–0.92 (m, 2H), 1.06 (t, $J=7.1$ Hz, 3H), 2.56–2.74 (m, 2H), 4.03–4.09 (m, 2H), 4.56 (br s, 1H), 5.93 (br s, 1H), 6.90–6.92 (m, 1H), 7.19–7.21 (m, 3H), 7.32–7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −2.1, 9.7, 14.1, 28.0, 36.4, 47.2, 61.0, 69.0, 76.7, 128.0, 128.2, 128.3, 134.4, 139.9, 140.8, 162.7.

4.2.23. 5-(*tert*-Butyl)-2-phenyl-*N*-(*p*-nosyl)-3-pyrroline-3-ethylcarboxylate (3x). IR (film) ν_{max} 2966, 1719, 1532, 1350, 1170, 1108, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 9H), 1.10 (t, $J=6.6$ Hz, 3H), 4.08–4.14 (m, 2H), 4.45 (br s, 1H), 5.98 (br s, 1H), 6.74–6.76 (m, 1H), 7.29–7.32 (m, 3H), 7.41–7.43 (m, 2H), 7.94 (d, $J=8.9$ Hz, 2H), 8.28 (d, $J=8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 27.9, 36.2, 61.2, 68.9, 78.3, 124.2, 128.1, 128.2, 128.3, 129.1, 134.2, 138.9, 140.4, 143.5, 150.2, 162.3; HRMS (ICR-MALDI) calcd for $C_{23}H_{26}N_2O_6SNa$ [$(M+Na)^+$]: 481.1404, found: 481.1406.

4.2.24. 5-(*tert*-Butyl)-2-phenyl-1*H*-pyrrole-3-ethylcarboxylate (9). IR (film) ν_{max} 3340, 2961, 1709, 1251, 1141, 1096, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, $J=7.1$ Hz, 3H), 1.38 (s, 9H), 4.25 (q, $J=7.1$ Hz, 2H), 6.49 (d, $J=3.1$ Hz, 1H), 7.38–7.46 (m, 3H), 7.62–7.64 (m, 2H), 8.23 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

14.2, 31.2, 36.3, 59.4, 106.0, 111.5, 127.2, 128.1, 128.2, 128.8, 141.6, 143.2, 165.0.

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References and notes

1. Bird, C. W.; Cheeseman, G. W. H. In Katritzky, A. R., Rees, C. W., Eds.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1984; Vol. 4, p 89.
2. For recent reviews of pyrrole, pyrroline, and pyrrolidine containing natural products see: (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (b) Mauger, A. B. *J. Nat. Prod.* **1996**, *59*, 1205. (c) Haslam, E. *Shikimic Acid Metabolism and Metabolites*; Wiley: New York, 1993.
3. Examples of 3-pyrrolines in the synthesis of natural products or as analgous of pharmaceutically relevant compounds (a) Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6609. (b) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621. (c) Burley, I.; Hewson, A. T. *Tetrahedron Lett.* **1994**, *35*, 7099.
4. Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174.
5. (a) Padwa, A. In Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: New York, 1991; Vol. 4, p 1069. (b) Wade, P. A. In Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: New York, 1991; Vol. 4, p 1111. (c) Padwa, A.; Schoffstall, A. M. In Greenwich, C. T., Ed.; Advances in Cycloaddition; JAI, 1990; Vol. 2, p 1. (d) Padwa, A., Ed.; 1,3-Dipolar Cycloaddition Chemistry; Interscience: Wiley, 1984; Vol. I–II. (e) Padwa, A. In Taylor, E. C., Weissberger, A., Eds.; 1,3-Dipolar Cycloaddition Chemistry; Wiley: New York, 1984; Vol. 2, p 277. (f) Grashey, R.; Padwa, A. In Taylor, E. C., Weissberger, A., Eds.; 1,3-Dipolar Cycloaddition Chemistry; Wiley: New York, 1984; Vol. 1, p 733. (g) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (h) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (i) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (j) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1.
6. (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031.
7. Xu, Z.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549.
8. (a) Lang, R. W.; Hansen, H.-J. *Org. Synth.* **1984**, *62*, 202. (b) Scholz, D.; Weber-Roth, S.; Macoratti, E.; Francotte, E. *Synth. Commun.* **1999**, *29*, 1143.
9. Crystallographic data (excluding structure factors) for **3b** has been deposited with the Cambridge Crystallographic Data Centre as supplementary numbers 255162. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.
11. Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *27*, 2099.
12. Zhu, X.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716.
13. 2-Trimethylsilylethanesulfonamide ($SESNH_2$) is not commercially available and was made following the procedures in Ref. 11.

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Palladium-catalyzed sequential alkylation–alkenylation reactions: application towards the synthesis of polyfunctionalized fused aromatic rings

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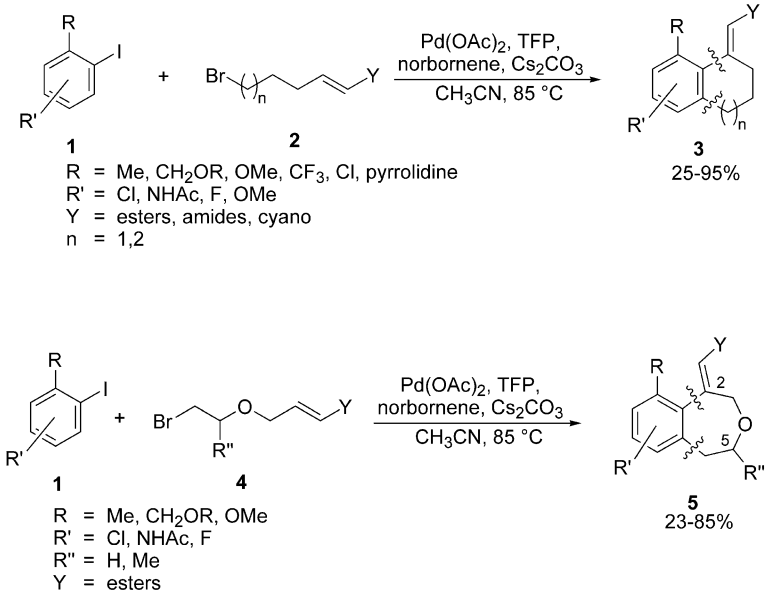
Abstract—The synthesis of polyfunctionalized fused aromatic carbo- and heterocycles from aryl iodides and bromoenoates via a tandem palladium-catalyzed aromatic substitution intramolecular Heck sequence is reported. Using $Pd(OAc)_2$ and tri-2-furylphosphine (TFP) in the presence of norbornene and Cs_2CO_3 in CH_3CN at 85 °C gave a variety of functionalized bi- and tricyclic fused aromatic rings in good yield.

1. Introduction

Carbocyclization is an important and valuable method for the synthesis of carbocyclic and heterocyclic compounds.[1] Over the past few years, palladium has emerged as one of the most reliable and versatile transition metals for the synthesis of fused aromatic carbocycles and heterocycles. In particular, the intramolecular Heck reaction has gained widespread acceptance due to its mild reaction conditions and functional group tolerance.[2]



Scheme 1. Synthesis of fused aromatic carbocycles and 2,5-disubstituted-4-benzoxepines.

Keywords: Palladium; Catalysis; Intramolecular Heck reaction; Norbornene; *ortho* Functionalization; Fused aromatic rings; Catellani reaction.
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Recently, we reported the synthesis of fused aromatic carbocycles from aryl iodides and difunctional acceptors[3] using modified Catellani[4] conditions. A variety of functional groups on the aryl moiety (**1**) were tolerated (Scheme 1)[3] and numerous six and seven-membered polyfunctionalized carbocycles (**3**) were synthesized using a variety of Heck acceptors in the difunctional acceptor **2**. This methodology was also extended towards the synthesis of 2-substituted-4-benzoxepines and 2,5-disubstituted-4-benzoxepines (**5**) (Scheme 1).[5]

Although our previously reported methodology examined the effect of substitution on the aromatic moiety, the effect of substituents on the carbocyclic ring formed in this tandem process was not evaluated. The resulting substituted fused aromatic carbocyclic core is widely found in natural products exhibiting notable biological and pharmaceutical properties.[6] Having a diverse range of substituents on the carbocyclic moiety provides the opportunity for subsequent modification, thereby accessing a wide range of medicinally important compounds from relatively simple and accessible starting materials. We now report a further extension of our methodology for the synthesis of more highly substituted fused aromatic six- and seven-membered carbocycles **7** (Fig. 1).

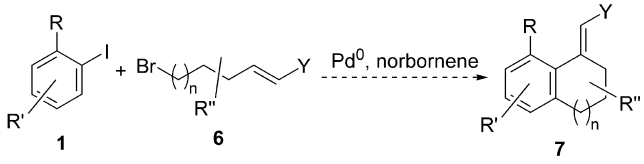


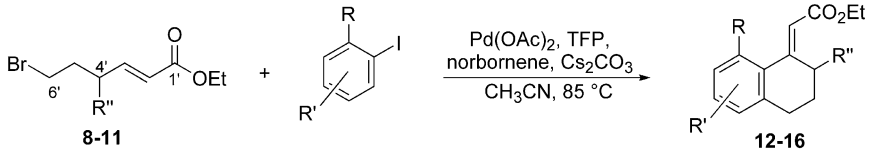
Figure 1.

2. Results and discussion

A number of functionalized bromoenoates (**6**) and aryl iodides were prepared and subjected to standard reaction conditions: $Pd(OAc)_2$ (10 mol%), TFP (20 mol%), norbornene (2 equiv), Cs_2CO_3 (2 equiv), CH_3CN, 85 °C.

We first examined the effect of substituents in the 4′ position of compounds **8–11** (Table 1). Using 2-iodotoluene and bromoenoate **8** (R″=Me), the desired product **12** was obtained in 81% yield (entry 1). While the 4′ hydroxyl derivative yielded decomposition products, protection of the 4′ hydroxyl group as a methoxymethyl (MOM) gave moderate to good yields for 2-iodotoluene and 4-fluoro-2-iodotoluene (entries 2, 3). Use of the tertiary protected methyl amine **10** gave **15** in 22% yield, while the secondary protected amine **11** provided the tricyclic lactam **16** in 45% yield. This result is interesting and insight into the observed product deserves further comment. The *trans* olefin

Table 1. Formation of six-membered carbocycles from 4′-substituted bromoenoates



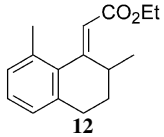
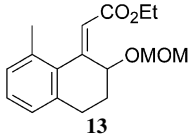
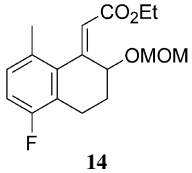
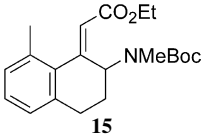
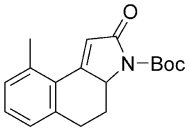
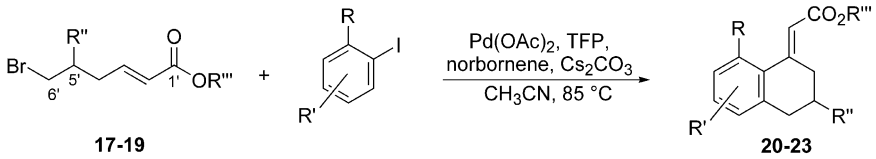
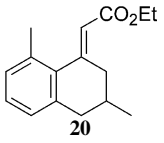
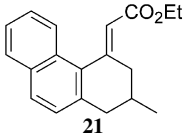
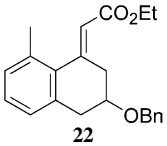
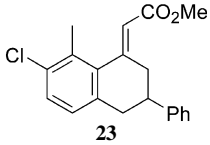
Entry	R″	Bromoenoate	Aryl iodide	Product	Isolated yield (%)
1	Me	**8**	2-Iodotoluene	 **12**	81
2	OMOM	**9**	2-Iodotoluene	 **13**	70
3	OMOM	**9**	4-Fluoro-2-iodotoluene	 **14**	40
4	NMeBoc	**10**	2-Iodotoluene	 **15**	22
5	NHBoc	**11**	2-Iodotoluene	 **16**	45

Table 2. Formation of six-membered carbocycles from 5′-substituted bromoenoates

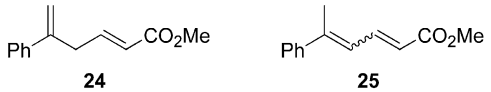


17-19 20-23

Entry	R″	Bromoenoate	Aryl iodide	Product	Isolated yield (%)
1	Me	**17**	2-Iodotoluene	 **20**	83
2	Me	**17**	1-Iodonaphthalene	 **21**	70
3	OBn	**18**	2-Iodotoluene	 **22**	58
4	Ph	**19**	2-Chloro-6-iodotoluene	 **23**	44

geometry of **11** prevents intramolecular attack of the nitrogen onto the carbonyl functionality, thus making the starting substrate unreactive toward lactamization. However, following the benzannulation catalytic cycle, the olefin geometry sets the ester functionality in a position that allows for lactamization to occur. Therefore, although this unexpected product was obtained in modest yield, this result is advantageous since three bonds and two additional rings were formed in a relatively simple one-pot process.

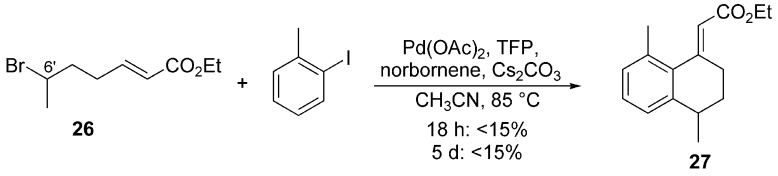
We next investigated the effect of substitution at the 5′ position of the bromoenoate (Table 2). For 2-iodotoluene and 1-iodonaphthalene, methyl substitution at the 5′ position gave the expected carbocycles **20** and **21** in 83 and 70% yields, respectively. Protection of the secondary alcohol using the larger benzyl protecting group afforded **22** in 58% yield, suggesting that steric effects play a role for substituents at the 5′ position. Reaction of **19** with 6-chloro-2-iodotoluene afforded the desired product **23** in 44% yield as well as 33% of elimination products **24** and **25**[7] as identified by ^{1}H NMR spectroscopy and MS (Fig. 2). While product **24** likely arises from the elimination of HBr promoted by Cs_2CO_3, elimination product **25** is presumably an isomerization product of **24**. We note that the low yield of products may be due to competing oxidative addition into the aryl chloride. However, we previously reported the reaction of 6-chloro-2-iodotoluene with bromoenoate **2** ($n=2$, Y = CO_2Et) gave the desired product in 86% yield,[3b] indicating that this process is not likely responsible for reducing the yields. Again, no benzannulation was observed when the unprotected alcohol was used, instead ethyl (2*E*,4*E*)-6-hydroxy-2,4-hexadienoate was isolated.[8]



24 25

Figure 2.

Under typical reaction conditions (for 18 h), use of the 6′ substituted bromoenoate **26** resulted in a very low yield (<15%) of cyclized product **27** (Scheme 2) as well as unreacted starting material. Attempts to increase conversion by increasing reaction time also failed. While disappointing, this result was not surprising since *ortho* insertion under these reaction conditions has been reported to be very slow for secondary alkyl halides.[4a,b]



26 27

Scheme 2. Formation of a six-membered carbocycle **27** from a 6′-substituted bromoenoate.

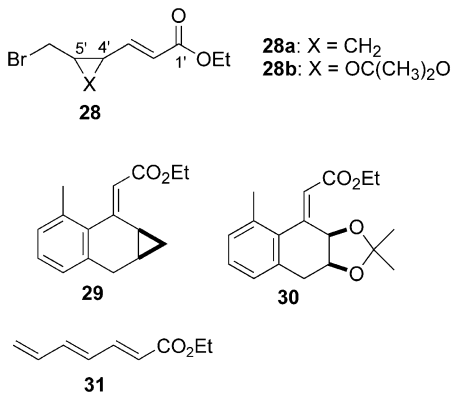


Figure 3. Tricyclic carbo- and heterocycles.

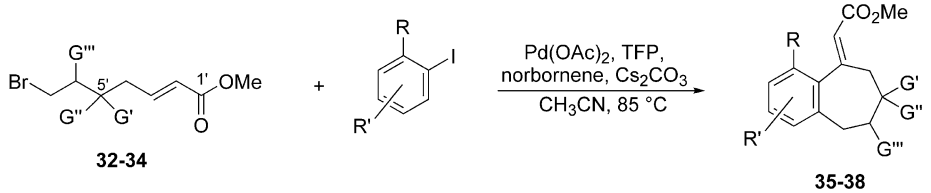
Successful cyclization reactions with substituents in the 4′ position and 5′ position led us to explore the potential of tethered substituents joining positions 4′ and 5′ with the objective of forming tricyclic products. Substrates **28** (**28a**: X=CH_2, **28b**: X=$OC(CH_3)_2O$) were subjected to the reaction conditions with different aryl iodides (Fig. 3). Unfortunately, low yields (<30%) of the cyclized products were obtained for all cases (Fig. 3).

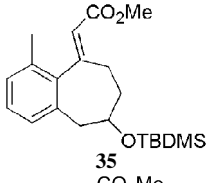
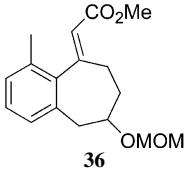
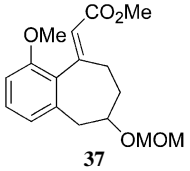
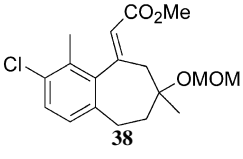
For X=CH_2 (**28a**), triene **31** was obtained in 25% yield in addition to the desired cyclized product **29**. The side-product could arise from insertion of Pd(0) into the carbon–bromine bond, followed by a cyclopropylcarbinyl–homoallyl rearrangement[9] and subsequent β-hydride elimination.

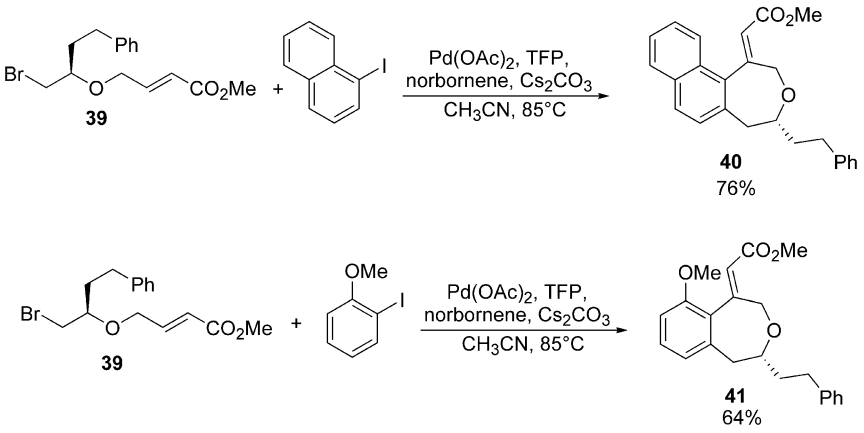
We next focused on the extension of reaction scope for substituted seven-membered rings (Table 3). A *tert*-butyldimethylsilylether (TBDMS) in the 6′ position (**32**) resulted in 54% yield of **35** when 2-iodotoluene was used. Use of the smaller MOM protected alcohol (**33**) provided **36** in a slightly higher yield of 61%, further supporting our steric arguments (vide supra). When **33** was reacted with 2-iodoanisole, a similar yield of 59% was obtained (**37**). Lastly, when bromoenoate **34** and 2-chloro-6-iodotoluene were subjected to the reaction conditions, carbocycle **38** was obtained in a low 33% yield.

Encouraged by the results obtained for the reactions of functionalized bromoenoates, we attempted additional benzannulation reactions using a substituted oxygenated bromoenoate. We reported that when R″=CH_3 (**4**) (Scheme 1), the reaction with 1-iodonaphthalene afforded the benzoxepine product in 72% yield.[5] We therefore synthesized the substituted oxygenated bromoenoate **39** and subjected it to our reaction conditions in the presence of different aryl iodides (Scheme 3). In general, good yields of the expected benzoxepines **40** (76% yield) and **41** (64% yield) were obtained.

Table 3. Formation of seven-membered carbocycles



Entry	G′, G″, G″	Bromoenoate	Aryl iodide	Product	Isolated yield (%)
1	H, H, OTBDMS	**32**	2-Iodotoluene	 **35**	54
2	H, H, OMOM	**33**	2-Iodotoluene	 **36**	61
3	H, H, OMOM	**33**	2-Iodoanisole	 **37**	59
4	Me, H, OMOM	**34**	2-Chloro-6-iodotoluene	 **38**	33



Scheme 3. Formation of 2,5-disubstituted-4-benzoxepines.

3. Conclusions

The palladium-catalyzed synthesis of highly substituted six- and seven-membered fused aromatic carbocycles, as well as 2,5-disubstituted-4-benzoxepines from aryl iodides and substituted oxygenated bromoenoates was described. A variety of functional groups along the chain on the bromoenoate (alkyl, OR, NR_2) are tolerated, affording bi- and tricyclic fused aromatic rings under relatively mild reaction conditions in moderate to good yields. Further manipulation of the functionalized compounds towards the synthesis of more complex as well as bioactive molecules is in progress.

4. Experimental

4.1. General

The following includes general experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for new compounds. Melting points were recorded using a Fisher–Johns melting point apparatus and are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were obtained using either Varian Gemini 300 MHz or Varian Unity 400 MHz spectrometers. ^{1}H spectra were referenced to tetramethylsilane (TMS, 0 ppm) and ^{13}C spectra were referenced to solvent carbons (77.23 ppm for $CDCl_3$). No special notation is used for equivalent carbons. IR spectra were obtained using a Nicolet DX FT IR spectrometer as thin films on NaCl plates. Optical rotations were obtained using a Perkin–Elmer 243 B polarimeter. High-resolution mass spectra were obtained using a VG 70-250S (double focusing) mass spectrometer at 70 eV unless otherwise noted.

Diethyl ether and tetrahydrofuran (THF) were distilled under nitrogen from Na/benzophenone immediately prior to use. Dichloromethane and acetonitrile were distilled under nitrogen from CaH_2 immediately prior to use. Neutral silica (Silicycle, Quebec, Canada) for flash chromatography was used as received. All reagents, metal catalysts and ligands were purchased from Sigma-Aldrich or Strem-Chemical Company and used as received unless otherwise noted. Reactions were performed under an atmosphere of nitrogen.

4.2. General procedure for the cyclization reaction

A round-bottom flask equipped with a condenser was charged with Cs_2CO_3 (0.400 mmol, 2 equiv), $Pd(OAc)_2$ (0.020 mmol, 10 mol%), tri-2-furylphosphine (0.040 mmol, 20 mol%), and norbornene (0.400 mmol, 2 equiv). A solution of bromoenoate (0.400 mmol, 2 equiv) and aryl iodide (0.200 mmol, 1 equiv) in CH_3CN (2 mL) was added. The resulting mixture was heated at 85 °C for 19 h, cooled and then quenched with saturated aqueous NH_4Cl (3 mL). The aqueous layer was extracted with Et_2O (3×) and the combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and filtered. Removal of the solvent gave a crude product that was purified by flash chromatography.

4.2.1. Ethyl (2*E*)-(2,8-dimethyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate (12). Following the general procedure for the cyclization reaction using 2-iodotoluene and **8**, **12** was isolated as a pale yellow oil (37.1 mg, 81%) by flash chromatography using 5% EtOAc/hexanes as eluant. R_f=0.68 on silica gel (10% EtOAc/hexanes). IR (neat) ν= 2952, 1714, 1621, 1467, 1371, 1263, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–6.92 (m, 3H), 5.80 (s, 1H), 4.20 (q, 2H, J=7.1 Hz), 4.08 (m, 1H), 2.64–2.36 (m, 2H), 2.43 (s, 3H), 2.22–2.12 (m, 1H), 1.30 (t, 3H, J=7.1 Hz), 1.10 (d, 3H, J=6.8 Hz), 1.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 160.2, 142.1, 136.1, 135.1, 129.3, 127.8, 124.4, 117.8, 59.8, 32.2, 30.1, 29.4, 21.5, 20.8, 14.4; HRMS calcd for $C_{16}H_{20}O_2$ $[M]^+$ 244.1463, found 244.1463.

4.2.2. Ethyl (2*Z*)-[2-(methoxymethoxy)-8-methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene]acetate (13). Following the general procedure for the cyclization reaction using 2-iodotoluene and **9**, **13** was isolated as a colorless oil (41.0 mg, 70%) by flash chromatography using 10% EtOAc/hexanes as eluant. R_f=0.40 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2931, 1714, 1632, 1465, 1374, 1268, 1158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–6.94 (m, 3H), 6.04 (t, 1H, J=3.8 Hz), 5.93 (s, 1H), 4.66 (dd, 2H, J= 15.0, 6.6 Hz), 4.22 (q, 2H, J=7.1 Hz), 3.16 (s, 3H), 3.06–2.95 (m, 1H), 2.80–2.68 (m, 1H), 2.47 (s, 3H), 2.22–2.06 (m, 2H), 1.31 (t, 3H, J=7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.2, 154.1, 139.5, 135.8, 134.0, 129.4, 128.1, 125.9, 119.3, 95.4, 69.3, 60.2, 55.4, 29.3, 25.4, 21.2, 14.3;

HRMS calcd for $C_{17}H_{22}O_4$ $[M]^+$ 290.1516, found 290.1518.

4.2.3. Ethyl (2*Z*)-[5-fluoro-2-(methoxymethoxy)-8-methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene]acetate (14). Following the general procedure for the cyclization reaction using 4-fluoro-2-iodotoluene and **9**, **14** was isolated as a colorless oil (24.5 mg, 40%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=0.30$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2935$, 1714, 1634, 1476, 1372, 1249, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12–6.84 (m, 2H), 6.04 (t, 1H, $J=3.8$ Hz), 5.93 (s, 1H), 4.64 (dd, 2H, $J=10.7$, 6.6 Hz), 4.23 (q, 2H, $J=7.1$ Hz), 3.13 (s, 3H), 3.06–2.60 (m, 2H), 2.43 (s, 3H), 2.36–1.95 (m, 2H), 1.32 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 14.3, 18.1, 18.2, 21.0, 28.5, 55.5, 60.4, 68.9, 95.7, 114.3, 114.6, 119.6, 126.0, 126.3, 130.0, 130.1, 130.8, 131.3, 135.1, 135.2, 150.6, 150.7, 153.7, 153.8, 156.8, 160.0, 166.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.88 (s, 1F); HRMS calcd for $C_{17}H_{21}FO_4$ $[M]^+$ 308.1421, found 308.1424.

4.2.4. Ethyl (2*Z*)-[2-[(*tert*-butoxycarbonyl)(methyl)-amino]-8-methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene]-acetate (15). Following the general procedure for the cyclization reaction using 2-iodotoluene (0.300 mmol scale) and **10**, **15** was isolated as a colorless oil (25.0 mg, 22%) by flash chromatography using 50% EtOAc/hexanes as eluant. $R_f=0.67$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=$ 2974, 1700, 1457, 1366 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–6.87 (m, 3H), 6.03 (s, 1H), 5.84 (brs, 1H), 4.20 (q, 2H, $J=7.1$ Hz), 2.66–2.56 (m, 2H), 2.55 (s, 3H), 2.48 (s, 3H), 2.44–2.32 (m, 2H), 1.50 (s, 9H), 1.29 (t, 3H, $J=$ 7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 165.3, 158.9, 149.7, 142.0, 136.4, 134.9, 130.1, 128.2, 124.8, 123.6, 79.6, 77.4, 60.4, 53.4, 30.2, 28.6, 26.7, 21.2, 14.5; HRMS calcd for $C_{17}H_{22}O_4$ $[M]^+$ 359.2101, found 359.2096.

4.2.5. *tert*-Butyl 9-methyl-2-oxo-2,3a,4,5-tetrahydro-3*H*-benzo[*e*]indole-3-carboxylate (16). Following the general procedure for the cyclization reaction using 2-iodotoluene and **11** (0.300 mmol scale), **16** was isolated as a colorless oil (41.0 mg, 45%) by flash chromatography using 25% EtOAc/hexanes as eluant. $R_f=0.36$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=2977$, 1770, 1698, 1608 1318 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.04 (m, 3H), 6.21 (s, 1H), 4.62–4.54 (dd, 1H, $J=11.5$, 3.0 Hz), 3.14–3.05 (m, 2H), 2.94–2.82 (m, 1H), 2.48 (s, 3H), 1.83–1.62 (m, 1H), 1.59 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 169.8, 158.2, 149.9, 138.6, 138.5, 130.2, 129.8, 127.7, 127.2, 120.1, 83.1, 62.0, 30.2, 28.9, 28.4, 22.6; HRMS calcd for $C_{18}H_{21}NO_3$ $[M]^+$ 299.1523, found 299.1521.

4.2.6. Ethyl (2*E*)-(3,8-dimethyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate (20). Following the general procedure for the cyclization reaction using 2-iodotoluene and **17**, **20** was isolated as a colorless oil (38.8 mg, 83%) by flash chromatography using 5% EtOAc/hexanes as eluant. $R_f=$ 0.59 on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2951$, 1715, 1615, 1434, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–6.94 (m, 3H), 5.94 (t, 3H, $J=1.8$ Hz), 3.75 (s, 3H), 3.32 (dd, 1H, $J=16.7$, 6.2 Hz), 2.80–2.70 (m, 2H), 2.48 (s, 3H), 2.34 (dd, 1H, $J=14.9$, 10.7 Hz), 1.98–1.78 (m, 1H), 1.11 (d, 3H, $J=6.6$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.2, 155.4, 141.2, 136.0, 135.0, 129.8, 128.2, 125.8, 117.9, 51.4, 39.3, 37.5, 29.7, 22.3, 22.2; HRMS calcd for $C_{15}H_{18}O_2$ $[M]^+$ 230.1316, found 230.1306.

4.2.7. Ethyl (2*E*)-(2-methyl-2,3-dihydrophenanthren-4(1*H*)-ylidene)acetate (21). Following the general procedure for the cyclization reaction using 1-iodonaphthalene and **17**, **21** was isolated as a colorless oil (37.1 mg, 70%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=0.61$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=$ 2950, 1714, 1625, 1433 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, 1H, $J=8.4$ Hz), 7.81 (d, 1H, $J=7.9$ Hz), 7.80 (d, 1H, $J=8.2$ Hz), 7.71 (d, 1H, $J=8.2$ Hz), 7.46 (m, 2H), 7.22 (d, 1H, $J=8.2$ Hz), 6.27 (s, 1H), 3.77 (s, 3H), 3.53 (dd, 1H, $J=16.3$, 5.7 Hz), 2.91 (dd, 1H, $J=15.7$, 4.2 Hz), 2.83 (dd, 1H, $J=16.1$, 10.3 Hz), 2.51 (dd, 1H, $J=15.7$, 10.3 Hz), 2.20–1.95 (m, 1H), 1.16 (d, 3H, $J=6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 154.5, 138.6, 133.3, 132.8, 130.1, 128.9, 128.5, 126.7, 126.6, 125.2, 125.1, 118.7, 51.1, 39.1, 37.1, 29.8, 21.7; HRMS calcd for $C_{17}H_{22}O_4$ $[M-OC_2H_5]^+$ 266.1306, found 266.1307.

4.2.8. Ethyl (2*E*)-[3-(benzyloxy)-8-methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene]acetate (22). Following the general procedure for the cyclization reaction using 2-iodotoluene and **18**, **22** was isolated as a colorless oil (37.0 mg, 58%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=0.53$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2947$, 1711, 1620, 1433, 1361 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–6.96 (m, 8H), 5.97 (s, 1H), 4.59 (q, 2H, $J=11.9$ Hz), 3.87 (quintet, 1H, $J=$ 5.8 Hz), 3.74 (s, 1H), 3.55 (dd, 1H, $J=16.0$, 5.8 Hz), 3.25 (dd, 1H, $J=16.1$, 6.7 Hz), 2.99 (dd, 1H, $J=15.2$, 4.5 Hz), 2.84 (dd, 1H, $J=15.1$, 7.5 Hz), 2.46 (s, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.1, 152.7, 138.6, 137.5, 136.1, 134.8, 130.1, 128.5, 128.4, 127.7, 127.6, 126.6, 126.5, 119.2, 73.3, 70.4, 51.6, 36.9, 35.2, 22.2; HRMS calcd for $C_{21}H_{22}O_3$ $[M]^+$ 322.1562, found 322.1568.

4.2.9. Methyl (2*E*)-(7-chloro-8-methyl-3-phenyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate (23). Following the general procedure for the cyclization reaction using 2-chloro-6-iodotoluene and **19**, **23** was isolated as a brown solid (28.5 mg, 44%) along with a mixture of elimination products **24** and **25** (26.5 mg, 33%,) by flash chromatography using 3→5% Et_2O/hexane as eluant. IR (neat) $\nu=$ 3034, 2953, 1714, 1619, 1458, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.19 (m, 7H), 6.95 (d, 1H, $J=$ 8.1 Hz), 5.93 (t, 1H, $J=1.8$ Hz), 3.73 (s, 3H), 3.48 (ddt, 1H, $J=17.1$, 6.9, 1.8 Hz), 3.32 (ddd, 1H, $J=17.1$, 10.5, 1.8 Hz), 3.03–2.75 (m, 3H), 2.53 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.7, 153.8, 144.9, 139.2, 138.1, 134.2, 132.9, 128.9, 128.6, 127.0, 126.5, 126.2, 119.6, 51.2, 40.3, 37.5, 36.7, 19.0; HRMS calcd for $C_{20}H_{19}O_2Cl$ $[M]^+$ 326.1074, found 326.1064.

4.2.10. Ethyl (2*E*)-(4,8-dimethyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate (27). Following the general procedure for the cyclization reaction using 2-iodotoluene and **26**, **27** was isolated as a colorless oil (5.51 mg, 12%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=$ 0.63 on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2951$,

1715, 1618, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.00 (m, 3H), 5.92 (t, 1H, $J=1.7$ Hz), 4.21 (q, 2H, $J=7.1$ Hz), 3.33–3.22 (m, 1H), 3.14–3.04 (m, 1H), 2.76–2.68 (m, 1H), 2.47 (s, 3H), 2.10–1.82 (m, 2H), 1.31 (t, 3H, $J=7.1$ Hz), 1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 19.7, 21.8, 27.0, 29.5, 29.9, 33.9, 60.0, 118.4, 123.2, 128.2, 129.7, 134.9, 136.3, 146.2, 155.1, 167.1; HRMS calcd for $C_{16}H_{20}O_2$ $[M]^+$ 244.1468, found 244.1463.

4.2.11. Ethyl (2*E*)-(3-methyl-1,1a,7,7a-tetrahydro-2*H*-cyclopropa[*b*]naphthalen-2-ylidene)acetate (29). Following the general procedure for the cyclization reaction using 2-iodotoluene and **28a**, **29** was isolated as a colorless oil (12.5 mg, 26%) along with hepta-2,4,6-trienoic acid ethyl ester (**31**)[10] (7.61 mg, 25%) by flash chromatography using 10% EtOAc/hexanes as eluant and further purification by flash chromatography using 80% CH_2Cl_2/hexanes. $R_f=0.73$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2979$, 1704, 1613, 1466, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16–6.87 (m, 3H), 5.89 (s, 1H), 4.22 (q, 2H, $J=7.1$ Hz), 3.75 (ddd, 1H, $J=8.2$, 8.2, 4.4 Hz), 3.16–2.94 (m, 2H), 2.43 (s, 3H), 1.80–1.66 (m, 1H), 1.32 (t, 3H, $J=7.1$ Hz), 0.92 (ddd, 1H, $J=8.0$, 8.0, 5.0 Hz), 0.43 (q, 1H, 4.9 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.9, 157.9, 136.7, 135.2, 134.2, 130.3, 128.5, 126.5, 117.2, 59.9, 30.7, 21.5, 17.3, 14.7, 14.4, 11.2; HRMS calcd for $C_{16}H_{18}O_2$ $[M]^+$ 242.1309, found 242.1307.

4.2.12. Ethyl (2*Z*)-(2,2,5-trimethyl-9,9a-dihydronaphtho[2,3-*d*][1,3]dioxol-4(3a*H*)-ylidene)acetate (30). Following the general procedure for the cyclization reaction using 2-iodotoluene and **28b**, **30** was isolated as a colorless oil (14.0 mg, 23%) by flash chromatography using 5:35:60 EtOAc/CH_2Cl_2/hexanes as eluant. $R_f=0.30$ on silica gel (5:35:60 EtOAc/CH_2Cl_2:hexanes). IR (neat) $\nu=2985$, 1715, 1646, 1372 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16–6.87 (m, 3H), 6.34 (d, 1H, $J=7.5$ Hz), 5.99 (s, 1H), 4.80 (dt, 1H, $J=7.3$, 2.6 Hz), 2.94 (dd, 1H, $J=15.4$, 2.3 Hz), 2.59 (dd, 1H, $J=15.3$, 2.9 Hz), 2.43 (s, 3H), 1.35 (s, 3H), 1.33 (t, 3H, $J=7.1$ Hz), 0.93 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.0, 150.3, 136.4, 135.6, 134.8, 129.6, 128.5, 126.5, 122.1, 109.6, 73.6, 72.4, 60.7, 34.0, 26.2, 25.2, 20.2, 14.4; HRMS calcd for $C_{18}H_{22}O_4$ $[M-CH_3]^+$ 287.1287, found 287.1283.

4.2.13. Methyl (2*E*)-(8-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene)acetate (35). Following the general procedure for the cyclization reaction using 2-iodotoluene (0.300 mmol scale) and **32**, **35** was isolated as a colorless oil (58.0 mg, 54%) by flash chromatography using 5% EtOAc/hexanes as eluant. $R_f=0.75$ on silica gel (10% EtOAc/hexanes). IR (neat) $\delta=$ 2952, 1727, 1659, 1435, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.15 (s, 1H), 7.05 (brs, 1H), 5.89 (brs, 1H), 3.82 (brs, 3H), 3.76 (brs, 1H), 3.10–2.88 (m, 1H), 2.83–2.65 (m, 2H), 2.32 (s, 3H), 2.20–1.87 (m, 3H), 0.97 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$) ν 166.9, 166.8, 161.9, 150.0, 143.5, 136.0, 133.3, 129.0, 127.7, 127.3, 120.0, 118.6, 71.7, 71.4, 71.2, 51.3, 45.3, 39.1, 37.6, 36.4, 35.0, 29.9, 29.1, 26.03, 25.98, 20.4, 18.3, 18.2, 0.2, −4.2, −4.3, −4.4, −4.5; HRMS calcd for $C_{21}H_{32}O_3Si$ $[M]^+$ 360.2125, found 360.2121.

4.2.14. Methyl (2*E*)-[8-(methoxymethoxy)-4-methyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene]acetate (36). Following the general procedure for the cyclization reaction using 2-iodotoluene (0.300 mmol scale) and **33**, **36** was isolated as a colorless oil (53.0 mg, 61%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=$ 0.31 on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2947$, 1715, 1639, 1435, 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (brs, 2H), 6.99 (brs, 1H), 5.74 (brs, 1H), 4.70 (brs, 2H), 4.00 (brs, 1H), 3.75 (brs, 3H), 3.37 (brs, 3H), 2.87 (d, 1H, $J=5.1$ Hz), 2.62–1.70 (m, 4H), 2.27 (brs, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.7, 161.9, 161.5, 142.7, 141.6, 135.5, 134.8, 133.4, 129.2, 127.6, 127.1, 118.8, 95.0, 75.5, 72.5, 55.5, 51.3, 41.5, 38.7, 34.6, 32.4, 28.4, 27.1, 20.4; HRMS calcd for $C_{16}H_{18}O_2$ $[M]^+$ 290.1526, found 290.1518.

4.2.15. Methyl (2*E*)-[4-methoxy-8-(methoxymethoxy)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene]acetate (37). Following the general procedure for the cyclization reaction using 2-iodoanisole (0.300 mmol scale) and **33**, **37** was isolated as a colorless oil (54.0 mg, 59%) by flash chromatography using 25% EtOAc/hexanes as eluant. $R_f=$ 0.18 on silica gel (75% CH_2Cl_2/hexanes). IR (neat) $\nu=$ 2947, 1714, 1643, 1578, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, 1H, $J=8.1$ Hz), 6.83 (d, 1H, $J=8.2$ Hz), 6.78 (d, 1H, $J=7.3$ Hz), 5.88 (s, 1H), 4.68 (q, 2H, $J=6.8$ Hz), 3.90–3.84 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.38 (s, 3H), 3.25 (brs, 1H), 2.85 (d, 2H, $J=6.2$ Hz), 2.70 (brs, 1H), 2.05–1.96 (m, 1H), 1.85–1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 157.1, 155.4, 137.1, 131.0, 128.8, 122.4, 120.0, 110.2, 95.0, 74.1, 56.0, 55.5, 51.2, 40.0, 33.0, 27.9; HRMS calcd for $C_{17}H_{22}O_5$ $[M]^+$ 306.1467, found 306.1467.

4.2.16. Methyl (2*E*)-[3-chloro-7-(methoxymethoxy)-4,7-dimethyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene]acetate (38). Following the general procedure for the cyclization reaction using 2-chloro-6-iodotoluene and **34**, **38** was isolated as a colorless oil (35.0 mg, 33%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=$ 0.32 on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2936$, 1721, 1640, 1445, 1368 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (brd, 1H, $J=8.0$ Hz), 6.90 (d, 1H, $J=8.0$ Hz), 5.75 (s, 1H), 4.88 (brs, 1H), 4.79 (brs, 1H), 4.55 (brs, 1H), 4.21 (q, 2H, $J=7.0$ Hz), 3.36 (brs, 3H), 3.11 (brt, 1H, $J=$ 13.1 Hz), 2.57 (brs, 1H), 2.29 (s, 3H), 2.20–2.03 (m, 1H), 2.00–1.71 (m, 2H), 1.43 (brs, 3H), 1.32 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.7, 166.3, 154.9, 153.3, 145.3, 139.4, 133.4, 133.1, 132.0, 128.2, 128.2, 127.2, 127.0, 123.2, 91.2, 90.8, 80.1, 60.3, 60.1, 55.4, 41.1, 39.3, 30.6, 29.3, 28.5, 22.4, 17.8, 14.5; HRMS calcd for $C_{19}H_{25}ClO_4$ $[M]^+$ 352.1448, found 352.1441.

4.2.17. Methyl (2*Z*)-[(4*R*)-4-(2-phenylethyl)-4,5-dihydronaphtho[1,2-*d*]oxepin-1(2*H*)-ylidene]acetate (40). Following the general procedure for the cyclization reaction using 1-iodonaphthalene and **39**, **40** was isolated as slightly yellow oil (56.6 mg, 76%) by flash chromatography using 10% Et_2O/hexane as eluant. $[\alpha]_D^{25}$ −45.2 (*c* 1.0, $CHCl_3$); IR (neat) $\nu=3068$, 3027, 2949, 2858, 1711, 1215, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, 1H, $J=7.8$ Hz), 7.80 (m, 2H), 7.45 (m, 2H), 7.30–7.12 (m, 6H), 5.96 (t, 1H,

J=2.7 Hz), 5.07 (m, 2H), 3.79 (s, 3H), 3.37 (dd, 1H, J=14.1, 7.5 Hz), 2.66 (m, 3H), 1.67 (m, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 162.5, 141.8, 134.8, 133.2, 132.3, 130.7, 128.5, 128.3, 127.3, 126.6, 125.8, 125.1, 125.0, 118.8, 75.0, 69.2, 51.4, 37.9, 36.3, 32.1; HRMS calcd for $C_{25}H_{24}O_3$ $[M]^+$ 372.1725, found 372.1736.

4.2.18. Methyl (2*Z*)-[(4*R*)-9-methoxy-4-(2-phenylethyl)-4,5-dihydro-3-benzoxepin-1(2*H*)-ylidene]acetate (41). Following the general procedure for the cyclization reaction using 2-iodoanisole and **39**, **41** was isolated as a colorless oil (45.0 mg, 64%) by flash chromatography using 10% Et_2O/hexanes as eluant and further purification by flash chromatography using 0→10% acetone/CH_2Cl_2. $[\alpha]_D^{25}$ −76.9 (c 1.0, $CHCl_3$); IR (neat) ν=3027, 2965, 2838, 1710, 1269, 1172, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.14 (m, 6H), 6.88 (d, 1H, J=8.7 Hz), 6.70 (d, 1H, J=8.7 Hz), 6.00 (t, 1H, J=2.4 Hz), 5.08 (dd, 1H, J=18.9, 2.4 Hz), 4.82 (dd, 1H, J=18.9, 2.4 Hz), 3.78 (s, 3H), 3.75 (s, 3H), 3.01 (dd, 1H, J=14.1, 6.3 Hz), 2.71 (m, 2H), 2.43 (dd, 1H, J=14.1, 3.0 Hz), 1.89 (m, 2H), 1.62 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.8, 158.7, 156.2, 141.9, 137.4, 129.2, 128.5, 128.3, 126.7, 125.8, 121.3, 118.4, 110.2, 75.4, 67.6, 55.6, 51.2, 37.9, 35.4, 32.1; HRMS calcd for $C_{22}H_{24}O_4$ $[M]^+$ 352.1675, found 352.1684.

4.2.19. Ethyl (2*E*)-6-bromo-4-methylhex-2-enoate (8). A solution of carbon tetrabromide (289 mg, 0.870 mmol, 1.5 equiv) in CH_2Cl_2 (1 mL) was added dropwise to a 0 °C solution of triphenylphosphine (228 mg, 0.870 mmol, 1.5 equiv) and ethyl (*E*)-6-hydroxy-4-methyl-hex-2-enoate[11] (100 mg, 0.581 mmol, 1 equiv) in CH_2Cl_2 (5 mL). The reaction was stirred at 0 °C for 1 h, diluted with 10% EtOAc/hexanes (20 mL) and filtered through celite. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (118 mg, 87%) as a pale yellow oil. R_f=0.78 on silica gel (25% EtOAc/hexanes). IR (neat) ν=1186, 1272, 1458, 1652, 1715, 2968 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, 3H, J=6.8 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.90 (m, 1H), 2.57 (m, 1H), 3.35 (ABX$_2$, 2H, $\Delta\nu_{AB}$=29.3 Hz, J_{AB}=3.7 Hz, J_{AX}=6.4 Hz, J_{BX}=6.4 Hz), 4.17 (q, 2H, J=7.0 Hz), 5.84 (d, 1H, J=15.7 Hz), 6.89 (dd, 1H, J=15.6, 8.2 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.8, 152.2, 121.3, 60.5, 38.7, 35.2, 31.3, 19.3, 14.4; HRMS calcd for $C_9H_{14}BrO_2$ $[M-H]^+$ 234.0253, found 234.0255.

4.2.20. 5-{[*tert*-Butyl(dimethyl)silyl]oxy}pent-1-en-3-ol (42). A −78 °C solution of oxalyl chloride (3.16 mL, 36.2 mmol, 1.15 equiv) in CH_2Cl_2 (100 mL) was added dropwise to a solution of dimethyl sulfoxide (5.14 mL, 72.5 mmol, 2.3 equiv) in CH_2Cl_2 (30 mL). The mixture was stirred at −78 °C for 15 min. A solution of 3-(*tert*-butyldimethylsilanyloxy)-propan-1-ol[12] (6.00 g, 31.5 mmol, 1 equiv) in CH_2Cl_2 (100 mL) was added dropwise and the reaction mixture was stirred for 1 h −78 °C. Triethylamine (12.3 mL, 88.3 mmol, 2.8 equiv) was added dropwise and the reaction mixture was stirred for 15 min at −78 °C then warmed to rt over 2 h. The reaction was quenched with water (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with 1% aqueous HCl, water, 5% aqueous $NaHCO_3$ and water. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude aldehyde was dissolved in THF (50 mL) and added dropwise to a −78 °C solution of vinylmagnesium bromide (47.2 mL, 47.2 mmol, 1.0 M in THF, 1.5 equiv). The mixture was stirred for 2 h at −78 °C then warmed to rt. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the aqueous layer was washed with EtOAc (3×). The combined organic extracts were washed with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (4.20 g, 60%) as a pale yellow oil. R_f=0.46 on silica gel (10% EtOAc/hexanes). IR (neat) ν=3424, 2955, 1472, 1256, 1099 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94–5.78 (m, 1H), 5.26 (dt, 1H, J=17.3, 1.5 Hz), 5.08 (dt, 1H, J=10.4, 1.5 Hz), 4.33 (brs, 1H), 3.94–3.72 (m, 2H), 3.34 (d, 1H, J=3.6 Hz), 1.84–1.62 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 140.7, 114.1, 72.4, 68.9, 38.3, 25.9, 18.1, −5.5; HRMS calcd for $C_{11}H_{24}O_2Si$ $[M-C(CH_3)_3]^+$ 159.0836, found 159.0841.

4.2.21. Ethyl (2*E*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-4-hydroxyhex-2-enoate (43). To a mixture of **42** (1.00 g, 4.62 mmol, 1 equiv) and methyl acrylate (12.5 mL, 116 mmol, 25 equiv) in CH_2Cl_2 (20 mL) was added Grubbs' 2nd generation catalyst (200 mg, 0.231 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude oil was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (1.18 g, 89%) as a pale yellow oil. R_f=0.67 on silica gel (10% EtOAc/hexanes). IR (neat) ν=3480, 2955, 1722, 1659, 1471, 1258 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (dd, 1H, J=15.5, 4.1 Hz), 6.10 (dd, 1H, J=15.6, 1.8 Hz), 4.52 (brs, 1H), 4.17 (q, 2H, J=7.1 Hz), 4.00–3.55 (m, 2H), 3.78 (brs, 1H), 1.92–1.61 (m, 2H), 1.27 (t, 3H, J=7.1 Hz), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.9, 150.0, 120.4, 71.1, 60.5, 42.9, 37.5, 26.0, 18.3, 14.4, −5.4; HRMS calcd for $C_{14}H_{28}O_4Si$ $[M-OEt]^+$ 243.1414, found 243.1416.

4.2.22. Ethyl (2*E*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(methoxymethoxy)hex-2-enoate (44). To a 0 °C solution of **43** (500 mg, 1.73 mmol, 1 equiv) in CH_2Cl_2 (7 mL) was added dropwise diisopropylethylamine (910 μL, 5.20 mmol, 3 equiv), then chloromethyl methyl ether (500 μL, 8.67 mmol, 5 equiv) was added dropwise and the resulting mixture was warmed to rt and stirred for 18 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the aqueous layer was washed with EtOAc (3×). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (419 mg, 73%) as a pale yellow oil. R_f=0.52 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2954, 1724, 1659, 1472, 1368, 1257 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (dd, 1H, J=15.7 Hz), 5.97 (d, 1H, J=15.7 Hz), 4.60 (q, 2H, J=6.7 Hz), 4.37 (q, 1H, J=6.3 Hz), 4.18 (q, 2H, J=7.1 Hz), 3.78–3.56 (m, 2H), 3.35 (s, 3H), 1.88–1.65 (m, 2H), 1.27 (t, 3H, J=7.1 Hz), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 148.2, 121.9, 95.1, 72.6, 60.6, 59.0, 55.8, 38.4, 26.1, 18.4, 14.4, −5.2; HRMS

calcd for $C_{16}H_{32}O_5Si$ $[M-C(CH_3)_3]^+$ 275.1322, found 275.1315.

4.2.23. Ethyl (2*E*)-6-hydroxy-4-(methoxymethoxy)hex-2-enoate (45). To a 0 °C solution of **44** (75.0 mg, 0.225 mmol, 1 equiv) in THF (2 mL) was added hydrogen fluoride–pyridine (70:30) (0.130 mL, 4.50 mmol, 20 equiv). The resulting mixture was stirred at 0 °C for 30 min then warmed to rt and stirred for 1 h. The reaction was diluted with ether (10 mL) and quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and filtered. Removal of the solvent gave a crude oil (38.1 mg, 78%) that was used without further purification. $R_f=0.13$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=3418$, 2951, 1714, 1659, 1446, 1370, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, 1H, $J=15.7$, 6.3 Hz), 6.02 (dd, 1H, $J=15.7$, 1.3 Hz), 4.64 (q, 2H, $J=6.7$ Hz), 4.46 (dt, 1H, $J=7.1$, 6.0 Hz), 4.21 (q, 2H, $J=7.1$ Hz), 3.86–3.70 (m, 2H), 3.41 (s, 3H), 1.94–1.78 (m, 2H), 1.30 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 147.1, 122.0, 95.0, 73.8, 60.6, 59.2, 55.9, 37.2, 14.2; HRMS calcd for $C_{10}H_{18}O_5$ $[M-OEt]^+$ 173.0813, found 173.0814.

4.2.24. Ethyl (2*E*)-6-bromo-4-(methoxymethoxy)hex-2-enoate (9). A solution of carbon tetrabromide (63.5 mg, 0.191 mmol, 1.1 equiv) in CH_2Cl_2 (500 μL) was added dropwise to a 0 °C solution of triphenylphosphine (50.2 mg, 0.191 mmol, 1.1 equiv) and **45** (38.0 mg, 0.174 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL). The reaction was stirred at 0 °C for 1 h, diluted with 10% EtOAc/hexanes (10 mL) and filtered through celite. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (40.0 mg, 83%) as a pale yellow oil. $R_f=0.71$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=2951$, 1723, 1660, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, 1H, $J=15.8$, 6.6 Hz), 6.04 (dd, 1H, $J=15.8$, 0.7 Hz), 4.64 (dd, 2H, $J=18.1$, 6.9 Hz), 4.46 (dt, 1H, $J=7.0$, 5.5 Hz), 4.21 (q, 2H, $J=7.1$ Hz), 3.60–3.42 (m, 2H), 3.40 (s, 3H), 2.24–2.00 (m, 2H), 1.30 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 165.9, 146.3, 122.9, 94.9, 73.2, 60.6, 55.9, 37.9, 28.9, 14.2; HRMS-ESI calcd for $C_{10}H_{17}O_4NaBr$ $[M]^+$ 303.0202, found 303.0201.

4.2.25. *tert*-Butyl methyl(2-oxotetrahydrofuran-3-yl)-carbamate (46). To a 0 °C solution of 2-(*tert*-butoxycarbonylamino)-γ-butyrolactone[13] (500 mg, 2.50 mmol, 1 equiv) and iodomethane (464 μL, 7.45 mmol, 3 equiv) in DMF (15 mL) was added NaH (130 mg, 3.23 mmol, 60% dispersion in oil, 1.3 equiv). The resulting mixture was warmed to rt and stirred for 18 h. The reaction was diluted with EtOAc (15 mL) and quenched with water (15 mL). The aqueous layer was washed with EtOAc (3×) and the combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$ and filtered. Removal of the solvent gave a crude white solid (46.0 mg, 87%) that was used without further purification. The product is a mixture of rotamers in a 3:2 ratio. $R_f=0.49$ on silica gel (50% EtOAc/hexanes). IR (neat) $\nu=2977$, 1782, 1694, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major rotamer δ 4.84 (brt, 1H, $J=11.3$ Hz), 4.45 (brt, 1H, $J=9.1$ Hz), 4.23 (ddd, 1H, $J=9.1$, 9.1, 6.9 Hz), 2.87 (brs, 3H), 2.45 (brs, 2H), 1.47 (s, 9H); minor rotamer δ 4.45 (brt, 1H, $J=9.1$ Hz), 4.35 (brt, 1H, $J=9.4$ Hz), 4.23 (ddd, 1H, $J=9.1$, 9.1, 6.9 Hz), 2.95 (brs, 3H), 2.45 (brs, 2H), 1.47 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 174.3, 155.5, 154.4, 81.2, 80.6, 65.3, 57.1, 56.0, 34.0, 32.5, 29.8, 28.2, 26.3, 25.6; HRMS calcd for $C_{10}H_{17}NO_4$ $[M]^+$ 215.1165, found 215.1158.

4.2.26. Ethyl (2*E*)-4-[(*tert*-butoxycarbonyl)(methyl)-amino]-6-hydroxyhex-2-enoate (47). To a −78 °C solution of **46** (2.13 g, 9.89 mmol, 1 equiv) in THF (60 mL) was added diisobutylaluminum hydride (15.0 mL, 15.0 mmol, 1.0 M in hexanes, 1.5 equiv). The resulting mixture was stirred at −78 °C for 1.5 h. To a separate round-bottom flask was added NaH (415 mg, 10.4 mmol, 60% dispersion in oil, 1.05 equiv) and THF (40 mL). Triethyl phosphonoacetate (1.96 mL, 9.89 mmol, 1 equiv) was added dropwise at 0 °C then warmed to rt and stirred for 30 min. The reaction mixture was cooled to −78 °C and the diisobutylaluminum hydride solution of **46** was added via cannula. The resulting mixture was stirred at −78 °C for 10 min then warmed to rt and stirred for 18 h. The reaction was quenched with 10% aqueous HCl (60 mL) and the aqueous layer was washed with ether (3×). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using 75% EtOAc/hexanes as eluant to yield the desired product (1.60 g, 56%) as a pale yellow oil. The product is a mixture of rotamers in a 3:1 ratio. $R_f=0.30$ on silica gel (50% EtOAc/hexanes). IR (neat) $\nu=3441$, 2978, 1694, 1392 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major rotamer δ 6.90 (dd, 1H, $J=16.1$, 3.5 Hz), 5.99–5.87 (m, 1H), 5.09 (brs, 1H), 4.21 (q, 2H, $J=7.1$ Hz), 3.74–3.38 (m, 2H), 2.67 (brs, 3H), 1.94–1.64 (m, 2H), 1.48 (s, 9H), 1.30 (t, 3H, $J=7.0$ Hz); minor rotamer δ 6.90 (dd, 1H, $J=16.1$, 3.5 Hz), 5.99–5.87 (m, 1H), 4.21 (q, 2H, $J=7.1$ Hz), 3.74–3.38 (m, 2H), 3.33 (brs, 1H), 2.67 (brs, 3H), 1.94–1.64 (m, 2H), 1.46 (s, 9H), 1.30 (t, 3H, $J=7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 146.9, 122.9, 121.2, 81.0, 60.9, 60.7, 58.8, 58.3, 51.6, 33.0, 29.6, 28.6, 28.5, 14.4; HRMS calcd for $C_{10}H_{17}NO_4$ $[M]^+$ 215.1165, found 215.1158.

4.2.27. Ethyl (2*E*)-6-bromo-4-[(*tert*-butoxycarbonyl)-(methyl)amino]hex-2-enoate (10). A solution of carbon tetrabromide (1.63 g, 4.93 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL) was added dropwise to a 0 °C solution of triphenylphosphine (1.29 g, 4.93 mmol, 1.05 equiv) and **47** (1.35 g, 4.70 mmol, 1 equiv) in CH_2Cl_2 (50 mL). The reaction was stirred at 0 °C for 1 h, diluted with 10% EtOAc/hexanes (10 mL) and filtered through celite. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 25% EtOAc/hexanes as eluant to yield the desired product (49.0 mg, 30%) as an orange oil. $R_f=0.56$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=2978$, 1694, 1454, 1392, 1367 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, 1H, $J=15.9$, 4.9 Hz), 5.87 (dd, 1H, $J=15.9$, 1.9 Hz), 4.92 (brs, 1H), 4.21 (q, 2H, $J=7.1$ Hz), 3.35 (t, 2H, $J=6.0$ Hz), 2.74 (s, 3H), 2.35–2.15 (m, 2H), 1.48 (s, 9H), 1.30 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.2, 155.8, 145.6, 122.7, 80.6, 60.9, 55.0, 34.3, 29.9, 29.2, 28.5, 14.4; HRMS calcd for $C_{17}H_{22}O_4$ $[M-C(CH_3)_3]^+$ 293.0274, found 293.0262.

4.2.28. Ethyl (2*E*)-4-[(*tert*-butoxycarbonyl)amino]-6-hydroxyhex-2-enoate (48). To a −78 °C solution of 2-(*tert*-butoxycarbonylamino)-γ-butyrolactone[13] (2.00 g, 9.94 mmol, 1 equiv) in THF (60 mL) was added diisobutylaluminum hydride (15.0 mL, 15.0 mmol, 1.0 M in hexanes, 1.5 equiv). The resulting mixture was stirred at −78 °C for 1.5 h. To a separate round-bottom flask was added NaH (41.7 mg, 10.4 mmol, 60% dispersion in oil, 1.05 equiv) and THF (40 mL). Triethyl phosphonoacetate (1.96 mL, 9.89 mmol, 1 equiv) was added dropwise at 0 °C then warmed to rt and stirred for 30 min. The reaction mixture was cooled to −78 °C and the diisobutylaluminum hydride solution was added via cannula. The resulting mixture was stirred at −78 °C for 10 min then warmed to rt and stirred for 18 h. The reaction was quenched with 10% aqueous HCl and the aqueous layer was washed with ether (3×). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using 75% EtOAc/hexanes as eluant to yield the desired product (1.68 g, 62%) as an orange oil. R_f=0.34 on silica gel (50% EtOAc/hexanes). IR (neat) ν=3350, 2979, 1698, 1504, 1366, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (dd, 1H, J=15.6, 4.7 Hz), 5.97 (dd, 1H, J=15.9, 1.9 Hz), 5.03 (d, 1H, J=8.5 Hz), 4.56 (brs, 1H), 4.20 (q, J=14.2, 7.1 Hz), 3.71 (t, 2H, J=9.3 Hz), 3.07 (brs, 1H), 2.03–1.52 (m, 2H), 1.45 (s, 9H), 1.29 (t, 3H, J=7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.3, 156.2, 147.9, 121.0, 80.3, 60.6, 58.6, 48.5, 37.2, 28.3, 14.2; HRMS-ESI calcd for $C_{14}H_{25}NO_5Na$ $[M]^+$ 310.1648, found 310.1624.

4.2.29. Ethyl (2*E*)-6-bromo-4-[(*tert*-butoxycarbonyl)-amino]hex-2-enoate (11). A solution of carbon tetrabromide (890 mg, 2.69 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL) was added dropwise to a 0 °C solution of triphenylphosphine (700 mg, 2.69 mmol, 1.05 equiv) and **48** (700 mg, 2.56 mmol, 1 equiv) in CH_2Cl_2 (30 mL). The reaction was stirred at 0 °C for 1 h then warmed to rt. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 50% EtOAc/hexanes as eluant to yield the desired product (436 mg, 51%) as an oil. R_f=0.49 on silica gel (25% EtOAc/hexanes). IR (neat) ν=3360, 2980, 1715, 1682, 1520 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, 1H, J=15.7, 5.5 Hz), 5.97 (dd, 1H, J=15.7, 1.2 Hz), 4.59 (brs, 1H), 4.50 (brs, 1H), 4.20 (q, J=7.1 Hz), 3.50–3.27 (m, 2H), 2.24–2.02 (m, 2H), 1.45 (s, 9H), 1.29 (t, 3H, J=7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.0, 154.9, 146.5, 121.7, 80.1, 60.6, 50.5, 37.4, 28.6, 28.3, 14.2; HRMS calcd for $C_{13}H_{23}BrNO_4$ $[M-C(CH_3)_3]^+$ 279.0103, found 279.0106.

4.2.30. *tert*-Butyl(dimethyl)[(2-methylpent-4-enyl)oxy]-silane (49). To a 0 °C solution of imidazole (420 mg, 6.11 mmol, 1.15 equiv) and 2-methyl-4-pentenol[14] (536 mg, 5.35 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was added *tert*-butyldimethylsilyl chloride (930 mg, 6.16 mmol, 1.15 equiv). The mixture was stirred for 10 min at 0 °C then warmed to rt overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using hexanes yielding the desired product (812 mg, 71%) as a as a pale yellow oil. NMR spectra are identical to its enatiomerically-enriched form previously reported.[15]

4.2.31. Methyl (2*E*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-5-methylhex-2-enoate (50). To a solution of **58** (300 mg, 1.40 mmol, 1 equiv) and methyl acrylate (3.15 mL, 35.0 mmol, 25 equiv) in CH_2Cl_2 (5 mL) was added Grubbs' 2nd generation catalyst (59.4 mg, 0.070 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (290 mg, 76%) as a colorless oil. R_f=0.52 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2954, 1729, 1657, 1436, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (dt, 1H, J=15.6, 7.3 Hz), 5.78 (d, 1H, J=15.6 Hz), 3.69 (s, 3H), 3.40 (ABX, 2H, $\Delta\nu_{AB}$=25.2 Hz, J_{AB}=9.9 Hz, J_{AX}=5.5 Hz, J_{BX}=6.4 Hz), 2.33 (m, 1H), 1.98 (m, 1H), 1.75 (octet, 1H, J=6.7 Hz), 0.86 (s, 9H), 0.84 (s, 3H), 0.55 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.1, 148.5, 122.2, 77.5, 77.2, 76.9, 67.6, 51.4, 36.2, 35.5, 26.0, 18.4, 16.5, −5.3; HRMS calcd for $C_{14}H_{28}O_3Si$ $[M-OCH_3]^+$ 241.1631, found 241.1624.

4.2.32. Methyl (2*E*)-6-bromo-5-methylhex-2-enoate (17). To a solution of dibromotriphenylphosphorane (271 mg, 0.649 mmol, 1.2 equiv) in CH_2Cl_2 (1.5 mL) was added a solution of **50** in CH_2Cl_2 (1 mL). The mixture was stirred at rt for 1 h then diluted with CH_2Cl_2 (5 mL) and quenched with water (2 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% ether/hexanes as eluant to yield the desired product (108 mg, 86%) as a yellow oil. R_f=0.32 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2927, 1725, 1657, 1435, 1272, 1196 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (dt, 1H, J=15.5, 7.5 Hz), 5.89 (dt, 1H, J=15.5, 1.3 Hz), 3.73 (s, 3H), 3.35 (d, 2H, J=5.5 Hz), 2.38 (m, 1H), 2.18 (m, 1H), 2.00 (m, 1H), 1.04 (d, 3H, J=6.8 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.9, 146.4, 123.4, 51.7, 40.2, 37.5, 34.8, 18.9; HRMS calcd for $C_8H_{12}BrO_2$ $[M-H]^+$ 220.0098, found 220.0099.

4.2.33. Methyl (2*E*)-6-bromo-5-hydroxyhex-2-enoate (51). To a solution of 1-bromopent-4-en-2-ol[16] (700 mg, 4.24 mmol, 1 equiv) and methyl acrylate (9.88 mL, 106 mmol, 25 equiv) in CH_2Cl_2 (15 mL) was added Grubbs' 2nd generation catalyst (180 mg, 0.212 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (756 g, 80%) as a colorless oil. R_f=0.19 on silica gel (25% EtOAc/hexanes). IR (neat) ν=3444, 2952, 1715, 1652, 1436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (dt, 1H, J=15.6, 7.3 Hz), 5.69 (dt, 1H, J=15.6, 1.5 Hz), 3.99–3.92 (m, 1H), 3.74 (s, 3H), 5.2 (ABX, 2H, $\Delta\nu_{AB}$=45.4 Hz, J_{AB}=10.4, J_{AX}=3.8 Hz, J_{BX}=6.4 Hz), 2.55–2.47 (m, 2H), 2.35 (brs, OH); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.8, 143.9, 124.3, 69.9, 51.8, 39.3, 38.0; HRMS calcd for $C_7H_{11}BrO_3$ $[M]^+$ 222.9966, found 222.9969.

4.2.34. Methyl (2*E*)-5-(benzyloxy)-6-bromohex-2-enoate (18). To a 0 °C solution of **51** (750 mg, 3.36 mmol, 1 equiv)

CH_2Cl_2 (7 mL) and cyclohexane (14 mL) was added benzyl trichloroacetimidate (94.0 μL, 5.04 mmol, 1.5 equiv) and trifluoromethanesulfonic acid (5 μL, 0.504 mmol, 15 mol%). The resulting mixture was stirred at 0 °C for 20 min then warmed to rt and stirred for 1 h. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with 3% aqueous NaOH (10 mL). The organic layer was washed with water (3×), dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (71.3 mg, 83%) as a colorless oil. R_f=0.48 on silica gel (25% EtOAc/hexanes). IR (neat) ν= 2590, 1725, 1660, 1435, 1322, 1177 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.20 (m, 5H), 6.93 (dt, 1H, J= 14.8, 7.3 Hz), 5.94 (dd, 1H, J=15.7, 1.3 Hz), 4.61 (q, 2H, J=37.5, 11.5 Hz), 3.74 (s, 3H), 3.77–3.68 (m, 1H), 3.48–3.38 (m, 2H), 2.68–2.50 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.8, 144.1, 137.8, 129.0, 128.7, 128.2, 128.1, 124.2, 72.1, 51.8, 36.0, 34.0; HRMS-ESI calcd for $C_{14}H_{17}O_3NaBr$ $[M]^+$ 335.0253, found 335.0251.

4.2.35. [1-(Bromomethyl)but-3-enyl]benzene (52). To a 0 °C solution of 2-phenylpent-4-enol[17] (834 mg, 5.14 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added carbon tetrabromide (2.39 g, 7.20 mmol, 1.4 equiv) and triphenylphosphine (3.78 g, 14.4 mmol, 2.8 equiv). The mixture was stirred for 10 min at 0 °C then warmed to rt and stirred overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using hexane as eluant to yield the desired product (724 mg, 63%) as a colorless liquid. IR (neat) ν=3073, 3028, 2918, 2850, 1640, 149, 1451, 1233, 918; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.15 (m, 5H), 5.65 (m, 1H), 5.04 (m, 2H), 3.60 (dd, 2H, J=6.6, 2.7 Hz), 3.06 (m, 1H), 2.65 (m, 1H), 2.46 (m, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 141.7, 135.3, 128.4, 127.6, 127.0, 117.1, 47.3, 38.3, 38.0; HRMS calcd for $C_{11}H_{13}Br$ $[M]^+$ 224.0201, found 224.0210.

4.2.36. Methyl (2*E*)-6-bromo-5-phenylhex-2-enoate (19). To a solution of **52** (479 mg, 2.13 mmol, 1 equiv) and methyl acrylate (4.80 mL, 53.3 mmol, 25 equiv) in CH_2Cl_2 (5 mL) was added Grubbs' 2nd generation catalyst (93.0 mg, 0.110 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (381 mg, 63%) as a slightly pink oil. IR (neat) ν=3076, 3030, 2950, 2854, 1726, 1658, 1433, 1275, 1207; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.14 (m, 5H), 6.80 (m, 1H), 5.83 (dt, 1H, J=15.6, 1.2 Hz), 3.67 (s, 3H), 3.57 (m, 2H), 3.13 (m, 1H), 2.84 (m, 1H), 2.60 (m, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.5, 145.6, 140.7, 128.7, 127.5, 127.4, 123.1, 51.4, 46.7, 37.6, 36.4; HRMS calcd for $C_{11}H_{13}Br$ $[M-OMe]^+$ 251.0072, found 251.0077.

4.2.37. 4-Bromopentan-1-ol (53). To a mixture of 4-bromopentyl acetate[18] (2.00 g, 9.57 mmol, 1 equiv) in MeOH (70 mL) was added K_2CO_3 (1.45 g, 10.5 mmol, 1.1 equiv). The reaction was stirred at rt for 2 h then quenched with saturated aqueous NH_4Cl (70 mL). The aqueous layer was washed with EtOAc (3×) and the combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. Removal of the solvent gave a crude brown oil (1.40 g, 87%) that was used without further purification. NMR spectra match the previously reported data.[19]

4.2.38. Ethyl (2*E*)-6-bromohept-2-enoate (26). To a −78 °C solution of oxalyl chloride (402 μL, 10.5 mmol, 1.1 equiv) in CH_2Cl_2 (30 mL) was added a solution of dimethyl sulfoxide (654 μL, 9.22 mmol, 2.2 equiv) in CH_2Cl_2 (15 mL). The mixture was stirred at −78 °C for 30 min. A solution of **53** (700 mg, 4.19 mmol, 1 equiv) in CH_2Cl_2 (45 mL) was then added dropwise and the reaction mixture was stirred at −78 °C for 15 min. Triethylamine (2.92 mL, 9.22 mmol, 5 equiv) was added dropwise and the reaction mixture was stirred at −78 °C for 15 min then warmed to rt and stirred for 1 h. The reaction mixture was cooled to −78 °C and a solution of (carbethoxymethylene)-triphenylphosphorane (2.92 g, 8.38 mmol, 2 equiv) in CH_2Cl_2 (45 mL) was added dropwise. The mixture was stirred at −78 °C for 15 min then warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with water, brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (716 mg, 73%) as an orange oil. R_f=0.70 on silica gel (10% EtOAc/hexanes). IR (neat) ν= 2982, 1721, 1656, 1268 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (dt, 1H, J=15.5, 6.9 Hz), 5.86 (dt, 1H, J=17.1, 1.5 Hz), 4.17 (q, 2H, J=7.1 Hz), 4.13–4.02 (m, 1H), 2.52–2.27 (m, 2H), 2.05–1.83 (m, 2H), 1.72 (d, 3H, J=6.7 Hz), 1.28 (t, 3H, J=7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 147.1, 122.5, 60.6, 50.6, 39.5, 30.8, 26.9, 14.8; HRMS calcd for $C_9H_{15}BrO_2$ $[M-H]^+$ 234.0264, found 234.0255.

4.2.39. [2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)cyclopropyl]methanol (54). Diethylzinc (1.10 mL, 10.7 mmol, 2 equiv) and diiodomethane (865 μL, 10.7 mmol, 2 equiv) were added dropwise to a solution of (2*Z*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}but-2-en-1-ol[20] (1.00 g, 5.37 mmol, 1 equiv) in ether (100 mL). The reaction was stirred at rt for 24 h then quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was washed with ether (3×) and the combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 25% EtOAc/hexanes as eluant to yield the desired product (700 mg, 60%) as a colorless oil. R_f=0.64 on silica gel (25% EtOAc/hexanes). IR (neat) ν=3484, 2956, 1472, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 (dd, 1H, J=11.5, 5.3 Hz), 3.95 (ddd, 1H, J=11.8, 5.6 Hz), 3.34–3.16 (m, 2H), 1.44–1.30 (m, 1H), 1.30–1.15 (m, 1H), 0.91 (s, 9H), 0.82–0.69 (m, 1H), 0.19 (q, 1H, J=5.3 Hz), 0.11 (d, 6H, J=5.3 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 63.9, 63.1, 25.8, 18.2, 17.3, 8.4, −5.3, −5.6; HRMS calcd for $C_{11}H_{24}O_2Si$ $[M]^+$ 217.1612, found 217.1623.

4.2.40. Ethyl (2*E*)-3-[2-({[*tert*-butyl(dimethyl)silyl]oxy}-methyl)cyclopropyl]acrylate (55). To a −78 °C solution of oxalyl chloride (440 μL, 5.07 mmol, 1.1 equiv) in CH_2Cl_2 (30 mL) was added a solution of dimethyl sulfoxide (720 μL, 10.0 mmol, 2.2 equiv) in CH_2Cl_2 (15 mL). The

mixture was stirred at −78 °C for 30 min. A solution of **54** (1.00 g, 4.61 mmol, 1 equiv) in CH_2Cl_2 (45 mL) was then added dropwise and the reaction mixture was stirred at −78 °C for 15 min. Triethylamine (3.21 mL, 23.0 mmol, 5 equiv) was added dropwise and the reaction mixture was stirred at −78 °C for 15 min then warmed to rt and stirred for 1 h. The reaction mixture was cooled to −78 °C and a solution of (carbethoxymethylene)triphenylphosphorane (3.21 g, 9.22 mmol, 2 equiv) in CH_2Cl_2 (45 mL) was added dropwise. The mixture was stirred at −78 °C for 15 min then warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with water, brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (1.21 g, 92%) as an orange oil. R_f=0.61 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2955, 1718, 1645, 1472, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, 1H, J=15.4, 10.2 Hz), 5.92 (d, 1H, J=15.4 Hz), 4.17 (q, 2H, J=7.1 Hz), 3.83 (dd, 1H, J=11.3, 5.8 Hz), 3.59 (dd, 1H, J=11.3, 7.4 Hz), 1.75–1.67 (m, 1H), 1.56–1.47 (m, 1H), 1.27 (t, 3H, J=7.1 Hz), 1.17–1.09 (m, 1H), 0.89 (s, 9H), 0.71 (q, 2H, J=5.2 Hz), 0.05 (d, 6H, J=2.7 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.7, 150.1, 120.6, 62.8, 60.2, 26.1, 23.5, 19.5, 18.5, 14.6, 13.1, −5.1; HRMS calcd for $C_{15}H_{28}O_3Si$ $[M-C(CH_3)_3]^+$ 227.1106, found 227.1103.

4.2.41. 3 Ethyl (2*E*)-3-[2-(bromomethyl)cyclopropyl]-acrylate (28a). To a solution of dibromotriphenylphosphorane (2.24 mg, 5.06 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added a solution of **55** in CH_2Cl_2 (7 mL). The mixture was stirred at rt for 1 h then diluted with CH_2Cl_2 (25 mL) and quenched with water (15 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (904 mg, 92%) as a yellow oil. R_f=0.63 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2981, 1713, 1646, 1311, 1266 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, 1H, J=15.4, 9.9 Hz), 5.99 (d, 1H, J=15.4 Hz), 4.19 (q, 2H, J=7.1 Hz), 3.56 (dd, 1H, J=10.4, 7.7 Hz), 3.39 (dd, 1H, J=10.4, 8.2 Hz), 1.96–1.74 (m, 2H), 1.38–1.31 (m, 1H), 1.29 (t, 3H, J=7.1 Hz), 0.78 (q, 1H, J=5.8 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 147.2, 122.2, 60.5, 34.0, 23.8, 22.6, 17.2, 14.5; HRMS calcd for $C_9H_{13}BrO_2$ $[M]^+$ 232.0092, found 232.0099.

4.2.42. Ethyl (2*E*)-3-[3-(bromomethyl)oxiran-2-yl]acrylate (56). To a solution of 3-chloroperoxybenzoic acid (4.32 g, 18.0 mmol, 70% active, 3 equiv) in CH_2Cl_2 (30 mL) was added to a solution of ethyl (2*E*,4*E*)-6-bromohexa-2,4-dienoate[21] (1.28 g, 5.84 mmol, 1 equiv) in CH_2Cl_2 (2 mL). The mixture was stirred at rt for 24 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 25% EtOAc/hexanes as eluant to yield the desired product (1.34, 92%) as a colorless oil. R_f=0.28 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2983, 1714, 1368, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, 1H, J=15.6, 7.0 Hz), 6.16 (d, 1H, J=15.8 Hz), 4.20 (q, 2H, J=7.1 Hz), 3.49–3.36 (m, 3H), 3.24 (ddd, 1H, J=5.6, 5.6, 1.8 Hz), 1.29 (t, 3H, 7.0 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 165.3, 142.4, 125.1, 61.1, 59.9, 58.2, 31.5, 14.7; HRMS calcd for $C_9H_{15}BrO_3$ $[M]^+$ 234.9965, found 234.9969.

4.2.43. Ethyl (2*E*)-6-bromo-4,5-dihydroxyhex-2-enoate (57). To a solution of **56** (100 mg, 4.25 mmol, 1 equiv) in THF (2 mL) was added 0.75 M aqueous H_2SO_4 (3.12 mL, 2.34 mmol, 5.5 equiv). The mixture was stirred at rt for 24 h then neutralized to pH 7 with 1.0 M aqueous $NaHCO_3$.The aqueous layer was extracted with EtOAc (3×) and the combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product that was purified by flash chromatography using 50% EtOAc/hexanes as eluant to yield the desired product (76.9 mg, 71%) as a colorless oil. R_f=0.31 on silica gel (50% EtOAc/hexanes). IR (neat) ν=3427, 2981, 1698, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (dd, 1H, J=15.6, 4.8 Hz), 6.16 (d, 1H, J=15.8 Hz), 4.50 (t, 1H, J=3.6 Hz), 4.21 (q, 2H, J=7.1 Hz), 3.90 (dt, 2H, J=11.2, 4.8 Hz), 3.60–3.49 (m, 2H), 3.2 (brs, 2H), 1.30 (t, 3H, 7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 145.0, 122.9, 73.4, 72.3, 60.9, 35.4, 14.2; HRMS-ESI calcd for $C_{10}H_{18}O_4Br$ $[M]^+$ 253.0069, found 253.0061.

4.2.44. Ethyl (2*E*)-3-[5-(bromomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]acrylate (28b). To a solution of **57** (780 mg, 3.08 mmol, 1 equiv) in acetone (20 mL) was added iodine (160 mg, 0.616 mmol, 20 mol%). The reaction mixture was stirred at rt for 3 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL). The volatiles were evaporated and the resulting mixture was diluted with CH_2Cl_2 (25 mL). Saturated aqueous $Na_2S_2O_3$ (25 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (750 mg, 83%) as a colorless oil. R_f=0.64 on silica gel (25% EtOAc/hexanes). IR (neat) ν=2986, 1716, 1661, 1382 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (dd, 1H, J=15.5, 5.5 Hz), 6.17 (dd, 1H, J=15.5, 1.0 Hz), 4.84 (t, 1H, 6.2 Hz), 4.51 (q, 1H, J=6.6 Hz), 4.22 (q, 2H, J=7.0 Hz), 3.27 (ABX, 2H, $\Delta\nu_{AB}$=28.1 Hz, J_{AB}=10.4 Hz, J_{AX}=6.7 Hz, J_{BX}=7.0 Hz), 1.53 (s, 3H), 1.40 (s, 3H), 1.30 (t, 1H, J=7.0 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 165.7, 141.0, 123.8, 109.9, 78.0, 76.6, 60.7, 30.1, 27.9, 25.4, 14.2; HRMS calcd for $C_{11}H_{17}BrO_4$ $[M-CH_3]^+$ 277.0073, found 277.0075.

4.2.45. {[1-(Bromomethyl)pent-4-enyl]oxy}(*tert*-butyl)dimethylsilane (58). To a 0 °C solution of 1-bromohex-5-en-2-ol[22] (1 g, 5.58 mmol, 1 equiv) in CH_2Cl_2 (35 mL) was added 2,6-lutidine (980 mg, 8.38 mmol, 1.5 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.54 mL, 6.70 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 30 min then warmed to rt and stirred for 2 h. The reaction was quenched with water (35 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic

layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (1.40 g, 88%) as a pale yellow oil. $R_f=0.91$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=2956, 1642, 1472, 1256\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (dddd, 1H, $J=17.0$, 10.1, 6.5, 6.5 Hz), 5.07–4.94 (m, 2H), 3.85 (quintet, 1H, $J=$ 5.8 Hz), 3.38–3.27 (m, 2H), 2.16–2.06 (m, 2H), 1.82–1.55 (m, 2H), 0.90 (s, 9H), 0.08 (d, 6H, $J=6.0$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 138.4, 115.0, 71.5, 37.8, 34.9, 29.3, 26.0, 18.3, −4.2; HRMS calcd for $C_{12}H_{25}BrOSi$ $[M-C(CH_3)_3]^+$ 235.0156, found 235.0154.

4.2.46. Methyl (2*E*)-7-bromo-6-{[*tert*-butyl(dimethyl)-silyl]oxy}hept-2-enoate (32). To a solution of **58** (1.00 g, 3.42 mmol, 1 equiv) and methyl acrylate (7.71 mL, 85.6 mmol, 25 equiv) in CH_2Cl_2 (12 mL) was added Grubbs' 2nd generation catalyst (145 mg, 0.171 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (770 mg, 64%) as a pale orange oil. $R_f=0.79$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=2952$, 1732, 1435, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (dddd, 1H, $J=17.0$, 10.2, 6.5, 6.5 Hz), 5.07–4.94 (m, 2H), 3.85 (quintet, 1H, $J=5.8$ Hz), 3.39–3.26 (m, 2H), 2.22–2.00 (m, 2H), 1.82–1.53 (m, 2H), 0.90 (s, 9H), 0.08 (d, 6H, $J=6.0$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.2, 148.9, 121.4, 71.2, 51.7, 37.1, 33.8, 27.6, 25.9, 18.2, −4.3; HRMS calcd for $C_{14}H_{27}BrO_3Si$ $[M-CH_3]^+$ 335.0671, found 335.0678.

4.2.47. 6-Bromo-5-(methoxymethoxy)hex-1-ene (59). To a 0 °C solution of 1-bromohex-5-en-2-ol[22] (2.00 mL, 11.2 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added dropwise diisopropylethylamine (5.84 mL, 33.5 mmol, 3 equiv). Chloromethyl methyl ether (3.21 mL. 55.9 mmol, 5 equiv) was added dropwise and then the reaction mixture was warmed to rt and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (2.12 g, 85%) as a colorless oil. $R_f=0.57$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2947$, 1641, 1442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (dddd, 1H, $J=17.0$, 6.6, 3.5, 3.5 Hz), 5.08–4.93 (m, 2H), 4.69 (AB, 2H, $J=7.1$ Hz), 3.78–3.65 (m, 1H), 3.50–3.43 (m, 2H), 3.40 (s, 3H), 2.23–2.02 (m, 2H), 1.80–1.65 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 137.9, 115.4, 96.4, 76.4, 56.1, 36.0, 32.7, 29.4; HRMS calcd for $C_8H_{15}BrO_2$ $[M-OCH_3]^+$ 189.9988, found 189.9993.

4.2.48. Methyl (2*E*)-7-bromo-6-(methoxymethoxy)hept-2-enoate (33). To a solution of **59** (1.50 g, 6.72 mmol, 1 equiv) and methyl acrylate (15.1 mL, 168 mmol, 25 equiv) in CH_2Cl_2 (25 mL) was added Grubbs' 2nd generation catalyst (285 mg, 0.336 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (1.48 g, 78%) as a colorless oil. $R_f=0.25$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=$ 2950, 1722, 1658, 1436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (dt, 1H, $J=15.5$, 6.9 Hz), 5.87 (d, 1H, $J=15.7$ Hz), 4.74 (AB, 1H, $J=7.0$ Hz), 4.68 (AB, 1H, $J=7.0$ Hz), 3.73 (s, 3H), 3.80–3.65 (m, 1H), 3.47 (d, 2H, $J=5.0$ Hz), 3.41 (s, 3H), 2.33 (septet, 2H, $J=8.2$ Hz), 3.80–3.65 (m, 1H), 2.28–1.79 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.1, 148.4, 121.7, 96.6, 76.4, 56.1, 51.6, 35.4, 32.0, 27.9; HRMS calcd for $C_{10}H_{17}BrO_4$ $[M-OCH_3]^+$ 249.0121, found 249.0126.

4.2.49. 5-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylpentane-1,3-diol (60). A solution of *tert*-butyldimethylsilyl chloride (4.68 g, 31.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added dropwise to a solution of 3-methyl-1,3,5-pentanetriol (5.00 g, 37.3 mmol, 1.2 equiv) and triethylamine (5.19 mL, 37.3 mmol, 1.2 equiv) in CH_2Cl_2 (15 mL). The mixture was stirred at rt overnight then quenched with water (25 mL). The aqueous layer was separated and extracted with EtOAc (3×). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using 50% EtOAc/hexanes as eluant to yield the desired product (3.73 g, 50%) as a pale yellow oil. $R_f=0.50$ on silica gel (50% EtOAc/hexanes). IR (neat) $\nu=3382$, 2929, 1470, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.43 (brs, 1H), 4.02–3.77 (m, 4H), 3.61 (brs, 1H), 1.98–1.77 (m, 2H), 1.70–1.54 (m, 2H), 1.30 (s, 3H), 0.90 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 74.6, 60.7, 59.8, 42.5, 41.7, 26.6, 26.0, 18.2, −5.5; HRMS calcd for $C_{12}H_{28}O_3Si$ $[M]^+$ 249.1871, found 249.1885.

4.2.50. Ethyl (2*E*)-7-{[*tert*-butyl(dimethyl)silyl]oxy}-5-hydroxy-5-methylhept-2-enoate (61). To a −78 °C solution of oxayl chloride (579 μL, 6.64 mmol, 1.1 equiv) in CH_2Cl_2 (35 mL) was added a solution of dimethyl sulfoxide (943 μL, 13.3 mmol, 2.2 equiv) in CH_2Cl_2 (20 mL). The mixture was stirred at −78 °C for 30 min. A solution of **60** (1.50 g, 6.04 mmol, 1 equiv) in CH_2Cl_2 (60 mL) was then added dropwise and the reaction mixture was stirred at −78 °C for 15 min. Triethylamine (4.21 mL, 30.2 mmol, 5 equiv) was added dropwise and the reaction mixture was stirred at −78 °C for 15 min then warmed to rt and stirred for 1 h. The reaction mixture was cooled to −78 °C and a solution of (carbethoxymethylene)triphenylphosphorane (4.21 g, 12.1 mmol, 2 equiv) in CH_2Cl_2 (60 mL) was added dropwise. The mixture was stirred at −78 °C for 15 min and warmed to rt and stirred for 24 h. The reaction was quenched with water (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 25% EtOAc/hexanes as eluant to yield the desired product (1.14 g, 60%) as a colorless oil. $R_f=0.55$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=3500, 2931, 1722, 1652, 1472\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (dt, 1H, $J=15.4$, 7.7 Hz), 5.87 (d, 1H, $J=15.7$ Hz), 4.19 (q, 2H, $J=4.4$ Hz), 3.95–3.87 (m, 2H), 2.42 (d, 2H, $J=7.7$ Hz), 1.83–1.60 (m, 2H), 1.29 (t, 3H, $J=7.1$ Hz), 1.24 (s, 3H), 0.90 (s, 9H), 0.10 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.5, 145.2, 124.2,

72.8, 60.8, 60.4, 45.5, 41.1, 27.0, 26.0, 18.2, 14.5, −5.5; HRMS calcd for $C_{16}H_{22}O_4Si$ $[M-OH]^+$ 299.2037, found 299.2042.

4.2.51. Ethyl (2*E*)-7-{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethoxy)-5-methylhept-2-enoate (62). To a 0 °C solution of **61** (336 mg, 1.06 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added dropwise diisopropylethylamine (555 μL, 3.18 mmol, 3 equiv). Chloromethyl methyl ether (306 μL, 5.31 mmol, 5 equiv) was added dropwise and then the reaction mixture was warmed to rt and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (300 g, 79%) as a colorless oil. R_f=0.85 on silica gel (10% EtOAc/hexanes). IR (neat) ν= 2954, 1723, 1656, 1467 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (ddd, 1H, J=15.7, 7.7, 7.7 Hz), 5.83 (ddd, 1H, J= 16.8, 1.1, 1.1 Hz), 4.71 (AB, 1H, J=7.0 Hz), 4.68 (AB, 1H, J=7.7 Hz), 4.17 (q, 2H, J=7.1 Hz), 3.71 (ddd, 2H, J=7.1, 7.1, 1.1 Hz), 3.35 (s, 3H), 2.44 (dd, 2H, J=7.4, 1.1 Hz), 1.78 (ddd, 2H, J=6.7, 6.7, 2.2 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.23 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.5, 145.2, 124.1, 91.0, 77.3, 60.4, 59.1, 55.6, 43.2, 42.2, 26.1, 24.4, 18.4, 14.4, −5.2; HRMS calcd for $C_{18}H_{36}O_5Si$ $[M-CH_3]^+$ 229.1436, found 229.1439.

4.2.52. Ethyl (2*E*)-7-hydroxy-5-(methoxymethoxy)-5-methylhept-2-enoate (63). To a 0 °C solution of **62** (920 mg, 2.55 mmol, 1 equiv) in THF (20 mL) was added hydrogen fluoride–pyridine (70:30) (1.40 mL, 51.0 mmol, 20 equiv). The resulting mixture was stirred at 0 °C for 30 min then warmed to rt and stirred for 2 h. The reaction was diluted with ether (60 mL) and quenched with saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product that was purified by flash chromatography using 25% EtOAc/hexanes as eluant to yield the desired product (511 mg, 81%) as a colorless oil. R_f=0.15 on silica gel (25% EtOAc/hexanes). IR (neat) ν= 3440, 2980, 1714, 1652, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (ddd, 1H, J=15.4, 7.7, 7.7 Hz), 5.87 (ddd, 1H, J=15.6, 1.1, 1.1 Hz), 4.78 (AB, 1H, J=7.4 Hz), 4.73 (AB, 1H, J=7.7 Hz), 4.19 (q, 2H, J=7.1 Hz), 3.80 (m, 2H), 3.39 (s, 3H), 2.59 (brs, 1H), 2.52 (d, 2H, J=7.7 Hz), 1.95–1.65 (m, 2H), 1.32 (s, 3H), 1.29 (t, 3H, J=7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 144.2, 124.6, 91.1, 78.9, 60.5, 59.2, 55.9, 42.9, 41.6, 23.9, 14.4; HRMS calcd for $C_{12}H_{22}O_5$ $[M-OH]^+$ 345.2101, found 345.2097.

4.2.53. Ethyl (2*E*)-7-bromo-5-(methoxymethoxy)-5-methylhept-2-enoate (34). A solution of carbon tetrabromide (722 mg, 2.18 mmol, 1.05 equiv) in CH_2Cl_2 (20 mL) was added dropwise to a 0 °C solution of triphenylphosphine (571 mg, 2.18 mmol, 1.05 equiv) and **63** (512 mg, 2.07 mmol, 1 equiv) in CH_2Cl_2 (20 mL). The reaction was stirred at 0 °C for 1 h then warmed to rt. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 20% EtOAc/hexanes as eluant to yield the desired product (272 mg, 45%) as a colorless oil. R_f=0.65 on silica gel (25% EtOAc/hexanes). IR (neat) ν= 2980, 1714, 1656, 1447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (ddd, 1H, J=15.6, 7.6, 7.6 Hz), 5.88 (ddd, 1H, J= 15.4, 1.1, 1.1 Hz), 4.71 (s, 2H), 4.20 (q, 2H, J=7.1 Hz), 3.48–3.40 (m, 2H), 3.38 (s, 3H), 2.52–2.36 (m, 2H), 2.23–2.00 (m, 2H), 1.30 (t, 3H, J=7.1 Hz), 1.26 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.2, 143.6, 124.6, 91.1, 78.8, 60.4, 55.7, 43.6, 42.7, 27.4, 23.5, 14.3; HRMS calcd for $C_{12}H_{21}BrO_5$ $[M]^+$ 309.0709, found 309.0701.

4.2.54. Ethyl (2*R*)-2-(allyloxy)-4-phenylbutanoate (64). To a suspension/solution of ethyl (*R*)-(−)-2-hydroxy-4-phenylbutyrate (2.01 g, 9.65 mmol, 1 equiv) and silver(I) oxide (6.70 g, 29.0 mmol, 3 equiv), $MgSO_4$ (289 mg, 2.40 mmol, 25 mol%) in Et_2O (40 mL) was added allyl bromide (2.51 mL, 29.0 mmol, 3 equiv). The reaction mixture was stirred at rt for 3 days protected from the light. Celite was then added and the mixture was filtrated through Celite and washed with Et_2O. Evaporation of the solvent gave the crude product which was purified by flash chromatography using 10% Et_2O/hexane as the eluant to give the desired product (1.19 g, 49%) as a colorless liquid. $[\alpha]_D^{25}$ +35.8 (*c* 1.1, $CHCl_3$); IR (neat) ν=3027, 2982, 2932, 2865, 1746, 1178, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.14 (m, 5H), 5.92 (m, 1H), 5.25 (m, 2H), 4.18 (m, 3H), 3.88 (m, 2H), 2.75 (m, 1H), 2.06 (q, 2H, J=8.4 Hz), 1.26 (t, 3H, J=7.2 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 172.6, 141.0, 134.0, 128.3, 128.2, 125.8, 117.5, 77.1, 71.3, 60.6, 34.4, 31.2, 14.1; HRMS calcd for $C_{15}H_{20}O_3$ $[M]^+$ 248.1412, found 248.1423.

4.2.55. [(3*R*)-3-(Allyloxy)-4-bromobutyl]benzene (65). To a 0 °C suspension of lithium aluminum hydride (199 mg, 5.25 mmol, 1.1 equiv) in Et_2O (5 mL) was added slowly a solution **64** (1.19 g, 4.77 mmol, 1 equiv) in Et_2O (5 mL). The resulting mixture was warmed to rt and stirred for 6 h. Water (5 mL) was then carefully added at 0 °C followed by 10% aqueous KOH (7.5 mL) at rt and finally water (10 mL). The mixture was extracted with Et_2O (4×) and the combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude alcohol was then dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Carbon tetrabromide (2.37 g, 7.16 mmol, 1.5 equiv) and triphenylphosphine (1.88 g, 7.16 mmol, 1.5 equiv) were then added and the reaction mixture was stirred for 15 min before warming to rt overnight. The mixture was diluted with Et_2O (20 mL) was added and the resulting suspension was filtrated through celite and concentrated. The crude product was purified by flash chromatography using 2→5% Et_2O/hexane as eluant to provide the desired product (1.03 g, 80% over 2 steps) as a colorless liquid. $[\alpha]_D^{25}$ +18.1 (*c* 0.95, $CHCl_3$); IR (neat) ν= 3027, 2926, 2859, 1495, 1454, 1080, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5H), 5.95 (m, 1H), 5.31 (dq, 1H, J=17.1, 1.5 Hz), 5.20 (dd, 1H, J=10.5, 1.5 Hz), 4.14 (ddt, 1H, J=12.5, 6.0, 0.9 Hz), 4.00 (ddt, 1H, J=12.5, 6.0, 0.9 Hz), 3.55–3.39 (m, 3H), 2.72 (m, 2H), 1.97 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 141.4, 134.5, 128.3, 128.2, 125.8, 117.2, 77.1, 70.7, 34.8, 34.6, 31.2; HRMS calcd for $C_{13}H_{17}OBr$ $[M]^+$ 268.0463, found 268.0468.

4.2.56. Methyl (2*E*)-4-{[(1*R*)-1-(bromomethyl)-3-phenylpropyl]oxy}but-2-enoate (39). To a mixture of **65** (342 mg,

1.27 mmol, 1 equiv) and methyl acrylate (2.83 mL, 31.7 mmol, 25 equiv) in CH_2Cl_2 (5 mL) was added Grubbs' 2nd generation catalyst (53.9 mg, 0.0635 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 15% Et_2O/hexane as eluant to yield the desired product (306 mg, 74%) as an amber oil. $[\alpha]_D^{25}$ +26.9 (*c* 0.96, $CHCl_3$); IR (neat) ν=3034, 2950, 2865, 1725, 1665, 1304, 1279, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$-*d*) δ 7.32–7.24 (m, 2H), 7.22–7.15 (m, 3H), 6.97 (dt, 1H, *J*=15.9, 4.2 Hz), 6.15 (dt, 1H, *J*=15.9, 1.8 Hz), 4.30 (ddd, 1H, *J*=15.9, 4.2, 1.8 Hz), 4.12 (ddd, 1H, *J*=15.9, 4.2, 1.8 Hz), 3.75 (s, 3H), 3.50 (m, 1H), 3.42 (d, 2H, *J*=5.1 Hz), 2.72 (m, 2H), 1.97 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$-*d*) δ 166.6, 144.1, 141.1, 128.4, 128.3, 126.0, 120.9, 78.1, 68.2, 51.5, 34.7, 34.3, 31.2; HRMS calcd for $C_{15}H_{19}O_3Br$ $[M]^+$ 326.0518, found 326.0525.

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References and notes

1. (a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111–124. (b) Ojima, I.; Tzamariuodaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635–662. (c) Negishi, E.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–393. (d) Pache, S.; Lautens, M. *Org. Lett.* **2003**, *5*, 4827–4830.
2. (a) Guiry, P. J.; Kiely, D. *Curr. Org. Chem.* **2004**, *8*, 781–794. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. (c) Link, J. T.; Organic reactions; Wiley: Hoboken, NJ, 2002; Vol. 60. (d) Braese, S.; de Meijere, A. In *Handbook of organopalladium chemistry for organic synthesis*; Negishi, E.-I., de Meijere, A., Eds.; Wiley: Hoboken, 2002; Chapter 2, pp 1223–1254. (e) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449–7476. (f) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (g) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314–321. (h) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007. (i) Link, J. T.; Overman, L. In *Metal catalyzed cross coupling reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 2, pp 99–154. (j) Gibson, S. E.; Middleton, R. *J. Contemp. Org. Synth.* **1996**, *3*, 447–471.
3. (a) Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1045–1046. (b) Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127–8134.
4. (a) Catellani, M.; Fagnola, M. C. *Angew. Chem.* **1994**, *106*, 2559–2561. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2421–2422. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem.* **1997**, *109*, 142–145. Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119–122. (c) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336–4346. (d) Catellani, M. *Synlett* **2003**, 298–313.
5. Lautens, M.; Paquin, J.-F.; Piguel, S. *J. Org. Chem.* **2002**, *67*, 3972–3974.
6. (a) Chavan, S. P.; Rao, Y. T. S.; Govande, C. A.; Zubaidha, P. K.; Dhondge, V. D. *Tetrahedron Lett.* **1997**, *38*, 7633–7634. (b) Kumar, P.; Saravanan, K. *Tetrahedron* **1998**, *54*, 2161–2168. (c) Demir, A. S.; Camkerten, N.; Gercek, Z.; Duygu, N.; Reis, O.; Arikan, E. *Tetrahedron* **1999**, *55*, 2441–2448. (d) Ferraz, H. M. C.; Silva, L. F., Jr. *Tetrahedron* **2001**, *57*, 9939–9949. (e) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043–8053.
7. Salerno, G.; Panza, M.; Chiusoli, G. P.; Costa, M. *J. Organomet. Chem.* **1990**, *394*, 569–581.
8. Le Baut, G.; Sparfel, L.; Clairc, C.; Floc'h, R.; Ducrey, P. *Eur. J. Med. Chem.* **1983**, *18*, 447–455.
9. (a) Silver, M. A.; Shafer, P. A.; Nordlander, J. E.; Rüchardt, C.; Roberts, R. D. *J. Am. Chem. Soc.* **1960**, *82*, 2646. (b) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720–4721. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1995**, *34*, 2223–2224.
10. Bohlmann, F.; Ganzer, M.; Kruger, M.; Nordhoff, E. *Tetrahedron* **1983**, *39*, 123–128.
11. Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204–2210. Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533–4540.
12. Hu, T.; Schaus, J. V.; Lam, K.; Palfreyman, M. G.; Wuonola, M.; Gustafson, G.; Panek, J. S. *J. Org. Chem.* **1998**, *63*, 2401–2406.
13. Pattenden, G.; Reynolds, S. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, *4*, 379–385.
14. Becker, D.; Haddad, N. *Tetrahedron* **1993**, *49*, 947–964.
15. Schinzer, D.; Bauer, A.; Schieber, J. *Chem. Eur. J.* **1999**, *5*, 2492–2500.
16. De Camp Schuda, A.; Mazzocchi, P. H.; Fritz, G.; Morgan, T. *Synthesis* **1986**, 309–312.
17. Bloodworth, A. J.; Courtneidge, J. L.; Curtius, R. J.; Spencer, M. D. *J. Chem. Soc., Perkin Trans. 1* **1990**, *11*, 2951–2955.
18. Yadav, V. K.; Fallis, A. G. *J. Org. Chem.* **1986**, *51*, 3372–3374.
19. Guindon, Y.; Yoakim, C.; Morton, H. E. *Tetrahedron Lett.* **1983**, *24*, 2969–2972.
20. Soulie, J.; Ta, C.; Lallemand, J.-Y. *Tetrahedron* **1992**, *48*, 443–452.
21. Durrant, G.; Green, R. H.; Lambeth, P. F.; Lester, M. G.; Taylor, N. R. *J. Chem. Soc., Perkin Trans. 1* **1983**, *9*, 2211–2214.
22. Suh, Y.-G.; Koo, B.-A.; Ko, J.-A.; Cho, Y.-S. *Chem. Lett.* **1993**, *11*, 1907–1910.

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Iridium-catalyzed selective *N*-allylation of hydrazines

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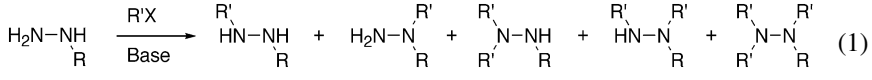
Abstract—A highly chemo- and regioselective iridium-catalyzed allylic amination is described. The reaction of various hydrazones and hydrazides with allylic carbonates proceeds at ambient temperature in the presence of an $[Ir(COD)Cl]_2$/pyridine catalyst, ammonium iodide, and diethylzinc to afford the corresponding *N*-allylation products in high yields with excellent chemo- and regioselectivities. Only the more nucleophilic nitrogen of a given hydrazine derivative undergoes the C–N bond formation to yield a branched allylic isomer as the exclusive product.

1. Introduction

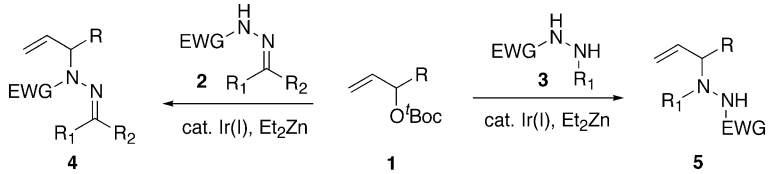
Hydrazines and their derivatives are an important class of compounds that have found wide utility in organic synthesis.[1,2] While hydrazines have traditionally been employed as reagents for the derivatization and characterization of carbonyl compounds, the N–N linkage has been used as a key structural motif of various bioactive active agents in recent years. In particular, an increasing number of N–N bond containing heterocycles and peptidomimetics have made their ways to commercial applications as pharmaceutical and agricultural agents.[3,4]



(1)

For the synthesis of substituted hydrazine derivatives, a number of methods have been developed over the years largely making use of S_N2 type displacement. These alkylative approaches, however, typically involve tedious synthetic sequences requiring extensive use of protecting groups because of the inherent difficulty in achieving selective alkylation at one of the two available nitrogens while avoiding overalkylation (Eq. 1).[3] Moreover, such methods are only applicable, for the most part, with primary electrophiles due to the lower reactivity of secondary alkyl halides and competing elimination pathways. In this regard, reductive amination[5] is particularly valuable for the installation of secondary alkyl chains, but limited only to cases where the requisite imine formation is possible. Thus, a methodology that would allow for the easy installation of branched alkyl groups to a hydrazine scaffold in one step with selectivity for a particular nitrogen would be of potential synthetic value.

Our approach to the selective alkylation of hydrazines is the formation of the C–N bond using η^3-allylmetal chemistry as outlined in Scheme 1.[6–13] Based on findings in zinc(II) alkoxide mediated allylic etherification reactions,[14,15] we wondered whether the 'zinc effect' would also be viable for the *N*-allylation reactions of hydrazones **2** and hydrazides **3**.



Scheme 1. Strategy for *N*-allylation of hydrazones and hydrazines.

Keywords: Iridium; Catalysis; Hydrazones; Hydrazides; Hydrazines; Amination; Allylation.
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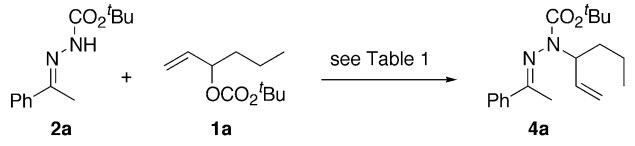
Although our prior work on allylic etherification exploited palladium catalysis, we chose to explore the use of an iridium catalyst for this endeavor, as such catalysts had been shown to exhibit a pronounced regiochemical preference for the formation of branched products.[16–19] It was also hoped that the use of diethylzinc as a basic mediator in this reaction would overcome the inherent problem of chemoselectivity, allowing for the selective delivery of an allylic electrophile to one nitrogen over the other (*N* vs *N′*-allylation). Described herein are our results towards meeting these challenges.

2. Results and discussion

Initial studies were focused on the model reaction between acetophenone-derived hydrazone **2a** and allylic carbonate **1a**, in which various reaction parameters were probed to identify an effective catalytic system (Table 1). Guided by literature precedents,[12,16,18] we chose $[Ir(COD)Cl]_2$ as the precatalyst while employing pyridine and Et_2Zn as the ligand and base, respectively.[20] Gratifyingly, these conditions adopted from our previous studies on allylic etherification proved effective to give rise to the desired *N*-allylation product **4a** with complete regioselectivity (entry 1). While THF was found to be an optimal solvent, a set of control experiments clearly indicated the importance of each component of the reaction system (entries 3–6), in which the effect of 1 equiv of NH_4I on the yield of the reaction was particularly noteworthy.[21]

Table 1. Development of Ir-catalyzed *N*-allylation of hydrazones[a]



2a **1a** **4a**

Entry	$[Ir(COD)Cl]_2$/ pyridine	Et_2Zn (equiv)	NH_4I (equiv)	% Yield
1	2.5 mol%/5 mol%	0.5	1.0	76
2[b]	5.0 mol%/10 mol%	0.5	1.0	89
3	2.5 mol%/5 mol%	0.5	—	12
4	2.5 mol%/5 mol%	—	1.0	0
5	2.5 mol%/5 mol%	—	—	0
6	—	0.5	1.0	0

[a] All reactions were performed at 25 °C in THF (0.4 mL) with 0.30 mmol (1.5 equiv) of **2a** and 0.20 mmol (1.0 equiv) of **1a**.
[b] No reaction in dioxane. 40% yield in MeCN.

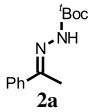
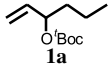
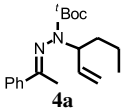
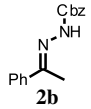
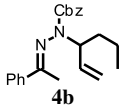
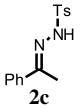
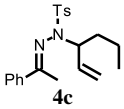
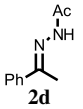
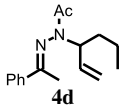
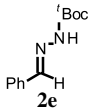
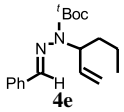
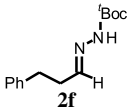
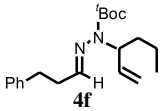
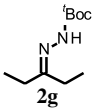
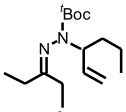
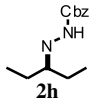
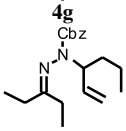
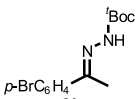
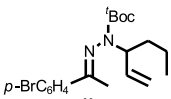
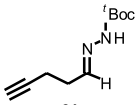
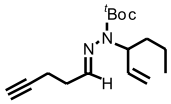
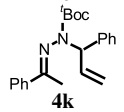
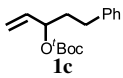
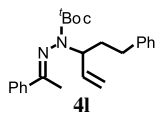
With conditions for the allylic amination established, we further examined the scope of the reaction with a wide range of substrates. As illustrated in Table 2, a variety of hydrazones derived from ketones and aldehydes participated well in the reaction. In addition to the *t*-Boc-protected hydrazone **2a** used in the initial study, both Cbz- and Ts-protected hydrazones **2b** and **2c** also proved competent reaction partners (entries 2, 3 and 8). Interestingly, the reaction of acetate **2d** worked poorly under these conditions, giving the product only in low yield as the main component of an inseperable mixture of products (entry 4). The presence of an electron withdrawing group was necessary, as substrates lacking one, such as simple phenylhydrazones, were unreactive (data not shown). The reaction tolerated an aryl bromide (**2i**) and a terminal alkyne (**2j**), and also fared well with an aromatic allylic carbonate (**1b**). Most notably, only the branched isomer of the desired product was formed in all cases examined.

Encouraged by the results of hydrazones, we endeavored to explore the feasibility of using the same catalytic system for the allylation of hydrazide **3a**. As summarized in Table 3, the desired *N*-allylation product **5a** could be obtained as a single regioisomer, with substitution at the primary nitrogen (*N′*-position). In all cases, little to no dialkylation was observed. In contrast to the reaction of hydrazones, the use of only 0.25 equiv of Et_2Zn, instead of 0.50 equiv, provided a higher yield (entries 1 vs 2). There was a substantial background reaction (13%) in the absence of Et_2Zn, presumably due to the greater nucleophilicity of hydrazides relative to hydrazones (entry 3), while the iridium catalyst was indispensable for the reaction (entry 6). In order to test the possibility that the latent nucleophilicity of the hydrazide might be sufficient to promote the alkylation without recourse to Et_2Zn as base, the reaction was performed under zinc free conditions (entries 7 and 8). Although the use of simple bases, Cs_2CO_3 and *i*-Pr_2NEt, improved the yield by a marginal amount relative to the background reaction (entries 3 vs 7 and 8), the lack of substantial reactivity highlighted the unique nature and role of Et_2Zn in this reaction.

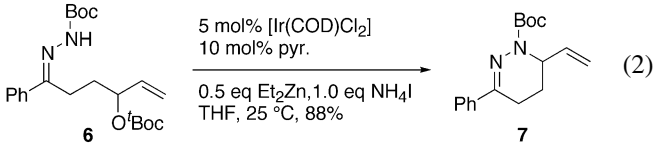
Having established working conditions, we surveyed the scope of the reaction with a variety of hyrazines and allylic carbonates (Table 4). Similar to the reaction of hydrazones, the *t*-Boc-, Cbz- and Ts-protected hydrazines **3a**, **3b** and **3c** participated well in the reaction, while the acetate-protected hydrazine **3d** failed to react under these conditions (entry 4). Also in accord with the hydrazones, hydrazines lacking an electron withdrawing substituent gave no reaction under these conditions. Good yields were uniformly obtained in the reactions of structurally diverse allylic carbonates and hydrazides (entries 5–8). In particular, it was noteworthy that a highly selective (*N* vs *N′*) allylation of *N*-acyl-*N′*-alkyl hydrazines could be achieved to form *N′*,*N′*-dialkyl hydrazides, although dialkylation was not observed to any serious extent in other reactions (entries 1–6 vs 7 and 8).

The new method was further extended to the synthesis of N–N bond-containing heterocycles via an intramolecular *N*-allylation reaction. Compound **6**, containing hydrazone and allylic carbonate moieties within the same molecule, was thus prepared (Scheme 2, vide infra) and tested for ring closure (Eq. 2). Upon subjection to our standard reaction conditions, hydrazone **6** underwent a smooth cyclization to give rise to the desired tetrahydropyridazine **7** in 88% yield. Finally, the utility of the *N*-allylated products was briefly explored through several transformations (Eqs. 3–5). Hydrazone **4h**, originally derived from acetophenone, could be converted to hydrazines **10** and **11** by standard hydrolysis[22] and reductive amination[5,23] reactions, respectively. Simple hydrogenation[25] of **4g** furnished the fully saturated *N*,*N′*-dialkyl hydrazide **12**.

Table 2. Ir(I)-Catalyzed *N*-allylation of hydrazones with allylic carbonates[a]

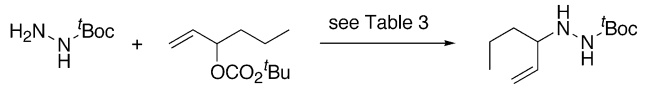
Entry	Hydrazone	Allylic carbonate	Product	%Yield
1	 **2a**	 **1a**	 **4a**	89
2	 **2b**	**1a**	 **4b**	86
3	 **2c**	**1a**	 **4c**	92
4	 **2d**	**1a**	 **4d**	17
5	 **2e**	**1a**	 **4e**	88
6	 **2f**	**1a**	 **4f**	82
7	 **2g**	**1a**	 **4g**	86
8	 **2h**	**1a**	 **4h**	75
9	 **2i**	**1a**	 **4i**	41
10	 **2j**	**1a**	 **4j**	71
11	**2a**	 **1b**	 **4k**	90
12	**2a**	 **1c**	 **4l**	83

[a] All reactions performed at room temperature in THF (0.4 mL) with 0.30 mmol (1.5 equiv) of hydrazone, 0.20 mmol allylic carbonate, 0.15 mmol of Et_2Zn (0.50 equiv with respect to hydrazone), 0.20 mmol of NH_4I (1.0 equiv with respect to electrophile), 5 mol% $[Ir(COD)Cl]_2$, and 10 mol% pyridine.



(2)

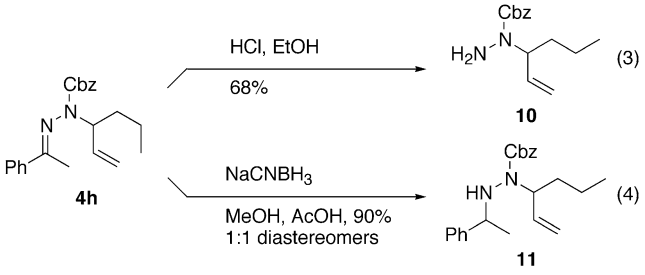
Table 3. Development of Ir-catalyzed *N*-allylation of hydrazines[a]



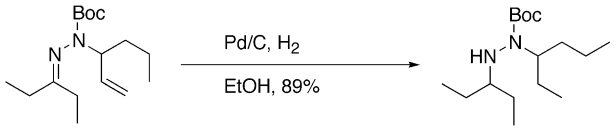
3a **1a** **5a**

Entry	[Ir(COD)Cl]$_2$/ pyridine	Et_2Zn (equiv)	NH_4I (equiv)	% Yield
1	5.0 mol%/10 mol%	0.50	1.0	74
2	5.0 mol%/10 mol%	0.25	1.0	93
3	2.5 mol%/5 mol%	—	1.0	13
4	2.5 mol%/5 mol%	0.50	—	<2
5	2.5 mol%/5 mol%	—	—	<2
6	—	0.50	1.0	0
7[b]	5.0 mol%/10 mol%	—	1.0	19
8[c]	5.0 mol%/10 mol%	—	1.0	19

[a] All reactions were performed at 25 °C in THF (0.4 mL) with 0.20 mmol of **1a** and 0.30 mmol (1.5 equiv) of **3a**.
[b] Cs_2CO_3 (1.0 equiv) was used as base.
[c] Diisopropylethylamine (1.0 equiv) was used as base.



4h **10** **11** (3) (4)



4g **12** (5)

3. Conclusion

In summary, we have developed a highly chemo- and regioselective iridium-catalyzed method for the *N*-allylation of hydrazones and hydrazines with allylic carbonates. The reaction provides the branched, *N*-allylated products in good yields under mild reaction conditions. Crucial to the success of the reaction is the utilization of diethylzinc as base, as well as ammonium iodide as a halide additive. The amination reactions of hydrazones and hydrazides described herein can provide rapid access to differentially substituted hydrazines without recourse to protecting group manipulation. Such expedient access to these compounds may be useful in further applications, such as the preparation of novel peptidomimetics or heterocycles.

4. Experimental

4.1. General

Unless otherwise noted, all reactions were conducted in

Table 4. Ir(I)-Catalyzed *N*-allylation of hydrazines with allylic carbonates[a]

Entry	Hydrazine	Electrophile	Product	%Yield
1	**3a**	**1a**	**5a**	93
2	**3b**	**1a**	**5b**	86
3	**3c**	**1a**	**5c**	57
4	**3d**	**1a**	**5d**	0
5	**3a**	**1b**	**5e**	88
6	**3a**	**1d**	**5f**	82
7	**3e**	**1a**	**5g**	85
8	**3f**	**1a**	**5i**	82

[a] All reactions performed at room temperature in THF (0.4 mL) with 0.30 mmol (1.5 equiv) of hydrazine, 0.20 mmol allylic carbonate, 0.075 mmol of Et_2Zn (0.25 equiv with respect to hydrazine), 0.20 mmol of NH_4I (1.0 equiv with respect to electrophile), 5 mol% [Ir(COD)Cl]$_2$, and 10 mol% pyridine.

flame-dried glassware under an argon atmosphere using anhydrous solvent (either distilled or passed through an activated alumina column or activated molecular sieves column). Commercially available reagents were used without further purification. Thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates and visualized using UV light, anisaldehyde, ceric sulfate or potassium permanganate stains. Flash chromatography was performed on EM Science silica gel 60 (40–63 μm) using the indicated solvent system. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian Mercury 300 MHz, a Varian Inova 400 MHz or a Varian Inova 500 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra were reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in Hertz (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift in ppm from the central peak of $CDCl_3$ (77.23 ppm). Infrared (IR) spectra were recorded on a Nicolet 730 FT-IR spectrometer and reported in frequency of the absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Princeton University Mass Spectrometry Facility and UCR Mass Spectrometry Facility.

4.2. Representative procedure for the preparation of hydrazones

To a suspension of *t*-butyl carbazate (5.4 g, 41 mmol) in hexanes (50 mL) was added acetophenone (7.2 mL, 61 mmol) dropwise. The reaction mixture was then heated to reflux for 8 h. After cooling to ambient temperature, the resulting precipitate was collected by suction filtration, washed with additional cold hexanes, and allowed to air dry under aspiration to afford the known hydrazone **2a**[24] (8.8 g, 91%). Other known hydrazones **2c**,[25] **2d**,[26] **2e**,[27] **2f**,[28] and **2g**[28] were also prepared following this procedure.

4.2.1. *N′*-(1-Phenyl-ethylidene)-hydrazinecarboxylic acid benzyl ester (2b). Following the same procedure as **2a**, the reaction of benzylcarbazate (831 mg, 5.0 mmol) with acetophenone (901 mg, 7.5 mmol) in hexane (10 mL) gave hydrazone **2b** (1.1 g, 98%). Recrystallization from EtOH gave analytically pure hydrazone **2b** as flocculent white crystals (1.06 g, 79%). Mp 134–135 °C. IR (film) 3200, 3050, 1700, 1730, 1540, 1230 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (br s, 1H), 7.79 (m, 2H), 7.46 (m, 2H), 7.42 (m, 6H), 5.32 (br s, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 149.1, 138.2, 136.2, 129.5, 128.9, 128.7, 128.6, 126.6, 67.8, 13.2; HRMS (DEI-MS) [M^+] Calcd for $C_{12}H_{16}N_2O_2$ 268.1212, found 268.1205.

4.2.2. *N′*-(1-Ethyl-propylidene)-hydrazinecarboxylic acid benzyl ester (2h). Following the same procedure as **2a**, the reaction of benzylcarbazate (0.83 g, 5.0 mmol) with 3-pentanone (0.79 mL, 0.65 g, 7.5 mmol) in hexane (10 mL) gave hydrazone **2h** (1.1 g, 98%) as a white solid. The product was used without further purification. Mp 39–43 °C. IR (film) 3250, 2970, 1720, 1530, 1460, 1230, 1040 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.39 (m, 5H), 5.25 (s, 2H), 2.35 (q, J=8.0 Hz, 2H), 2.20 (q, J=8.0 Hz, 2H), 1.14 (t, J=7.5 Hz, 3H), 1.10 (t, J=8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 154.2, 136.2, 128.8, 128.7, 128.6, 67.6, 30.2, 21.6, 11.3, 9.8; HRMS (DCI-MS) [M+] Calcd for $C_{13}H_{19}N_2O_2$ 235.1447, found 235.1442.

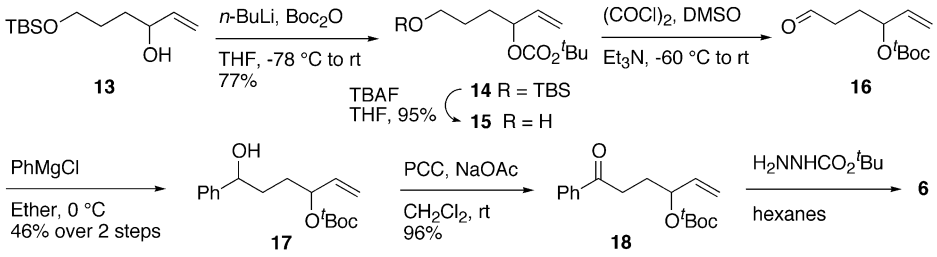
4.2.3. *N′*-[1-(4-Bromo-phenyl)-ethylidene]-hydrazinecarboxylic acid *t*-butyl ester (2i). Following the same procedure as **2a**, the reaction of *t*-butyl carbazate (661 mg, 5.0 mmol) with *p*-bromoacetophenone (1.49 g, 7.5 mmol) in hexane (10 mL) gave hydrazone **2g** (1.07 g, 68%) as a white solid after recrystallization from EtOH. Mp 167–168 °C. IR (film) 3190, 2980, 1730, 1700, 1530, 1140 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (br s, 1H), 7.62 (d, J=6.8 Hz, 2H), 7.45 (d, J=7.6 Hz, 2H), 2.13 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 146.3, 137.1, 131.6, 128.0, 123.6, 81.8, 28.5, 12.6; HRMS (DCI-MS) [M+] Calcd for $C_{13}H_{18}N_2O_2Br$ 313.0552, found 313.0540.

4.2.4. *N′*-Pent-4-ynylidene-hydrazinecarboxylic acid *t*-butyl ester (2j). To a solution of hex-5-ynal[29] (192 mg, 2.0 mmol) was added *t*-butyl carbazate (264 mg, 2.0 mmol). The reaction mixture was allowed to stir at room temperature until deemed complete by TLC. At this time, the reaction mixture was diluted with EtOAc, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude material by chromatography on deactivated (Et_3N) silica gel (4:1, then 2:1 hexanes/EtOAc), gave the desired hydrazone **2j** (172 mg, 41%) as a white crystalline solid. Mp 93–95 °C. IR (film) 3291, 3248, 3046, 2979, 2932, 1707, 1537, 1368, 1251, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (br s, 1H), 7.25 (t, J=5.0 Hz, 1H), 2.50 (m, 2H), 2.39 (m, 2H), 1.97 (t, J=2.4 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 145.1, 83.0, 81.4, 69.6, 31.2, 28.5, 16.4; HRMS (DCI-MS) [M+] Calcd for $C_{10}H_{17}N_2O_2$ 197.1290, found 197.1292.

4.3. General procedure for the preparation of allylic carbonates

To a solution of allylic alcohol in dry THF at −78 °C was added *n*-BuLi dropwise. After stirring for 30 min, a solution of Boc_2O in THF was added. The reaction mixture was allowed to warm to room temperature, and was then quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic phases were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography gave the pure allylic carbonates **1a–c**.[30]

4.3.1. Carbonic acid *t*-butyl ester 1,1-dimethyl-allyl ester (1d). Following the general procedure, the reaction of 2-methyl-but-3-en-2-ol (1.78 g, 20.7 mmol) with Boc_2O (4.51 g, 20.7 mmol) and *n*-BuLi (2.5 M in hexane, 9.1 mL, 22.7 mmol) in dry THF (40 mL) gave the desired allylic carbonate **1d** (2.75 g, 71%) as a clear, colorless oil. IR (film) 2982, 2936, 1741, 1368, 1285, 1126 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.13 (dd, J=17.5, 11.0 Hz, 1H), 5.21 (d, J=18.0 Hz, 1H), 5.14 (d, J=11.0 Hz, 1H), 1.51 (s, 3H), 1.49 (s, 9H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$):



Scheme 2. Preparation of hydrazone **6**.

δ 152.1, 142.5, 113.2, 81.7, 81.6, 28.1, 26.6; LRMS (EI) *m/z* 130 (53), 85 (33), 71 (100).

4.3.2. Carbonic acid *t*-butyl ester 4-(*t*-butyl-dimethyl-silanyloxy)-1-vinyl-butyl ester (14). To a solution of 6-(*t*-butyl-dimethyl-silanyloxy)-hex-1-en-3-ol[31] (**13**, 5.9 g, 26 mmol) in dry THF (25 mL) under argon at −78 °C was added *n*-BuLi (2.5 M in hexane, 11.3 mL, 28 mmol) dropwise. After stirring 3 min, a solution of Boc_2O (5.6 g, 26 mmol) in THF (25 mL) was added. The reaction was allowed to proceed at −78 °C for 30 min, and then the ice bath was removed. On warming to room temperature, the reaction was quenched with saturated NH_4Cl, and the bulk of the THF was concentrated in vacuo. The remaining phases were partitioned between EtOAc and water, and the aqueous layer was extracted with additional EtOAc. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting crude oil was purified by chromatography (hexane/EtOAc, 40:1→20:1) to give the desired allylic carbonate **14** (6.6 g, 77%) as a colorless, sticky oil. IR (film) 3087, 2955, 2858, 1742, 1276, 1235, 1169, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.77 (ddd, J=17.2, 10.4, 6.4 Hz, 1H), 5.25 (d, J=17.2 Hz, 1H), 5.16 (d, J=10.8 Hz, 1H), 4.98 (q, J=6.7 Hz, 1H), 3.60 (m, 2H), 1.67 (m, 1H), 1.54 (m, 2H), 1.45 (s, 9H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 163.6, 117.3, 82.1, 78.0, 62.8, 30.9, 28.5, 28.0, 26.1, 18.5, −5.1.

4.3.3. Carbonic acid *t*-butyl ester 4-hydroxy-1-vinyl-butyl ester (15). To a solution of allylic carbonate **14** (6.5 g, 20 mmol) in dry THF (20 mL) under argon was added TBAF (1.0 M in THF, 25 mL, 25 mmol). The reaction was complete (by TLC) after 4 h, at which time saturated NH_4Cl was added. The aqueous layer was then extracted with EtOAc, and the combined organic layers were then washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude oil. Purification by chromatography (hexane/EtOAc, 4:1→2:1) gave primary alcohol **15** (4.0 g, 95%) as a clear, colorless oil. IR (film) 3363, 2981, 2937, 2874, 1740, 1370, 1277, 1255, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.78 (ddd, J=17.2, 10.4, 6.8 Hz, 1H), 5.26 (d, J=17.2 Hz, 1H), 5.17 (d, J=10.4 Hz, 1H), 5.00 (q, J=6.8 Hz, 1H), 3.64 (q, J=6.0 Hz, 1H), 1.5–1.8 (m, 4H), 1.45 (s, 9H), 1.42 (t, J=5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 117.4, 82.3, 77.8, 62.6, 30.8, 28.4, 28.0.

4.3.4. Carbonic acid *t*-butyl ester 4-oxo-1-vinyl-butyl ester (16). To a solution of oxalyl chloride (0.74 mL, 8.5 mmol) in dry DCM (20 mL) under argon at −60 °C was added a solution of DMSO (1.2 mL, 17 mmol) in DCM (5 mL). After 5 min, a solution of the alcohol **15** (1.5 g, 6.8 mmol) in DCM (10 mL) was added. After a further 15 min, Et_3N (3.7 mL, 34 mmol) was added, and the reaction mixture then allowed to warm to room temperature. H_2O was then added, and the aqueous layer was extracted with additional DCM. The combined DCM layers were successively washed with 0.1 M HCl, H_2O, saturated $NaHCO_3$, H_2O, and brine; dried over Na_2SO_4; and concentrated in vacuo to give aldehyde **16** (1.40 g, 96%) as an orange oil. The crude product was used without further purification in the subsequent Grignard addition. IR (film) 2928, 2936, 2826, 2727, 1740, 1370, 1275, 1255, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.77 (s, 1H), 5.77 (ddd, J=17.1, 10.5, 6.3 Hz, 1H), 5.30 (d, J=17.4 Hz, 1H), 5.22 (d, J=10.5 Hz, 1H), 5.04 (q, J=6.1 Hz, 1H), 2.54 (t, J=7.4 Hz, 2H), 1.98 (q, J=7.0 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 153.0, 135.7, 117.9, 82.5, 76.8, 39.6, 28.0, 26.6.

4.3.5. Carbonic acid *t*-butyl ester 4-hydroxy-4-phenyl-1-vinyl-butyl ester (17). To a solution of the crude aldehyde **16** (1.4 g, 6.5 mmol) in dry Et_2O (7 mL) under argon at 0 °C was added PhMgCl (1.8 M in THF, 4.5 mL, 8.2 mmol) dropwise. The reaction was completed within 15 min (by TLC), and then quenched by addition of saturated NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic phases were washed with H_2O, saturated $NaHCO_3$, H_2O, and brine; dried over Na_2SO_4; and concentrated in vacuo to give a crude yellow oil. Purification by chromatography (hexanes/EtOAc, 7.5:1→5:1) gave the desired alcohol **17** (0.91 g, 46% over 2 steps) as a clear, colorless oil. The alcohol was characterized as a mixture of diastereomers. IR (film) 3416, 2980, 2934, 2868, 1739, 1369, 1276, 1255, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 4H), 7.25 (m, 1H), 5.74 (ddd, J=17.2, 10.8, 6.8 Hz, 1H), 5.23 (d, J=17.6 Hz, 1H), 5.16 (d, J=10.4 Hz, 1H), 5.15 (d, J=10.4 Hz, 1H; diastereomer), 5.00 (m, 1H), 4.66 (m, 1H), 1.95 (d, J=3.6 Hz, 1H), 1.65–1.85 (m, 3H), 1.60 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 144.6, 136.3, 128.7, 127.8, 126.0 (diastereomer), 126.0, 117.5, 82.2, 78.0, 77.7 (diastereomer), 74.4, 74.3 (diastereomer), 34.8, 34.5 (diastereomer), 30.8, 30.6 (diastereomer), 28.0.

4.3.6. Carbonic acid *t*-butyl ester 4-oxo-4-phenyl-1-vinyl-butyl ester (18). To a suspension of PCC (436 mg, 2.0 mmol) and NaOAc (33 mg, 0.40 mmol) in DCM (2 mL) was added a solution of alcohol **17** (394 mg, 1.35 mmol) in DCM (2 mL). After 1 h, an additional 145 mg of PCC was added, and the stirring was continued

for an hour before 20 mL of Et_2O was added. The reaction mixture was then filtered through florisil and concentrated in vacuo to give the crude ketone **18** (377 mg, 96%) as a clear, colorless oil. This material was used for the next reaction without further purification. IR (film) 3087, 3082, 2980, 2934, 1740, 1688, 1369, 1275, 1255, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, $J=7.8$ Hz, 2H), 7.56 (t, $J=7.4$ Hz, 1H), 7.45 (t, $J=7.6$ Hz, 2H), 5.84 (ddd, $J=17.1$, 10.5, 6.3 Hz, $J=1H$), 5.32 (d, $J=17.1$ Hz, 1H), 5.23 (d, $J=10.5$ Hz, 1H), 5.13 (q, $J=6.3$ Hz, 1H), 3.06 (t, $J=7.5$ Hz, 2H), 2.12 (q, $J=7.1$ Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 153.1, 137.0, 136.1, 133.3, 128.8, 128.2, 117.6, 82.4, 34.1, 28.6, 28.0.

4.3.7. Carbonic acid 4-(*t*-butoxycarbonyl-hydrazono)-4-phenyl-1-vinyl-butyl ester *t*-butyl ester (6). To a solution of the crude ketone **18** (370 mg, 1.3 mmol) in hexane (2 mL) was added *t*-butyl carbazate (250 mg, 1.9 mmol). After refluxing overnight, the solution was cooled to room temperature. Concentration of the solvent in vacuo and purification by chromatography (10:1 hexanes/EtOAc) gave three fractions of material: the desired (*E*)-hydrazone **6** (239 mg, 46%), a mixture of (*E*) and (*Z*) isomers (224 mg, 43%), and the undesired (*Z*)-isomer (50 mg, 10%), all as thick colorless liquids. Charaterization of the (*E*)-isomer. IR (film) 3238, 2980, 2933, 1742, 1528, 1494, 1368, 1273, 1252, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.74 (m, 2H), 7.32 (m, 3H), 5.82 (ddd, $J=17.2$, 10.8, 6.4 Hz, 1H), 5.33 (d, $J=17.2$ Hz, 1H), 5.27 (d, $J=10.8$ Hz, 1H), 5.05 (q, $J=6.3$ Hz, 1H), 2.65 (t, $J=8.4$ Hz, 2H), 1.87 (m, 2H), 1.54 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 153.0, 149.8, 137.0, 135.5, 129.4, 128.6, 126.4, 118.3, 82.8, 81.6, 77.0, 60.2, 28.5, 28.0, 21.7; HRMS (EI-MS) [M+] Calcd for $C_{22}H_{32}N_2O_2$ 404.2311, found 404.2294. Characterization of the minor (*Z*)-isomer. IR (film) 3366, 2979, 2933, 1744, 1714, 1483, 1368, 1275, 1255, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (br s, 1H), 7.47 (t, $J=7.2$ Hz, 2H), 7.40 (t, $J=7.2$ Hz, 1H), 7.17 (d, $J=6.8$ Hz, 2H), 5.73 (ddd, $J=17.2$, 10.8, 6.8 Hz, 1H), 5.23 (d, $J=17.2$ Hz, 1H), 5.15 (d, $J=10.4$ Hz, 1H), 5.00 (q, $J=6.4$ Hz, 1H), 2.60 (m, 2H), 1.87 (q, $J=7.6$ Hz, 2H), 1.43 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 152.8, 136.1, 133.8, 129.8, 129.6, 127.1, 117.5, 82.2, 81.3, 77.5, 34.2, 31.0, 28.4, 28.0.

4.3.8. *N′*-(3-Phenyl-propyl)-hydrazinecarboxylic acid *t*-butyl ester (3e). To a solution of *N′*-(3-phenyl-propyl-idene)-hydrazinecarboxylic acid *t*-butyl ester **2f** (267 mg, 1.1 mmol) in MeOH (5 mL) at 0 °C was added $NaCNBH_3$ (135 mg, 2.2 mmol), along with a few drops of AcOH to achieve a pH of 4–5. After 15 min, the ice bath was removed. Upon completion of the reaction (by TLC), saturated $NaHCO_3$ was added, and the aqueous layer was extracted with EtOAc. The combined EtOAc layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a colorless oil. Purification by chromatography (hexanes/EtOAc, 4:1 → 2:1) gave alkyl hydrazide **3e** (114 mg, 46%). IR (film) 3316, 2977, 2934, 2863, 1711, 1454, 1367, 1284, 1234, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 2H), 7.17 (m, 3H), 6.01 (br s, 1H), 3.95 (br s, 1H), 2.87 (t, $J=8.7$ Hz, 2H), 2.67 (t, $J=7.8$ Hz, 2H), 1.76 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 142.2, 128.6, 128.6, 126.0, 80.7, 51.7, 33.5, 29.7, 28.6; HRMS (EI-MS) [$M^+ - i$-C_4H_8] Calcd for $C_{10}H_{14}N_2O_2$ 194.1055, found 194.1052.

4.4. Representative procedure for allylic amination

To a solution of hydrazone **2a** (70 mg, 0.30 mmol) and allylic carbonate **1a** (40 mg, 0.20 mmol) in dry THF (0.2 mL) under argon was added Et_2Zn (1.0 M in hexanes, 0.15 mL, 0.15 mmol). The resulting solution was allowed to stir at 25 °C for 8 h to ensure complete consumption of Et_2Zn. After this time, NH_4I (29 mg, 0.20 mmol) was added, followed by a solution of [Ir(COD)Cl_2] (6.7 mg, 5 mol%) and pyridine (1.6 μL, 10 mol%) in THF (0.2 mL). After the reaction was deemed complete by TLC (typically less than 30 min), the reaction mixture was concentrated in vacuo and the resulting residue was purified by flash column chromatography to give the desired allylic amination product **4a** (56 mg, 89%) as a clear, colorless oil.

4.4.1. *N′*-(1-Phenyl-ethylidene)-*N*-(1-vinyl-butyl)-hydrazinecarboxylic acid *t*-butyl ester (4a). IR (film) 2960, 2930, 1690, 1370, 1300, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.81 (m, 2H), 7.39 (m, 3H), 6.04 (br m, 1H), 5.22 (d, $J=17.4$ Hz, 1H), 5.13 (dq, $J=10.2$, 0.9 Hz, 1H), 4.68 (br m, 1H), 2.22 (s, 3H), 1.30–1.74 (m, 4H), 1.46 (s, 9H), 0.92 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.4, 138.4, 138.1, 130.3, 128.5, 127.2, 116.5, 80.8, 62.5, 34.9, 28.7, 19.7, 17.3, 14.2; HRMS (DCI-MS) [M+] Calcd for $C_{19}H_{29}N_2O_2$ 317.2229, found 317.2221.

4.4.2. *N′*-(1-Phenyl-ethylidene)-*N*-(1-vinyl-butyl)-hydrazinecarboxylic acid benzyl ester (4b). Following the representative procedure, the reaction of hydrazone **2b** (80 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **4b** (60 mg, 86%) as a clear, colorless oil. IR (film) 3066, 3033, 2958, 2872, 1703, 1283 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, $J=7.0$ Hz, 2H), 7.43 (m, 3H), 7.36 (m, 5H), 6.05 (br m, 1H), 5.21 (m, 4H), 4.80 (br m, 1H), 2.20 (s, 3H), 1.76 (m, 1H), 1.62 (m, 1H), 1.36 (m, 2H), 0.93 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 153.1, 138.0, 137.6, 136.7, 130.6, 128.8, 128.6, 128.3, 127.2, 116.9, 67.6, 62.2, 34.7, 19.7, 17.3, 14.2; HRMS (DCI-MS) [M+] Calcd for $C_{22}H_{27}N_2O_2$ 351.2072, found 351.2074.

4.4.3. *N′*-(1-Phenyl-ethylidene)-*N*-(1-vinyl-butyl)-*N*-*p*-toluenesulfonylhydrazine (4c). Following the representative procedure, the reaction of hydrazone **2c** (86 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **4c** (68 mg, 92%) as a clear, colorless oil. IR (film) 3069, 3028, 2959, 2931, 2872, 1959, 1351, 1296, 1163, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, $J=7.0$ Hz, 2H), 7.67 (d, $J=7.0$ Hz, 2H), 7.52 (t, $J=7.5$ Hz, 1H), 7.47 (t, $J=7.5$ Hz, 2H), 7.27 (d, $J=8.0$ Hz, 2H), 5.68 (ddd, $J=18.5$, 10.5, 7.5 Hz, 1H), 4.93 (d, $J=17.5$ Hz, 1H), 4.83 (d, $J=10.5$ Hz, 1H), 4.43 (m, 1H), 2.66 (s, 3H), 2.45 (s, 3H), 1.33 (m, 4H), 0.88 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.8, 143.7, 137.6, 135.5, 135.1, 131.3, 129.3, 129.2, 128.7, 127.6, 117.2, 65.0, 35.6, 21.9, 19.6, 18.3, 14.0; HRMS (EI-MS) [M+] Calcd for $C_{21}H_{26}N_2O_2S$ 370.1715, found 370.1707.

4.4.4. Acetic acid *N′*-(1-phenyl-ethylidene)-*N*-(1-vinyl-

butyl)-hydrazide (4d). Following the representative procedure, the reaction of hydrazone **2d** (53 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave of **4d** (9 mg, 17%) as a clear, colorless oil. IR (film) 3072, 2959, 2931, 2872, 1651, 1446, 1379, 1301 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.20–7.40 (m, 5H), 5.82 (m, 1H), 5.27 (d, $J=18.0$ Hz, 1H), 5.16 (d, $J=10.5$ Hz, 1H), 4.40 (br m, 1H), 2.33 (s, 3H), 1.88 (s, 3H), 1.81 (m, 1H), 1.63 (m, 1H), 1.40 (m, 2H), 0.96 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 136.6, 131.5, 128.8, 128.4, 127.3, 117.9, 59.7, 33.8, 21.9, 19.7, 17.2, 14.1; HRMS (EI-MS) [M+] Calcd for $C_{16}H_{22}N_2O$ 258.17321, found 258.1719.

4.4.5. N'-Benzylidene-*N*-(1-vinyl-butyl)-hydrazinecarboxylic acid *t*-butyl ester (4e). Following the representative procedure, the reaction of hydrazone **2e** (66 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **4e** (53 mg, 88%) as a clear, colorless oil. IR (film) 3078, 2961, 2933, 2873, 1699, 1368, 1292, 1156 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.90 (br s, 1H), 7.71 (d, $J=7.5$ Hz, 2H), 7.39 (m, 3H), 6.06 (ddd, $J=17.5$, 10.5, 7.0, 1H), 5.19 (d, $J=17.0$ Hz, 1H), 4.82 (q, $J=7.0$ Hz, 1H), 1.94 (m, 1H), 1.67 (m, 1H), 1.56 (s, 9H), 1.37 (m, 2H), 0.96 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 151.6, 138.6, 136.1, 129.8, 128.7, 127.4, 115.8, 81.5, 62.8, 35.0, 28.6, 18.2, 14.0; HRMS (FAB-MS) [M+] Calcd for $C_{18}H_{26}N_2O_2$ 302.1994, found 302.2007.

4.4.6. N'-(3-Phenyl-propylidene)-*N*-(1-vinyl-butyl)-hydrazinecarboxylic acid *t*-butyl ester (4f). Following the representative procedure, the reaction of hydrazone **2f** (74 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **4f** (54 mg, 82%) as a clear, colorless oil. IR (film) 3064, 3027, 2960, 2932, 2873, 1697, 1454, 1367, 1294, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (t, $J=5.1$ Hz, 1H), 7.28 (m, 2H), 7.20 (m, 3H), 5.88 (ddd, $J=16.8$, 11.1, 6.9 Hz, 1H), 5.09 (d, $J=17.1$ Hz, 1H), 5.08 (d, $J=11.1$ Hz, 1H), 4.59 (dt, $J=8.7$, 6.8 Hz, 1H), 2.88 (t, $J=7.6$ Hz, 2H), 2.67 (m, 2H), 1.66 (m, 1H), 1.48 (m, 1H), 1.47 (s, 9H), 1.25 (sextet, $J=7.4$ Hz, 2H), 0.88 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8, 153.9, 141.3, 138.3, 128.6, 126.2, 115.8, 81.0, 60.8, 35.2, 34.5, 32.5, 28.6, 19.5, 14.0; HRMS (EI-MS) [M+] Calcd for $C_{20}H_{30}N_2O_2$ 330.2307, found 330.2294.

4.4.7. N'-(1-Ethyl-propylidene)-*N*-(1-vinyl-butyl)-hydrazinecarboxylic acid *t*-butyl ester (4g). Following the representative procedure, the reaction of hydrazone **2g** (60 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **4g** (49 mg, 86%) as a clear, colorless oil. IR (film) 3077, 2974, 2936, 2875, 1698, 1636, 1460, 1367, 1302, 1253, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.87 (br m, 1H), 5.15 (d, $J=17.4$ Hz, 1H), 5.09 (d, $J=10.2$ Hz, 1H), 4.53 (m, 1H), 2.39 (q, $J=7.5$ Hz, 2H), 2.24 (m, 2H), 1.20–1.60 (m, 4H), 1.43 (s, 9H), 1.34 (t, $J=7.5$ Hz, 3H), 1.02 (t, $J=7.5$ Hz, 3H), 0.90 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; imine carbonyl not observed due to quadrupolar broadening): δ 152.9, 137.8, 116.6, 80.3, 61.1, 34.4, 28.6, 28.5, 25.0, 24.1, 19.7, 14.1, 11.5, 10.4; HRMS (EI-MS) [M+] Calcd for $C_{16}H_{30}N_2O_2$ 282.2307, found 282.2295.

4.4.8. N'-(1-Ethyl-propylidene)-*N*-(1-vinyl-butyl)-hydrazinecarboxylic acid benzyl ester (4h). Following the representative procedure, the reaction of hydrazone **2h** (60 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **4h** (61 mg, 75%) as a clear, colorless oil. IR (film) 3068, 3033, 2961, 2936, 2874, 1702, 1287 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H), 5.86 (br m, 1H), 5.15 (d, $J=17.6$ Hz, 1H), 5.09 (m, 3H), 4.60 (m, 1H), 2.36 (q, $J=7.6$ Hz, 2H), 2.19 (m, 2H), 1.60 (m, 1H), 1.51 (m, 1H), 1.26 (sextet, $J=7.2$ Hz, 2H), 1.08 (t, $J=7.6$ Hz, 3H), 0.94 (t, $J=7.6$ Hz, 3H), 0.87 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.2, 153.5, 137.4, 136.8, 128.6, 128.3, 128.2, 117.0, 67.4, 61.4, 34.4, 28.5, 24.4, 19.6, 14.1, 11.3, 10.3; HRMS (EI-MS) [M+] Calcd for $C_{19}H_{28}N_2O_2$ 316.2151, found 316.2144.

4.4.9. N'-[1-(4-Bromo-phenyl)-ethylidene]-*N*-(1-vinyl-butyl)-hydrazinecarboxylic acid *t*-butyl ester (4i). Following the representative procedure, the reaction of hydrazone **2i** (94 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **4i** (32 mg, 41%) as a clear, colorless oil. IR (film) 2961, 2931, 2873, 1699, 1304, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, $J=8.5$ Hz, 2H), 7.53 (d, $J=8.5$ Hz, 2H), 6.04 (br m, 1H), 5.23 (d, $J=17.5$ Hz, 1H), 5.16 (d, $J=10.5$ Hz, 1H), 4.69 (br m, 1H), 2.21 (s, 3H), 1.72 (m, 1H), 1.59 (m, 1H), 1.49 (s, 9H), 1.35 (m, 2H), 0.94 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 152.2, 138.0, 137.2, 131.7, 128.7, 124.8, 116.5, 81.0, 62.2, 34.9, 28.6, 19.7, 17.1, 14.2; HRMS (EI-MS) [M+] Calcd for $C_{19}H_{27}N_2O_2Br$ 394.1255, found 394.1260.

4.4.10. N'-Pent-4-ynylidene-*N*-(1-vinyl-butyl)-hydrazinecarboxylic acid *t*-butyl ester (4j). Following the representative procedure, the reaction of hydrazone **2j** (42 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **4j** (40 mg, 71%) as a clear, colorless oil. IR (film) 3313, 2961, 2933, 2873, 1697, 1368, 1293, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (t, $J=4.4$ Hz, 1H), 5.90 (ddd, $J=17.2$, 10.4, 6.8 Hz, 1H), 5.08 (m, 2H), 4.60 (m, 1H), 2.53 (m, 2H), 2.42 (m, 2H), 1.94 (t, $J=2.8$ Hz, 1H), 1.74 (m, 1H), 1.52 (m, 1H), 1.45 (s, 9H), 1.26 (sextet, $J=7.4$ Hz, 2H), 0.88 (t, $J=7.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 153.7, 138.3, 115.8, 83.6, 81.2, 69.0, 61.0, 34.6, 62.7, 28.6, 19.4, 15.7, 14.0; HRMS (DCI-MS) [M+] Calcd for $C_{16}H_{26}N_2O_2$ 278.1994, found 278.1998.

4.4.11. *N*-(1-Phenyl-allyl)-N'-(1-phenyl-ethylidene)-hydrazinecarboxylic acid *t*-butyl ester (4k). Following the representative procedure, the reaction of hydrazone **2a** (70 mg, 0.30 mmol) with allylic carbonate **1b** (47 mg, 0.20 mmol) gave **4k** (63 mg, 90%) as a clear, colorless oil. IR (film) 3062, 2976, 2929, 1696, 1366, 1300, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, $J=6.4$ Hz, 2H), 7.44 (d, $J=7.6$ Hz, 2H), 7.33 (m, 5H), 7.22 (t, $J=7.6$ Hz, 1H), 6.34 (ddd, $J=17.6$, 9.6, 7.2 Hz, 1H), 5.89 (d, $J=6.8$ Hz, 1H), 5.29 (d, $J=16.8$ Hz, 1H), 5.28 (d, $J=10.8$ Hz, 1H), 2.14 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 152.2, 140.4, 138.2, 136.5, 130.3, 128.4, 128.2, 128.4, 127.4, 127.2, 118.0, 81.1, 65.7, 28.6, 17.4; HRMS (DCI-MS) [M+] Calcd for $C_{22}H_{27}N_2O_2$ 351.2072, found 351.2069.

4.4.12. *N*-(1-Phenethyl-allyl)-*N′*-(1-phenyl-ethylidene)-hydrazinecarboxylic acid *t*-butyl ester (4l). Following the representative procedure, the reaction of hydrazone **2a** (70 mg, 0.30 mmol) with allylic carbonate **1c** (52 mg, 0.20 mmol) gave **4l** (63 mg, 83%) as a clear, colorless oil. IR (film) 3026, 2976, 2930, 1700, 1366, 1302, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (m, 2H), 7.40 (m, 3H), 7.26 (m, 2H), 7.18 (m, 3H), 6.09 (br m, 1H), 5.23 (d, J=17.1 Hz, 1H), 5.17 (d, J=11.1 Hz, 1H), 4.70 (m, 1H), 2.63 (t, J=7.8 Hz, 2H), 2.26 (s, 3H), 2.06 (m, 1H), 1.91 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 152.4, 142.2, 138.3, 137.8, 130.4, 128.8, 128.6, 128.5, 127.2, 126.1, 116.9, 81.0, 61.9, 34.8, 32.9, 28.6, 17.4; HRMS (EI-MS) [M+] Calcd for $C_{24}H_{30}N_2O_2$ 378.2307, found 378.2288.

4.4.13. *N′*-(1-Vinyl-butyl)-hydrazinecarboxylic acid *t*-butyl ester (5a). Following the representative procedure, the reaction of hydrazine **3a** (40 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **5a** (40 mg, 93%) as a clear, colorless oil. IR (film) 3320, 2960, 1720, 1460, 1370, 1280, 1250, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.10 (br s, 1H), 5.55 (ddd, J=8.4, 10.0, 6.8 Hz, 1H), 5.12 (d, J=17.2 Hz, 1H), 5.11 (d, J=10.4 Hz, 1H), 3.89 (br s, 1H), 3.34 (br m, 1H), 1.41 (s, 9H), 1.2–1.4 (m, 4H), 0.87 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 139.4, 117.9, 80.5, 63.8, 35.3, 28.6, 19.1, 14.3; HRMS (DCI-MS) [M+] Calcd for $C_{11}H_{23}N_2O_2$ 215.1760, found 215.1759.

4.4.14. *N′*-(1-Vinyl-butyl)-hydrazinecarboxylic acid benzyl ester (5b). Following the representative procedure, the reaction of hydrazine **3b** (50 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **5b** (43 mg, 86%) as a clear oil. IR (film) 3320, 3070, 3030, 2960, 2930, 2870, 1720, 1460, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 6.21 (br s, 1H), 5.58 (dt, J=17.7, 9.0 Hz, 1H), 5.15 (m, 4H), 3.96 (br s, 1H), 3.39 (br s, 1H), 1.47 (m, 1H), 1.33 (m, 3H), 0.90 (t, J=6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4, 139.1, 136.4, 128.8, 128.5, 128.4, 118.3, 67.3, 63.9, 35.2, 19.1, 14.3; HRMS (DCI-MS) [M+] Calcd for $C_{14}H_{21}N_2O_2$ 249.1603, found 249.1596.

4.4.15. *N′*-(1-Vinyl-butyl)-*N*-*p*-toluenesulfonyl hydrazine (5c). Following the representative procedure, the reaction of hydrazine **3c** (56 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **5c** (31 mg, 57%) as a clear, colorless oil. IR (film) 3230, 2950, 2930, 2870, 1320, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, J=8.5 Hz, 2H), 7.33 (d, J=9.0 Hz, 2H), 6.01 (br s, 1H), 5.37 (dt, J=17.0, 10.0 Hz, 1H), 5.20 (dd, J=10.5, 1.5 Hz, 1H), 5.02 (d, J=17.0 Hz, 1H), 3.80 (br s, 1H), 2.87 (q, J=8.5 Hz, 1H), 2.45 (s, 3H), 1.36 (m, 1H), 1.22 (m, 3H), 0.80 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 137.5, 135.9, 129.8, 128.5, 119.5, 63.6, 34.9, 21.8, 19.0, 14.0; HRMS (DCI-MS) [M+] Calcd for $C_{13}H_{21}N_2O_2S$ 269.1323, found 169.1334.

4.4.16. *N′*-(1-Phenyl-allyl)-hydrazinecarboxylic acid *t*-butyl ester (5e). Following the representative procedure, the reaction of hydrazine **3a** (40 mg, 0.30 mmol) with allylic carbonate **1b** (47 mg, 0.20 mmol) gave **5e** (44 mg, 88%) as a clear oil. IR (film) 3315, 2978, 1715, 1454, 1367, 1277, 1253, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.35 (m, 5H), 6.00 (br s, 1H), 5.92 (ddd, J=17.6, 10.4, 7.6 Hz, 1H), 5.27 (d, J=17.2 Hz, 1H), 5.16 (d, J=10.0 Hz, 1H), 4.62 (br d, J=6.4 Hz, 1H), 4.21 (br s, 1H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 140.7, 138.5, 128.8, 128.1, 127.9, 117.5, 80.7, 67.4, 28.6; HRMS (DCI-MS) [M+] Calcd for $C_{14}H_{21}N_2O_2$ 249.1603, found 249.1612.

4.4.17. *N′*-(1,1-Dimethyl-allyl)-hydrazinecarboxylic acid *t*-butyl ester (5f). Following the representative procedure, the reaction of hydrazine **3a** (40 mg, 0.30 mmol) with allylic carbonate **1d** (37 mg, 0.20 mmol) gave **5f** (33 mg, 82%) as a sticky colorless oil. IR (film) 3270, 3225, 2980, 2930, 1710, 1455, 1365, 1280, 1255, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.91 (br s, 1H), 5.80 (dd, J=17.0, 10.5 Hz, 1H), 5.10 (d, J=17.0 Hz, 1H), 5.09 (d, J=10.5 Hz, 1H), 3.82 (br s, 1H), 1.46 (s, 9H), 1.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.2, 144.0, 113.7, 80.4, 58.6, 28.6, 24.8; HRMS (DCI-MS) [M+] Calcd for $C_{10}H_{21}N_2O_2$ 201.1603, found 201.1599.

4.4.18. *N′*-(3-Phenyl-propyl)-*N′*-(1-vinyl-butyl)-hydrazinecarboxylic acid *t*-butyl ester (5g). Following the representative procedure, the reaction of hydrazine **3e** (52 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **5g** (44 mg, 86%) as a clear, colorless oil. IR (film) 3234, 3064, 3026, 2959, 2931, 2871, 1743, 1695, 1392, 1633, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.10–7.30 (m, 5H), 5.56 (ddd, J=17.4, 10.5, 9.0 Hz, 1H), 5.22 (dd, J=10.2, 2.0 Hz, 1H), 5.10 (dd, J=17.1, 1.8 Hz, 1H), 4.90 (br s, 1H), 3.08 (br m, 1H), 2.72 (br m, 3H), 2.53 (br m, 1H), 1.78 (m, 2H), 1.64 (m, 1H), 1.46 (m, 1H), 1.46 (s, 9H), 1.38 (m, 2H), 0.90 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 142.7, 136.1, 128.8, 128.4, 125.8, 118.9, 79.6, 69.0, 54.5, 34.3, 33.4, 29.2, 28.6, 19.6, 14.3; HRMS (EI-MS) [M+] Calcd for $C_{20}H_{32}N_2O_2$ 332.2463, found 332.2467.

4.4.19. *N′*-Isopropyl-*N′*-(1-vinyl-butyl)-hydrazinecarboxylic acid *t*-butyl ester (5i). Following the representative procedure, the reaction of hydrazine **3f**[32] (75 mg, 0.30 mmol) with allylic carbonate **1a** (40 mg, 0.20 mmol) gave **5g** (56 mg, 85%) as a colorless, viscous oil. Characterized as a mixture of rotamers. IR (film) 3236, 3126, 3075, 2968, 2933, 2873, 1750, 1695, 1392, 1365, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.68 (m, 1H), 5.10 (m, 3H), 2.8–8.2 (br m, 2H), 1.55 (m, 1H), 1.41 (s, 9H), 1.41 (m, 1H), 1.33 (m, 2H), 1.00 (d, J=6.3 Hz, 6H), 0.84 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 156.3, 139.0, 137.3, 135.8, 118.3, 117.7, 116.7, 79.9, 79.4, 68.1, 66.2, 64.1, 54.4, 52.7, 51.2, 34.6, 34.3, 28.5, 28.0, 21.3, 19.4, 14.3; HRMS (EI-MS) [M+] Calcd for $C_{14}H_{28}N_2O_2$ 256.2150, found 256.2138.

4.4.20. 3-Phenyl-6-vinyl-5,6-dihydro-4H-pyridazine-1-carboxylic acid *t*-butyl ester (7). Following the representative procedure, the reaction of hydrazine **6** (40 mg, 0.10 mmol) gave **7** (25 mg, 88%) as a clear, colorless oil. IR (film) 3083, 3062, 2978, 2933, 1727, 1698, 1397, 1333, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, 8.2 Hz, 2H), 7.32 (m, 3H), 5.72 (ddd, J=16.9, 10.5, 4.0 Hz, 1H), 5.14 (d, J=10.5 Hz, 1H), 5.01 (d, J=16.3 Hz, 1H), 4.99 (br m, 1H), 2.62 (d, J=17.7, 5.1 Hz, 1H), 2.38 (ddd, J=17.9, 12.9, 6.9 Hz, 1H), 1.99 (m, 2H), 1.54 (s, 9H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 153.4, 146.0, 138.0, 135.2, 129.0, 128.5, 125.5, 115.9, 81.5, 51.9, 28.5, 21.8, 18.9; HRMS (EI-MS) [M+] Calcd for $C_{17}H_{22}N_2O_2$ 286.1681, found 286.1668.

4.4.21. *N*-(1-Vinyl-butyl)-hydrazinecarboxylic acid benzyl ester (10). To a solution of hydrazone **4b** (35 mg, 0.10 mmol) in EtOH (2 mL) was added 37% HCl dropwise (0.5 mL). After 10 min, the reaction mixture was diluted with H_2O and washed with EtOAc. The aqueous layer was then brought to a basic pH (ca. 14) with NaOH and extracted with EtOAc. The combined EtOAc layers were then dried over Na_2SO_4 and concentrated in vacuo to give a crude residue. Purification by chromatography (hexanes/EtOAc, 4:1) gave hydrazine **10** (17.4 mg, 68%) as a clear, colorless oil. IR (film) 3341, 3223, 6038, 3034, 2958, 2933, 2873, 1699, 1404, 1298, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 5.83 (ddd, J=16.8, 10.8, 6.4 Hz, 1H), 5.15 (s, 2H), 5.09 (d, J=10.4 Hz, 1H), 5.08 (d, J=18.4 Hz, 1H), 4.52 (br m, 1H), 3.71 (br s, 2H), 1.73 (m, 1H), 1.48 (m, 1H), 1.24 (sextet, J=7.4 Hz, 2H), 0.88 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 137.4, 136.7, 128.7, 128.4, 128.2, 116.1, 67.9, 59.5, 33.6, 19.6, 14.0; HRMS (EI-MS) [M+] Calcd for $C_{14}H_{20}N_2O_2$ 248.1524, found 248.1516.

4.4.22. *N′*-(1-Phenyl-ethyl)-*N*-(1-vinyl-butyl)-hydrazinecarboxylic acid benzyl ester (11). To a solution of hydrazone **4b** (70 mg, 0.2 mmol) in MeOH (0.5 mL) at 0 °C was added $NaCNBH_3$ (25 mg, 0.4 mmol), along with a few drops of AcOH to achieve a pH of 4–5. After 15 min, the ice bath was removed. Upon completion of the reaction (by TLC), saturated $NaHCO_3$ was added, and the aqueous layer was extracted with EtOAc. The combined EtOAc layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a colorless oil. Purification by chromatography (hexanes/EtOAc, 10:1) gave alkyl hydrazide **11** (64 mg, 90%) as a clear, sticky oil, which was characterized as a 1:1 mixture of diastereomers. IR (film) 3291, 3065, 3032, 2959, 2931, 2872, 1699, 1454, 1390, 1292, 1095, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 10H), 5.85 (m, 1H), 5.46 (m, 1H), 5.17 (s, 4H), 4.90 (m, 4H), 4.20 (m, 4H), 1.55 (m, 2H), 1.32 (m, 8H), 1.11 (m, 4H), 0.80 (t, J=7.2 Hz, 3H), 0.69 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 144.3, 144.0, 138.2, 137.9, 136.6, 128.8, 128.5, 128.4, 128.3, 128.0, 128.0, 127.6, 116.2, 116.0, 67.8, 67.8, 64.1, 63.1, 59.6, 34.6, 21.8, 21.5, 19.8, 19.7, 14.1, 14.0; HRMS (EI-MS) [M+] Calcd for $C_{22}H_{28}N_2O_2$ 352.2150, found 352.2140.

4.4.23. *N*-(1-Ethyl-butyl)-*N′*-(1-ethyl-propyl)-hydrazinecarboxylic acid *t*-butyl ester (12). Pd/C (ca. 7 mg) was added to a solution of the hydrazone **4g** (35 mg, 0.12 mmol) in EtOH (1 mL), and the reaction mixture was put under a balloon of hydrogen. After 8 h, the reaction was complete on TLC, and the reaction mixture was then filtered through celite. Concentration of the filtrate in vacuo gave dialkyl hydrazine **12** (31 mg, 89%) as a clear colorless oil. IR (film) 2969, 2934, 2875, 1693, 1460, 1366, 1329, 1178, 1152, 1104 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.20 (br s, 1H), 2.40 (q, J=7.3 Hz, 2H), 2.27 (br m, 2H), 1.45 (s, 9H), 1.2–1.8 (m, 8H), 1.15 (t, J=7.5 Hz, 3H), 1.06 (t, J=7.6 Hz, 3H), 0.91 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3, 79.8, 59.8, 35.2, 28.6, 28.4, 26.1, 24.1, 20.0, 14.3, 11.5, 10.4; HRMS (EI-MS) [M+] Calcd for $C_{16}H_{34}N_2O_2$ 286.2620, found 286.2633.

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References and notes

1. *The Chemistry of Hydrazo, Azo and Azoxy Groups*; Patai, S., Ed.; Wiley: New York, 1975.
2. Overberger, C. G.; Anselme, J.-P.; Lombardino, J. G. *Organic Compounds with Nitrogen–Nitrogen Bonds. Hydrazine and Its Derivatives*; The Ronald: New York, 1966; pp 9–20.
3. Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205–213.
4. Gante, J. *Synthesis* **1989**, 405–413.
5. Hutchins, R. O.; Hutchins, M. K. Reduction of C=N to CHNH by Metal Hydrides. In Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: New York, 1991; Vol. 8.
6. Miyabe, H.; Yoshida, K.; Kobayashi, Y.; Matsumura, A.; Takemoto, Y. *Synlett* **2003**, *7*, 1031–1033.
7. Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 4631–4634.
8. Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 896–897.
9. Takeuchi, R.; Shiga, N. *Org. Lett.* **1999**, *1*, 265–267.
10. Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525–9534.
11. Takeuchi, R. *Synlett* **2002**, 1954–1965.
12. Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164–15165.
13. Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797–4800.
14. Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369–4371.
15. Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336–1337.
16. Takeuchi, R.; Kashio, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 263–265.
17. Takeuchi, R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647–8655.
18. Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025–8026.
19. Bartels, B.; Yebra-García, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, 2569–2586.
20. Roberts, J. P.; Lee, C. Manuscript submitted for publication.
21. Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26–47.
22. Calabretta, R.; Gallina, C.; Giordano, C. *Synthesis* **1991**, 536–539.
23. Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447.
24. Baumgarten, H. E.; Chen, P. Y. N.; Taylor, H. W.; Hwang, D. R. *J. Org. Chem.* **1976**, *41*, 3805–3811.
25. Wu, P. L.; Peng, S. Y.; Magrath, J. *Synthesis* **1996**, 249–252.
26. Wu, P. L.; Peng, S. Y.; Magrath, J. *Synthesis* **1995**, 435–438.

27. Ghali, N. I.; Venton, D. L.; Hung, S. C.; Le Breton, G. C. *J. Org. Chem.* **1981**, *46*, 5413.
28. Hendrickson, J. B.; Sternbach, D. D. *J. Org. Chem.* **1975**, *40*, 3450–3452.
29. Smith, A. B.; Leahy, J. W.; Moda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Am. Chem. Soc.* **1992**, *114*, 2995–3007.
30. Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882–7883.
31. Lee, A. H. F.; Chan, A. S. C.; Li, T. *Tetrahedron* **2003**, *59*, 833–840.
32. Wieczerzak, E.; Kozlowska, J.; Lankiewicz, L.; Grzonka, Z. *Pol. J. Chem.* **2002**, *12*, 1693–1698.

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Diversity-generation from an allenoate–enone coupling: syntheses of azepines and pyrimidones from common precursors

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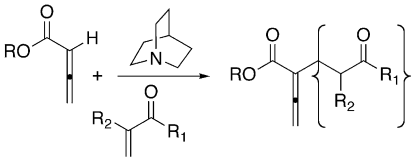
Abstract—Amine-catalyzed coupling reactions of allenoate esters and α,β-unsaturated carbonyls lead to a diverse range of α,α′-disubstituted allenoates. With appropriately substituted monomers, intermolecular reactions can lead to pyrimidone products. Alternatively, with amine substituted allenoates, a 7-*endo-dig* cyclization can be carried out such that a divergent pathway is observed that leads to azepine scaffolds.

1. Introduction

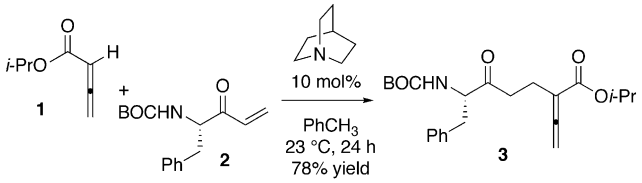
Catalytic reactions that lead to products of different structures from common precursors can be of utility in diversity-oriented syntheses. While five- and six-membered nitrogen-containing heterocycles are arguably the most prevalent azacycles found in natural products and natural product derivatives, the intriguing biological activity of numerous natural products containing seven- and eight-membered azacycles has made them attractive targets for synthesis also.[1,2] Furthermore, the ability to access members of each ring size from a common acyclic precursor seemed to us an important challenge. During our examination of the scope of the quinuclidine-catalyzed addition of allenic esters to α,β-unsaturated carbonyl compounds (Eq. 1),[3,4] we realized that this reaction provided an opportunity to use the allenic ester products as a platform for diversity generation of this type.[5]



(1)

2. Results and discussion

As a first step to achieving 7-membered azacycles, we needed to examine the scope of the allenic ester/enone coupling to include nitrogen functionalized monomers. We thus demonstrated that vinyl ketones derived from *N*-protected amino acids were suitable coupling partners in this reaction. As such, we found that enone **2** could be coupled to allenoate **1** to deliver substituted allenoate **3** in 78% isolated yield under the influence of quinuclidine (10 mol%, Eq. 2).[6]



(2)

The reaction proved efficient for a range of substrates ultimately derived from α-amino acids, as is shown in Table 1. In addition to benzyl substituted α-amino ketone derivative **2**, the isopropyl substituted derivative **4** serves as an excellent substrate affording allenoate **5** in 86% yield (entry 2). Heterocycle-substituted substrates also participate in the reaction. For example, pyrrolidine derivative **6** yields allenoate **7** in 80% yield (entry 3); piperidine analog **8** results in compound **9** in 76% yield (entry 4). 2,5-Disubstitution is also tolerated on the pyrrolidine as compound **10** undergoes conversion to **11** in 80% yield (entry 5).

With the ability to access allenoate-substituted α-amino vinyl ketones from the chiral pool, we set out to show that cyclization of the coupled products could lead to the synthesis of a range of chiral azepines.[7] Following the

Keywords: Heterocycle; Quinuclidine; Azacycle.
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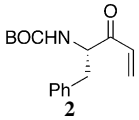
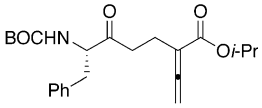
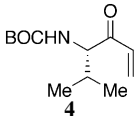
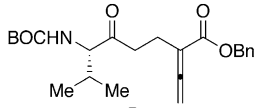
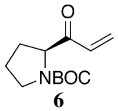
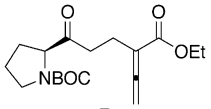
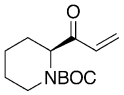
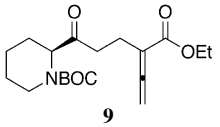
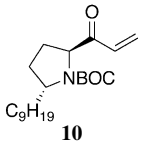
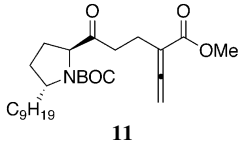
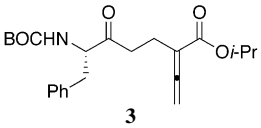
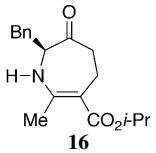
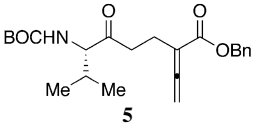
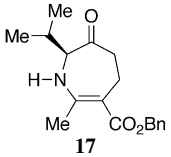
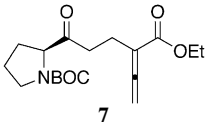
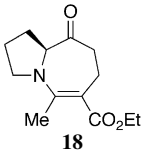
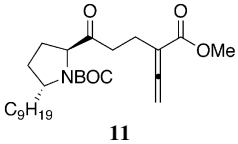
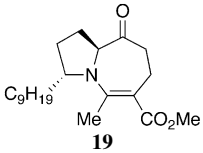
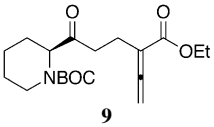
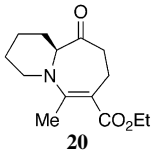
Table 1. Substrate scope for coupling of allenoate esters to α,β-unsaturated carbonyl compounds[a]

Entry	Substrate	Product	Yield[b]
1	 **2**	 **3**	78%
2	 **4**	 **5**	86%
3	 **6**	 **7**	80%
4	 **8**	 **9**	76%
5	 **10**	 **11**	80%

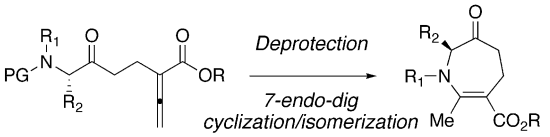
[a] All reactions were conducted at room temperature in $PhCH_3$ for 24 h in the presence of quinuclidine (10 mol %).
[b] Yields refer to isolated yield after silica gel chromatography.

Table 2. Substrate scope for 7-*endo-dig* cyclization to deliver azepines[a]

Entry	Substrate	Product	Yield[b]
1	 **3**	 **16**	90%
2	 **5**	 **17**	95%
3	 **7**	 **18**	97%
4	 **11**	 **19**	96%
5	 **9**	 **20**	82%

[a] BOC-group cleavage was achieved with TFA prior to cyclization. All reactions were then conducted at reflux in CH_3CN for 14 h in the presence of Hünig's base. See Experimental for details.
[b] Yields refer to isolated material.

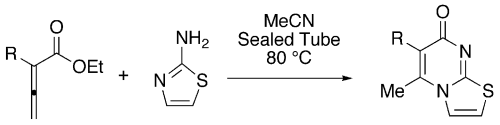
pioneering work of Mukai in this arena,[8] amine deprotection was projected to lead to the desired azepine scaffold through addition of nitrogen to the electron-deficient sp-carbon of the allenic esters. This intramolecular 7-*endo-dig* cyclization, followed by isomerization is depicted in Eq. 3.



(3)

Despite the potential acid-sensitivity of the allenoate moiety, the BOC-protected substrates proved to be excellent precursors to the azepine scaffold. In fact, a one-pot deprotection/cyclization was identified after minor experimentation. The α-amino acid-derived allenes were subjected to standard TFA deprotection conditions (1:1 TFA/CH_2Cl_2, 23 °C, 30 min), followed by reaction concentration to provide the intermediate amine salts. The deprotected residue was then redissolved in acetonitrile, followed by the addition of excess Hünig's base, at which point the solution was heated to reflux for 14 h. After workup, the desired azepines could be isolated without additional purification (Table 2). For example, benzyl-substituted allenoate **3** could be converted to azepine **16** in 90% isolated yield (entry 1). Likewise, isopropyl-substituted derivative **5** delivers azepine **17** in 95% yield (entry 2). The cyclic derivatives were also found to be excellent substrates for the conversion. Pyrrolidines **7** and **11** were converted to the corresponding azepines **18** and **19** in 97% and 96% yield, respectively (entries 3 and 4).[9] In addition, piperidine analog **9** afforded the corresponding 6,7-ring system **20** in 82% isolated yield. Of note, the resulting azepines are somewhat acid sensitive and cannot be purified by conventional silica gel chromatography, although they are stable to purification with basic alumina if necessary.

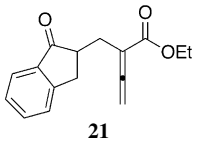
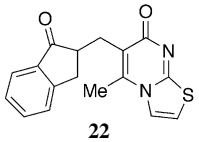
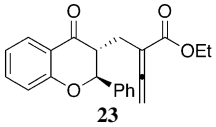
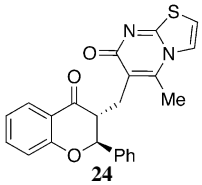
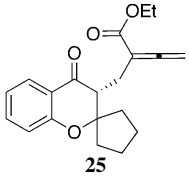
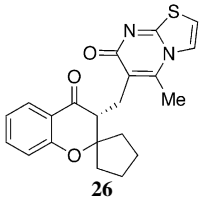
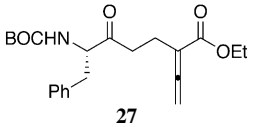
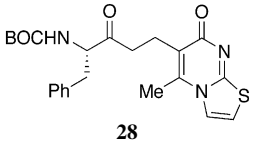
In order to further examine the utility of the substituted allenoate products as starting points for diverse products, we sought to examine their chemistry for delivering diverse pyrimidones in analogy to the precedent of Acheson (Eq. 4).[10] For example, allenoate esters could be condensed with 2-amino thiazoles to deliver pyrimidones of various structures.



(4)

Since the allenoate/enone coupling reaction delivers α-substituted allenoates of various structures, we were pleased to find that a variety of starting materials proceed through the condensation efficiently. As shown in Table 3, both simple ketone derived substrates, as well as those derived from α-amino acids serve with similar efficiency in the condensation. For example, substrates **21** and **23** prepared in our earlier study prove to deliver the corresponding pyrimidones **22** and **24** in excellent yields (84 and 87%, respectively; entries 1 and 2).[11] Spirocyclic allenoate **25** also delivers the corresponding pyrimidone **26**, albeit in somewhat reduced yield (50%, entry 3). Finally, α-amino ketone **27** is also a suitable precursor, affording pyrimidone **28** in 71% yield (entry 4).

Table 3. Allenoate condensation with 2-aminothiazole to deliver pyrimidones[a]

Entry	Substrate	Product	Yield[b]
1	 **21**	 **22**	84%
2	 **23**	 **24**	87%[c]
3	 **25**	 **26**	50%[d]
4	 **27**	 **28**	71%

[a] Entries 2–4 were conducted in a sealed tube at 80 °C for 36 h. Entry 1 was conducted in a sealed tube at 80 °C for 24 h.
[b] Yields refer to isolated yield after silica gel chromatography. Each entry refers to the average of two runs.
[c] Compound **24** was obtained as a mixture of diastereomers (~1:1).
[d] Compound **26** was also obtained by recrystallization.

3. Conclusions

The allenoate/enone condensation has thus been demonstrated to be an effective reaction with expanded substrate scope. The efficacy of α-amino acid derived vinyl ketones as substrates also significantly increases the utility of the reaction since it sets up a subsequent 7-*endo-dig* cyclization to allow for efficient synthesis of azepines. In combination with precedented condensation chemistry such as the reaction of allenoate with 2-amino thiazoles, the potential utility of the chemistry of allenoates as diversity-generating templates is supplemented. This starting material has now been shown to participate efficiently in a wide range of chemistry, including phosphine-catalyzed cycloadditions[12] and other powerful annulations.[13,14] In addition, our previous studies of amine-catalyzed couplings to enones set up three-component couplings with Baylis–Hillman adducts.[3] The present study now adds azepine and pyrimidone syntheses to expand the utility of these starting materials.

4. Experimental

4.1. General

Proton NMR spectra were recorded on Varian 400 or 500 spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ, 0.0). Spectral data is reported as follows: chemical shift (multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)), coupling constants (J) (Hz), integration). Carbon NMR spectra were recorded on a Varian 400 MHz (100 MHz) or Varian 300 MHz (75 MHz) spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to the residual solvent signal ($CDCl_3$, δ 77.16). NMR data were collected at 25 °C, unless otherwise indicated. Infrared spectra were obtained on a Perkin–Elmer Spectrum 1000 spectrometer. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F254 pre-coated plates (0.25 mm thickness), TLC R_f values are reported and visualization was accomplished by irradiation with a UV lamp and/or staining with cerium ammonium molybdinate (CAM) solutions. Flash column chromatography was performed using Silica Gel 60A (40 μm) from Scientific Adsorbents Inc. High resolution mass spectra were obtained from Mass Spectrometry Facilities at Boston College (Chestnut Hill, MA). The method of ionization is given in parentheses.

All reactions were carried out under a nitrogen atmosphere employing oven- and flame-dried glassware. Solvents were distilled over appropriate drying reagents prior to use.

4.2. Preparation of compounds

4.2.1. General procedure for the coupling of allenic esters to amino vinyl ketones. α,β-Unsaturated ketone **4** (165 mg, 0.780 mmol) was dissolved in 8.00 mL of toluene and buta-2,3-dienoic acid benzyl ester (163 μL, 0.940 mmol) was added. Quinuclidine (8.70 mg, 0.078 mmol) was then added. The reaction was stirred for 24 h at 23 °C, at which point the crude reaction mixture was loaded directly onto a silica gel column and purified by flash chromatography (gradient 0–40% EtOAc/hexanes) to afford 262 mg (86% yield) of desired product **5** as a clear oil.

4.2.1.1. Characterization data for products in Table 1. *Data for* **3**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.13 (m, 5H), 5.12–5.01 (overlapping m, 4H), 3.07 (dd, J=13.7, 6.4 Hz, 1H), 2.95, (dd, J=13.9, 6.6 Hz, 1H), 2.64–2.40 (m, 4H), 1.40 (s, 9H), 1.24 (d, J=6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.8, 207.5, 166.0, 154.9, 136.0, 129.1, 128.5, 126.8, 99.5, 79.7, 68.7, 60.2, 38.8, 37.9, 28.4, 22.1, 21.9; IR (film, cm^{-1}) 3368, 2980, 2935, 1965, 1941, 1709, 854; TLC R_f 0.32 (20% EtOAc/hexanes); Exact mass calcd for $[C_{23}H_{31}NO_5Na]^+$ requires m/z 424.2100. Found 424.2104 (ESI+).

Data for **5**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.27 (m, 5H), 5.22–5.12 (overlapping d, s, and t, $J_{triplet}$=3.1 Hz, 5H), 4.27 (dd, J=4.0, 8.8 Hz, 1H), 2.72–2.52 (m, 4H), 2.14 (m, 1H), 1.43 (s, 9H), 0.98 (d, J=6.6 Hz, 3H), 0.75 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.2, 207.8, 166.3, 155.6, 135.8, 128.3, 127.9, 127.7, 99.0, 80.0, 79.5, 66.6, 64.1, 38.7, 30.2, 28.4, 22.3, 20.0, 16.7; IR (film, cm^{-1}) 3377, 2971, 2934, 1966, 1938, 1710, 861; TLC R_f 0.33 (20% EtOAc/hexanes); Exact mass calcd for $[C_{23}H_{31}NO_5Na]^+$ requires m/z 424.2100. Found 424.2101 (ESI+).

Data for **7** (rotamers). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.15 (m, 2H), 4.34–4.18 (overlapping m and q, 3H), 3.60–3.41 (m, 2H), 2.72–2.60 (m, 2H), 2.56–2.51 (m, 2H), 2.21–2.08 (m, 1H), 1.96–1.80 (m, 2H), 1.46 and 1.40 (2s, 9H), 1.28 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.9, 208.4, 208.2, 166.4, 154.3, 153.5, 99.4, 99.2, 80.0, 79.6, 79.5, 65.1, 64.5, 61.0, 46.8, 46.7, 37.3, 36.7, 30.0, 28.9, 28.4, 28.3, 24.4, 23.7, 22.2, 21.8, 14.3; IR (film, cm^{-1}) 2979, 2935, 1967, 1941, 1709, 858; TLC R_f 0.24 (20% EtOAc/hexanes); Exact mass calcd for $[C_{18}H_{27}NO_5Na]^+$ requires m/z 360.1778. Found 360.1787 (ESI+).

Data for **9**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.15 (m, 2H), 4.74–4.58 (broad m, 1H), 4.20 (q, J=7.0 Hz, 2H), 4.09–3.94 (m, 1H), 2.91–2.52 (m, 5H), 2.19 (d, J=13.2 Hz. 1H), 1.62 (m, 5H), 1.46 (s, 9H), 1.28 (t, J=7.0 Hz, 3H); IR (film, cm^{-1}) 2983, 2947, 2875, 1975, 1951, 1714, 874; TLC R_f 0.38 (20% EtOAc/hexanes); Exact mass calcd for $[C_{19}H_{29}NO_5Na]^+$ requires m/z 374.1935. Found 374.1943 (ESI+).

Data for **11** (rotamers). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.15 (m, 2H), 4.39–4.37 (m, 1H), 3.99–3.89 (m, 1H), 3.75–3.74 (2 s, 3H), 2.74–2.54 (m, 1H), 2.54–2.52 (m, 2H), 2.22–2.10 (m, 1H), 1.95–1.62 (m, 4H), 1.45 and 1.38 (2 s, 9H), 0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.9, 207.5, 207.3, 166.6, 153.9, 152.9, 98.8, 98.6, 79.4, 79.4, 79.3, 79.2, 64.7, 64.3, 58.2, 57.8, 51.9, 51.9, 37.4, 37.0, 34.1, 33.4, 31.6, 29.4, 29.4, 29.3, 29.0, 28.2, 28.1, 27.8, 27.1, 26.8, 26.4, 26.3, 26.1, 22.4, 22.0, 21.7; IR (film, cm^{-1}) 2954, 2929, 2856, 1966, 1946, 1718, 855; TLC R_f 0.32 (20% EtOAc/hexanes); Exact mass calcd for $[C_{26}H_{43}NO_5Na]^+$ requires m/z 472.3039. Found 472.3049 (ESI+).

4.2.2. General procedure for the cyclization of allenic esters to azepines. Allene **7** (130 mg, 0.380 mmol) was dissolved in 4.00 mL TFA/CH_2Cl_2 (1:1 v/v) and stirred at

room temperature for 30 min. At this point the solvent was removed by azeotroping with toluene (3×20 mL) under vacuum at 80 °C. The crude residue was dissolved in 5 mL acetonitrile and DIPEA was added (204 μL, 1.14 mmol). The reaction mixture was heated to reflux for 14 h. After cooling, the reaction was concentrated, redissolved in CH_2Cl_2 (50 mL) and washed with sat. $NaHCO_3$ (1× 10 mL). The organic layer was dried over Na_2SO_4 and concentrated to yield the desired azepine **18** in 97% yield (87 mg) as a yellow oil.

4.2.2.1. Characterization data for products in Table 2. *Data for* **16**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.10 (m, 5H), 4.93 (m, 1H), 4.23 (m, 1H), 3.54 (bd, J=2.6 Hz, 1H), 3.18 (dd, J=4.0, 14.7, 1H), 2.85–2.59 (m, 5H), 1.99 (s, 3H), 1.25 (d, J=1.8 Hz, 3H), 1.24 (d, J=1.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.3, 168.5, 154.1, 136.7, 128.7, 128.6, 126.7, 99.4, 66.5, 63.5, 41.2, 35.7, 23.8, 23.5, 22.2, 22.1; IR (film, cm^{-1}) 3352, 3035, 2985, 2938, 1725, 1685, 1669, 1598; Exact mass calcd for $[C_{18}H_{23}NO_3Na]^+$ requires m/z 324.1576. Found 324.1579 (ESI+).

Data for **17**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.24 (m, 5H), 5.15, (dd, J=12.8, 14.3 Hz, 2H), 3.84 (t, J=5.1 Hz, 1H), 3.67 (d, J=3.7 Hz, 1H), 2.95–2.83 (m, 2H), 2.72–2.58 (m, 2H), 2.34 (m, 1H), 2.29 (s, 3H), 0.99 (d, J=7.0 Hz, 3H), 0.94 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.8, 168.7, 155.6, 136.9, 128.3, 127.8, 127.6, 98.4, 67.7, 65.4, 41.9, 27.8, 24.0, 23.8, 19.6, 17.9; IR (film, cm^{-1}) 3368, 2962, 2934, 2873, 1718, 1686; Exact mass calcd for $[C_{18}H_{23}NO_3Na]^+$ requires m/z 324.1576. Found 324.1573 (ESI+).

Data for **18**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.42 (d, J=7.7 Hz, 1H), 4.08 (q, J=7.1 Hz, 2H), 3.36 (m, 2H), 2.96 (m, 1H), 2.80 (m, 1H), 2.46 (m, 3H), 2.40 (s, 3H), 1.83–1.53 (m, 3H), 1.27 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.2, 169.6, 157.5, 98.1, 67.2, 59.3, 49.4, 40.8, 25.2, 25.0, 23.5, 19.8, 14.6; IR (film, cm^{-1}) 2977, 2855, 2874, 1721, 1674, 1558; Exact mass calcd for $[C_{13}H_{20}NO_3]^+$ requires m/z 238.1443. Found 238.1442 (ESI+).

Data for **19**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.40 (d, J=7.7 Hz, 1H), 3.89 (m, 1H), 3.68 (s, 3H), 3.02–2.87 (m, 2H), 2.55–2.37 (m, 2H), 3.40 (s, 3H), 2.08–2.01 (m, 1H), 1.81–1.71 (m, 1H), 1.62 (m, 1H), 1.50–1.40 (m, 1H), 1.24–1.13 (m, 16H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.6, 170.0, 156.9, 99.9, 68.6, 54.5, 50.8, 40.4, 36.7, 31.9, 30.1, 29.6, 29.6, 29.3, 26.2, 25.9, 24.0, 22.7, 18.6, 14.2; IR (film, cm^{-1}) 2930, 2855, 1725, 1685, 1560; Exact mass calcd for $[C_{21}H_{36}NO_3]^+$ requires m/z 350.2695. Found 350.2693 (ESI+).

Data for **20**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.15 (q, J=7.0 Hz, 2H), 3.56 (d, J=12.5 Hz, 1H), 2.92 (m, 1H), 2.57–2.42 (m, 4H), 2.29 (s, 3H), 2.13 (m, 1H), 1.62–1.47 (m, 5H), 1.28 (t, J=7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.5, 169.2, 158.3, 107.6, 64.2, 59.5, 45.9, 40.9, 26.2, 25.9, 24.5, 20.5, 19.8, 14.4; IR (film, cm^{-1}) 2938, 2868, 2851, 1719, 1690, 1572; Exact mass calcd for $[C_{14}H_{22}NO_3]^+$ requires m/z 252.1600. Found 252.1601 (ESI+).

4.2.3. General procedure for allenoate condensation with 2-aminothiazole to deliver pyrimidones. To a solution of allenoate **23** (35.1 mg, 0.100 mmol) in acetonitrile (1.00 mL) was added 2-aminothiazole (10.1 mg, 0.100 mmol). Upon stirring in a sealed tube, the solution was heated at 80 °C for 36 h. The reaction mixture was concentrated and the crude residue was purified by silica gel chromatography (0–4% MeOH/CH_2Cl_2) to afford pyrimidone **24** in 82% yield (33.4 mg) as a light orange solid.

4.2.3.1. Characterization data for products in Table 3. *Data for* **22**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, J=7.7 Hz, 1H), 7.58 (t, J=7.0 Hz, 1H), 7.44 (d, J=7.7 Hz, 1H), 7.39–7.34 (m, 2H), 6.94 (d, J=4.7 Hz, 1H), 3.35 (dd, J=17.2 Hz, 6.6 Hz, 1H) 3.05 (m, 5H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.8, 167.5, 163.8, 153.8, 141.7, 136.2, 134.8, 127.3, 126.7, 123.7, 121.7, 120.2, 109.5, 46.6, 33.2, 28.4, 16.3; IR (film, cm^{-1}) 3081, 2927, 1705, 1627, 1609, 1565, 1495, 1422; TLC R_f 0.17 (5% MeOH/CH_2Cl_2); Exact mass calcd for $[C_{17}H_{14}N_2O_2SNa]^+$ requires m/z 333.0674. Found 333.0675 (ESI+).

Data for **24**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (dd, J=7.9, 1.3 Hz, 1H), 7.79 (dd, J=7.9 Hz, 1.8 Hz, 1H), 7.60–7.43 (m, 6H), 7.41–7.25 (m), 7.18–6.98 (m, 5H), 6.80 (m, 2H), 5.77 (s, 1H), 5.45 (d, J=8.2 Hz, 1H), 3.99 (m, 1H), 3.53 (m, 1H), 3.04 (m, 1H), 2.76 (m, 2H), 2.31 (s, 3H), 2.05 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (two diastereomers) 194.5, 194.2, 167.0, 166.8, 163.8, 163.6, 160.6, 160.2, 141.1, 141.0, 137.3, 136.6, 136.1, 128.6, 128.5, 128.2, 127.7, 127.2, 126.9, 126.0, 121.8, 121.5, 121.4, 120.6, 120.2, 119.7, 119.1, 118.1, 118.0, 109.2, 84.0, 81.4, 49.1, 47.8, 29.9, 26.4, 22.9, 16.3, 15.8; IR (film, cm^{-1}) 3069, 2924, 2855, 1686, 1628, 1607, 1567, 1496, 1473, 1463, 1423; TLC R_f 0.13 (5% MeOH:CH_2Cl_2); Exact mass calcd for $[C_{23}H_{19}N_2O_3S]^+$ requires m/z 403.1116. Found 403.1124 (ESI+).

Data for **26**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (dd, J=7.7, 1.6 Hz, 1H), 7.48 (m, 1H), 7.17 (d, J=5.1 Hz, 1H), 6.98 (m, 2H), 6.84 (d, J=4.9 Hz, 1H), 3.25 (dd, J=13.5 Hz, 3.0 Hz), 2.88 (dd, J=11.4 Hz, 3.1 Hz, 1H), 2.70–2.64 (m, 1H), 2.27 (m, 1H), 2.16 (m, 1H), 2.05 (s, 3H), 1.98–1.92 (m, 2H), 1.84–1.67 (br m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.9, 167.5, 164.4, 160.1, 141.7, 136.4, 127.2, 122.0, 121.3, 120.2, 119.7, 119.1, 109.7, 93.7, 53.1, 36.9, 36.1, 26.4, 24.8, 24.1, 16.3; IR (film, cm^{-1}) 3068, 2955, 1687, 1632, 1607, 1565, 1495, 1425; TLC R_f 0.15 (5% MeOH:CH_2Cl_2); Exact mass calcd for $[C_{21}H_{20}N_2O_3SNa]^+$ requires m/z 403.1096. Found 403.1092 (ESI+).

Data for **28**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, J=4.9 Hz, 1H), 7.20 (m, 3H), 7.07 (d, J=6.6 Hz, 2H), 6.89 (d, J=4.9 Hz, 1H), 5.10 (d, J=7.1 Hz, 1H), 4.43 (m, 1H), 3.12 (dd, J=14.0 Hz, 5.8 Hz, 1H), 2.90–2.80 (m, 5H), 2.50 (s, 3H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.6, 167.1, 163.7, 155.0, 141.2, 136.1, 129.1, 128.4, 126.8, 121.7, 120.7, 109.3, 79.9, 60.4, 37.9, 37.5, 29.9, 28.5, 21.3, 16.1; IR (film, cm^{-1}) 3289, 3094, 3056, 2980, 2924, 1705, 1629, 1616, 1569, 1496, 1455, 1424; TLC R_f 0.18 (5% MeOH/CH_2Cl_2); Exact mass calcd for $[C_{23}H_{24}N_6O_8SNa]^+$ requires m/z 464.1620. Found 464.1626 (ESI+).

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References and notes

1. For an excellent review on 7, 8, and 9-membered azacycle synthesis and natural products, see (a) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131–9166. (b) O'Hagan, D. *Nat. Prod. Rep.* **1997**, 637–652.
2. For a discussion on the novel biological activity of glucose-derived 7-membered azasugars, see: Dhavale, D. D.; Markad, S. D.; Karanjule, N. S.; PrakashaReddy, J. *J. Org. Chem.* **2004**, *69*, 4760–4766.
3. Evans, C. A.; Miller *J. Am. Chem. Soc.* **2003**, *125*, 12394–12395.
4. The quinuclidine-catalyzed reaction initiates through conjugate addition, in analogy to the amine-catalyzed Baylis–Hilman reaction. For a review, see: Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891.
5. For several key references to nucleophilic catalysis via conjugate addition of P-nucleophiles, see (a) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933–7935. (b) Guo, C.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921–1923. (c) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595–7596. (d) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670–5671. (e) Wang, L.-C.; Luis, A.-L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403. (f) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405. (g) Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682–3683.
6. Vinyl ketone derivatives of α-amino acids are readily obtained in analogy to the following precedents: (a) Spaltenstein, A.; Leban, J. J.; Huang, J. J.; Reinhardt, K. R.; Viveros, O. H.; Sigafoos, J.; Crouch, R. *Tetrahedron Lett.* **1996**, *37*, 1343–1346. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818. (c) At this stage, we have not evaluated the extent to which racemization may have occurred at any step in the sequences.
7. For recent reviews concerning syntheses of 7- and 8-membered azacycles, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198.
8. (a) Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett.* **2001**, *3*, 3385–3387. (b) Mukai, C.; Ukon, R.; Kuroda, N. *Tetrahedron Lett.* **2003**, *44*, 1583–1586. (c) Mukai, C.; Kobayashi, M.; Kubota, S.; Takahashi, Y.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 2128–2136.
9. As noted in Ref. 6, product racemization has not yet been evaluated in these sequences. Circumstantially, we note that product **19** was isolated without erosion of diastereomeric purity.
10. (a) Acheson, R. M.; Bite, M. G.; Cooper, M. W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1908–1911. (b) Doad, G. J. S.; Okor, D. I.; Scheinmann, F.; Bates, P. A.; Hursthouse, M. B. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2993–3003.
11. Compound **24** is isolated as a mixture of diastereomers (~1:1 *cis*/*trans*) after pyrimidone formation.
12. (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535–544 and references therein. (b) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901–8905.
13. Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716–4717.
14. Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387–1390.

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Palladium-catalyzed phosphorus–carbon bond formation: cross-coupling reactions of alkyl phosphinates with aryl, heteroaryl, alkenyl, benzylic, and allylic halides and triflates

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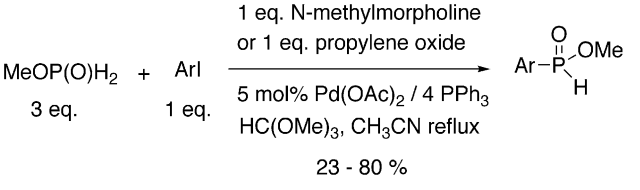
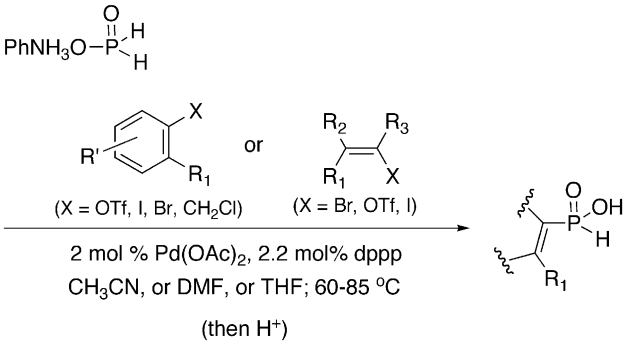
Abstract—The direct formation of H-arylphosphinates and related compounds can be accomplished using palladium catalysis. This full paper examines the scope and some mechanistic aspects of this phosphorus–carbon bond forming reaction. The reactions of alkenyl and allylic halides are also described for the first time. This novel cross-coupling provides a convenient access to a variety of substituted H-phosphinates.

1. Introduction

Cross-coupling reactions have become some of the most popular methods for the formation of carbon–heteroatom bonds.[1] Most notably, carbon bonds to nitrogen, oxygen, and sulfur are now commonly prepared using palladium catalysis, and to a lesser extent other transition metals such as copper and nickel. Buchwald, Hartwig, and others have been major contributors in this area.[1] The formation of carbon–phosphorus bonds via cross-coupling has also been examined.[2] In fact, the palladium-catalyzed cross-coupling of dialkyl phosphites $(RO)_2P(O)H$ with aryl- and alkenyl-halides was already described in the early eighties by Hirao and co-workers.[3] More recent reactions have focused mainly on the synthesis of phosphines and their derivatives.[2] However, the cross-coupling reactions of compounds containing two phosphorus–hydrogen bonds are much less common, because of the possibility for competing transfer hydrogenation with these substrates. For example, reductions of a variety of functional groups with hypophosphorous acid and its derivatives have been known and used preparatively for several decades.[4] Thus, it may not be surprising that the cross-coupling of hypophosphorous derivatives was not described until recently. In pioneering studies, Schwabacher was the first to report the palladium-catalyzed coupling of alkyl phosphinates ($ROP(O)H_2$) with aryl iodides (Eq. 1).[5] A few years earlier, Holt reported one example of cross-coupling between triethylammnonium hypophosphite and a dienyl triflate, but the generality of this reaction was not established.[6]



(1)



(2)

In the context of studies aiming at the synthesis of functionalized H-phosphinates as intermediates in the preparation of biologically-active compounds, we recognized the need for developing the cross-coupling of hypophosphorous acid derivatives with various electrophiles. As a result, we have been involved in the study of hypophosphites and alkyl phosphinates as nucleophilic

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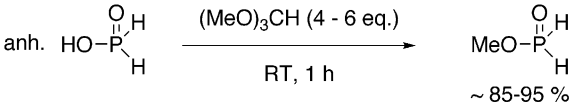
partners in palladium-catalyzed reactions. This work produced the remarkably general cross-coupling reaction of anilinium hypophosphite (AHP) with a variety of electrophilic partners, and this has been reported in two publications (Eq. 2).[7] More recently and based on our experience with AHP, we tackled the problem of preparing H-phosphinate esters directly from alkyl phosphinates and tried to significantly expand the scope of the Schwabacher coupling. This manuscript provides a full account of these studies, and follows up on our preliminary communication.[8] As mentioned above, Schwabacher developed the cross-coupling of methyl phosphinate,[5a] and later *tert*-butyl phosphinate,[5b] with aryl iodides. However, only reactive iodides were successfully employed, and the yields were generally moderate (ca. 50–60%), reaching 80% in the best case (4-iodotoluene). The cross-coupling of aryl bromides and triflates was unsuccessful.[5a] Aside from the competing transfer hydrogenation, a major problem was the rapid thermal decomposition of methyl phosphinate (complete decomposition in 1 h at 80 °C), which prevented the use of relatively unreactive electrophiles.[5a]

We have reported a novel synthesis of alkyl phosphinates, which is based on the esterification of hypophosphorous acid and some of its salts (ammonium and anilinium) with alkoxysilanes in a variety of solvents.[9] Under these conditions, the thermal decomposition of the alkyl phosphinates is surprisingly slow (less than 20% in 20 h at 80–110 °C in several different solvents).[9] We therefore, were in an excellent position to examine the cross-coupling reactions of alkyl phosphinates with a variety of electrophiles. In a proof of concept experiment, we reported the coupling of butyl phosphinate with iodobenzene in 80% isolated yield.[9] We have since investigated the palladium-catalyzed cross-coupling reactions of alkyl phosphinates in some detail, and those results are now discussed.

2. Results and discussion

2.1. Alkyl phosphinate preparation

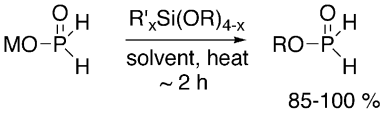
Schwabacher prepared methyl phosphinate using the Fitch method (Eq. 3),[10] and *tert*-butyl phosphinate was prepared in low yield (37%) through the transesterification of the methyl ester.[5b] The *tert*-butyl ester is only slightly more thermally stable than its methyl counterpart.[5b]



(3)

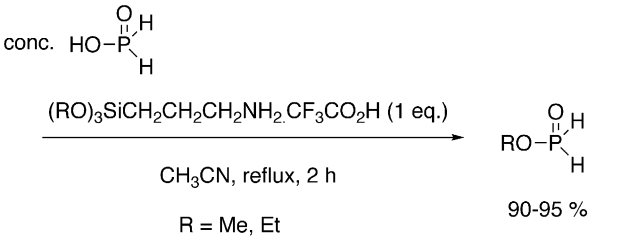
M = H, $PhNH_3$, NH_4

R = Me, Et, Bu, Allyl, Ph, Bn, *i*-Pr



(4)

In contrast, we have reported a convenient and general alkyl phosphinate synthesis (Eq. 4), which proceeds in high yield in a wide variety of solvents and does not require anhydrous H_3PO_2.[9] The solutions of alkyl phosphinates are used directly in subsequent reaction, and the thermal stability profile of the esters is excellent. Stock solutions of alkyl phosphinates can also be employed because they are stable at room temperature under N_2 for well over a month (<10% decomposition). This unique preparative method allows us to examine reactions which were previously difficult or impossible. For cross-coupling, the thermal limitations would be eliminated, so that only transfer hydrogenation must be dealt with, even if it is still the major expected problem. We also reported a variation on our alkyl phosphinate synthesis (Eq. 5), which employs salts of aminosilicates, and allows the removal of the silicate byproducts at the end of the reactions by simple aqueous wash.[9]

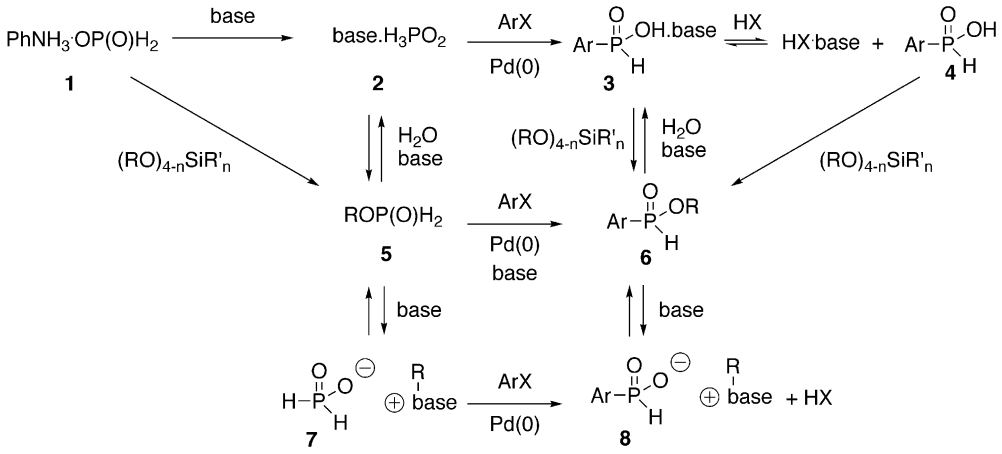


(5)

2.2. Cross-coupling reactions of aryl- and heteroaryl-halides or triflates

2.2.1. Mechanistic considerations. As expected, aryl iodides are the easiest substrates for cross-coupling with alkyl phosphinates because they are the most reactive toward palladium insertion into the C–I bond, so transfer hydrogenation is minimized as a competing side-reaction. With these substrates, the thermal decomposition of the alkyl phosphinate (prepared by the Fitch method, Eq. 3) is still not fast enough to cause the yield to drop below useful levels for the reactive substrates.[5a] However, electrophiles less reactive toward oxidative addition could not be employed in the Schwabacher coupling, and aryl bromides or triflates failed to give the desired products.[5a]

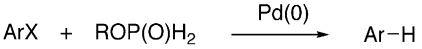
While our AHP-based cross-coupling (Eq. 2)[7] is successful on a wide range of electrophiles (including bromides and triflates), access to the H-phosphinate ester requires the separate esterification of the products. Our silicate-based esterification[11] and other methods[12] can be used to achieve this, but a direct one-step access to the ester is more desirable. This is especially true in the case of substrates containing basic functionalities, which cannot be esterified simply. We therefore investigated the direct coupling of alkyl phosphinates with aromatic and heteroaromatic electrophiles. The alkyl phosphinates were prepared according to Eq. 4; the electrophile, base, and palladium catalyst were subsequently added. As expected, aryl iodides reacted uneventfully to afford good yields of cross-coupled products, using Et_3N as the base. In fact, the cross-coupling still proceeds in high yield even without any added base. In this case, the alkyl phosphinate serves as HI scavenger and reduces the Pd(II) back to Pd(0). It also indicates that the coupling likely proceeds through the P(III) tautomer of the alkyl phosphinate, and that deprotonation of the phosphorus nucleophile is not necessary.



Scheme 1. Mechanistic pathways.

Unfortunately, electrophiles other than iodides were generally poor substrates. Initially, we found that DABCO worked better for those substrates using preformed alkyl phosphinates. However, we discovered that the presence of moisture in the batch of DABCO we employed appeared to be responsible for this success.[8] Indeed, Et_3N could be used in place of DABCO if 0.5–1 equiv water was added to it. This suggested a complex mechanism in which many pathways had to be considered.[8] Scheme 1 summarizes various reaction pathways. We reasoned that the role of water was to hydrolyze the preformed alkyl phosphinate to a hypophosphite salt (**5**→**3**, Scheme 1), which could then couple with the electrophile (**2**→**3**, Scheme 1 and Eq. 2), followed by in situ esterification of the product in the presence of the alkoxysilane (**3**→**6**, or **4**→**6**, Scheme 1). If that is true, then a one-pot cross-coupling procedure should take place without the need for any added water (path **1**→**2**→**3/4**→**6**, Scheme 1). This turned out to be correct, at least in practice: when anilinium hypophosphite, an alkoxysilane, anhydrous Et_3N or DABCO, and ArX were reacted in the presence of $Pd(OAc)_2$/dppp, good yields of H-phosphinate esters were obtained. The **1**→**2**→**3** sequence occurs during the AHP coupling (Eq. 2)[7a] and appears very general with respect to the ArX employed. Apparently, the direct coupling **5** to **6** only takes place when X=I (and in this case even in the absence of base). When water is present, hydrolysis of **5** leads to the rapid formation of salt **2**, which can then couple efficiently.

In order to better understand the mechanistic subtleties of this cross-coupling, a series of control experiments were conducted. The results are summarized in Table 1. The direct coupling of butyl phosphinate with iodobenzene occurs in good yield even in the absence of base (entry 1). As expected (see Eq. 2) the salt of H_3PO_2 with DABCO couples efficiently (entry 2), and variable amounts of compound **3** are observed in the ^{31}P NMR spectrum of the crude reaction mixtures in other runs. However, the esterification of isolated product **3** (prepared from H-phenylphosphinic acid and DABCO) into H-phosphinate ester **6** does not occur efficiently (entry 3).[11] This suggests that the hydrogen halide formed during the coupling step must play a key role, and we have previously established that acidity of H-arylphosphinate salt **3** is a key parameter in the esterification process.[11] Under anhydrous conditions with aryl bromides (which are less reactive than the iodides toward oxidative addition), no phosphinate ester is formed from butyl phosphinate (entry 4). Addition of water completely reverses this (entry 5). The failure of coupling **5**→**6** in the absence of water is likely due to ester dealkylation to form tetraalkyl ammonium hypophosphites **7** (entry 6) which are not capable of coupling (entry 7). When the P–C bond-forming step (cross-coupling) is slow, competing transfer hydrogenation[4] (Eq. 6) becomes significant or even dominant. For example, gas chromatographic analysis shows that the major product formed in entry 7 is naphthalene, whereas no P–C bond formation is observed. Salts **7** are also not esterified (entry 8). In the presence of water, hydrolysis of **5** is rapid even at room temperature, and leads to **2** (entry 9) which is then capable of undergoing coupling (entry 3). Entry 10 shows that the reverse reaction **2**→**5** is inefficient. In these pathways, H-phosphinate esters **6** are always much more stable than alkyl phosphinate **5** toward hydrolysis or nucleophilic dealkylation (entry 11 vs. entry 9). Finally, the one pot process delivers useful yields in the absence of water, as shown in entry 12.



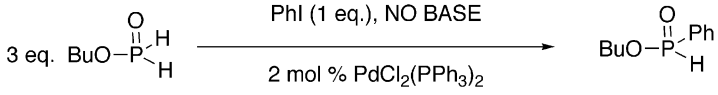
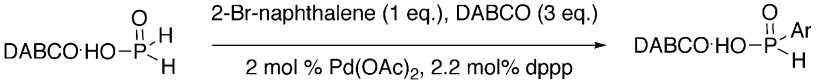
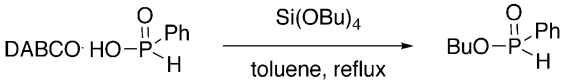
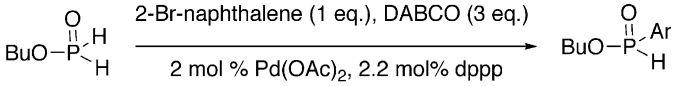
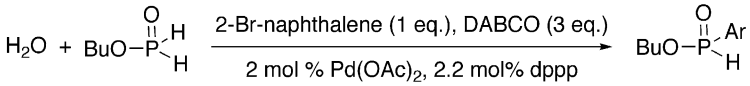
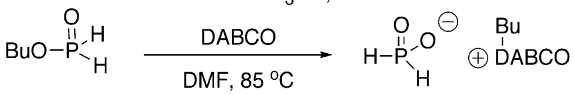
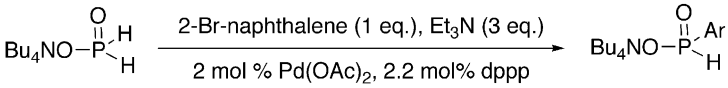
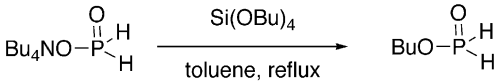
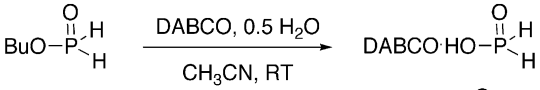
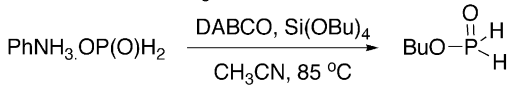
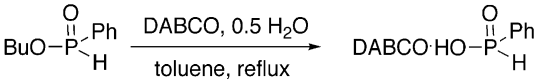
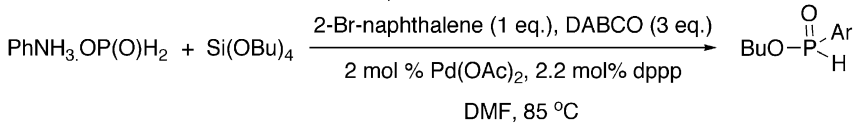
(6)

R = $PhNH_3$ **1**, baseH **2**, alkyl **5**, R'_4N **7**

The conclusion of these mechanistic studies is that the cross-coupling can take place in a one-pot process in the absence of water, and that the path must be **1**→**2**→**3**→**4**→**6**. An important consequence is that an asymmetric cross-coupling reaction (using a chiral ligand around palladium) is not likely to be successful with electrophiles other than iodides, since all the intermediates are achiral phosphinate salts, and since the esterification **4**→**6** should not be enantioselective because the chiral ligand is not involved in this step. In the case of aryl iodides, a direct coupling with the alkyl phosphinate is taking place and this is a minimum requirement to conserve potential chirality at the phosphorus atom. Initial experiments to achieve the asymmetric coupling of alkyl phosphinates with aryl iodides have however not been successful at this time.

2.2.2. Scope. The one-pot process[8] which was developed as a result of the above mechanistic considerations was

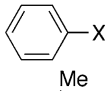
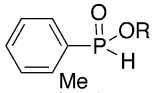
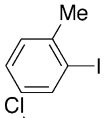
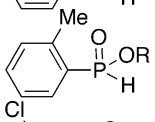
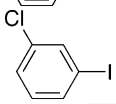
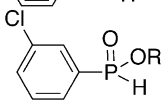
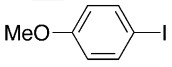
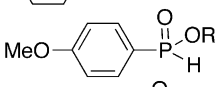
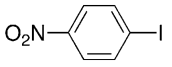
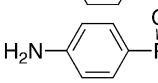
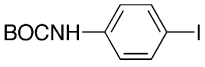
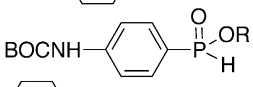
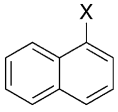
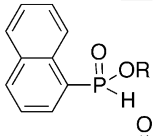
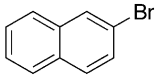
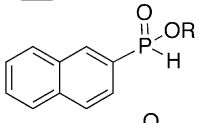
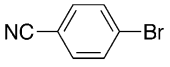
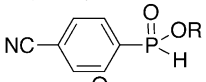
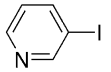
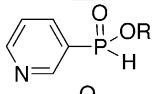
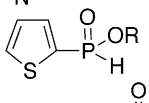
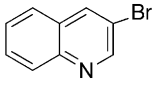
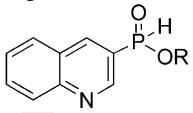
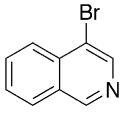
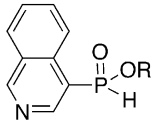
Table 1. Control experiments related to the mechanistic pathways[a]

Entry	Reaction	Model for step	^{31}P NMR yield, %[b] reaction outcome
1		**5→6**	100%
2		**2→3**	100%
3		**3→6**	11%
4		**5→6**	no H-phosphinate ester
5		**5→3** **4→6**	78%
6		**5→7**	65%
7		**7→8**	No cross-coupling product
8		**7→5**	No esterification
9		**5→2**	92%
10		**2→5**	17%
11		**6→3**	15%
12		**1→6**	74%

[a] See Scheme 1.
[b] NMR yields are determined by integrating all the signals in the spectrum.

subsequently tested on a variety of aromatic and heteroaromatic electrophiles. Some of these results are summarized in Table 2. In terms of ligand, PPh_3 is only satisfactory with aryl iodides (as in the Schwabacher coupling, see entry 1), while dppp is the most generally useful ligand. A similar trend was already noticed with the AHP cross-coupling of aryl electrophiles so this may not be surprising considering the postulated mechanism (Scheme 1). The H-phosphinate products were isolated in moderate to good yield. Several solvents can be employed, but acetonitrile appears to be the most generally useful. Although Et_3N can be used successfully (results not shown), DABCO was employed throughout because it gave better results (Table 2, Method B). Various substituted aryl iodides can be employed, including the sterically hindered 2-iodotoluene (entry 2) or the deactivated 4-iodoanisole (entry 4). Entry 5 shows an interesting example of cross-coupling/transfer hydrogenation where a nitroaromatic is also reduced to the corresponding aniline. It was not possible to find conditions where the nitro group remains completely intact. Aryl bromides and triflates could also be used (entries 7–9). However, unactivated bromobenzene does not react in high yield. This is probably due to a slower cross-coupling so that transfer hydrogenation (Eq. 6) becomes a major competing pathway. Indeed, deactivated bromoanisole does not give the H-arylphosphinate product. Heterocyclic substrates react successfully (entries 10–13). While the AHP coupling[7a] (Eq. 2) was successful with all the heterocycles

Table 2. Cross-coupling scope with (hetero)aromatic electrophiles

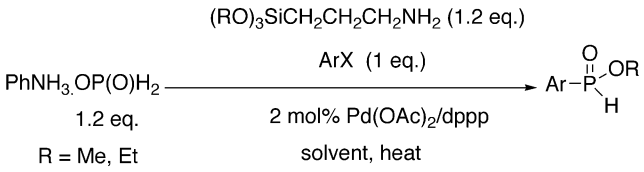
Entry	Electrophile	H-Phosphinate product	R	X	Method[a]	Isolated yield[b] %
1			Bu	I	A[c]	80
			Et	I	B[d]	61
			Et	I	C[c]	72
			Et	Br	B[d]	40[e]
2			Bu	—	B[c]	83
3			Bu	—	B[c]	63
4			Bu	—	B[c]	78
5			Bu	—	B[c]	53
6			Bu	—	B[c]	82
7			Me	Br	C[c]	100
			Bu	OTf	B[f]	80
8			Et	—	B[d]	69
			Et	—	C[c]	88
			Et	—	C[d]	74
9			Bu	—	B[f]	51
			Et	—	C[c]	92
10			Bu	—	B[c]	64
11			Bu	—	B[c]	36
12			Bu	—	B[f]	65
13			Bu	—	B[f]	78

[a] Method A: 3 equiv AHP, 3 equiv $(BuO)_4Si$, 3 equiv Et_3N, 2 mol% $Cl_2Pd(PPh_3)_2$; Method B: 3 equiv AHP, $(RO)_{4-n}SiR'_n$, 3 equiv DABCO, 2 mol% $Pd(OAc)_2$/dppp; Method C: 1.2 equiv AHP, 1.2 equiv $(RO)_3Si(CH_2)_3NH_2$, 2 mol% $Pd(OAc)_2$/dppp.
[b] Unless otherwise noted, yields are for isolated product which gave satisfactory spectral data (>95% purity).
[c] CH_3CN, reflux.
[d] Toluene, reflux.
[e] ^{31}P NMR yield.
[f] DMF, 85 °C.

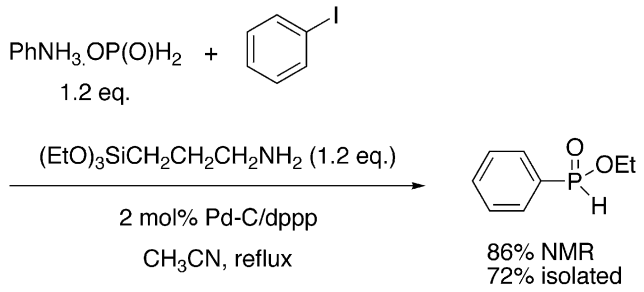
we tested, the nitrogen-containing ones would require either ion-exchange chromatography or a separate esterification step to access the corresponding H-heteroarylphosphinate ester. The silicate esterification[11] is also inefficient on those products, so different conditions (for example: PivCl+ROH) need to be employed.[12] Thus the present one-step cross-coupling of alkyl phosphinates is particularly useful for nitrogen-containing heterocycles.

2.2.3. Use of aminotrialkoxysilanes. Although the silicate by-products from the esterification of anilinum hypophosphite or H_3PO_2 can be removed during chromatography over silica gel (or in some cases by hexane/CH_3CN partitioning), a process in which these byproducts are removed by extraction has definite advantages. In Scheme 1, the three major species which are soluble in an organic solvent during an extractive work-up are the desired H-phosphinate esters **6**, the dialkyl phosphite $(RO)_2P(O)H$, and the silicates. In some cases, the dialkyl phosphite (which comes from the decomposition of the alkyl phosphinate) can be removed in vacuo. Therefore, if the silicates can be made water-soluble, one could hope to obtain the cross-coupling products in reasonably pure form after a simple aqueous work-up. In the past, we have shown

that aminosilicate-derived byproducts can be removed easily and that aminosilicates can replace other silicates, both in the esterification of hypophosphorous acid (Eq. 5),[9] and of H-phosphinic acids,[11] as long as an equivalent of acid (usually trifluoroacetic acid, TFA) is also added. We have now found that aminotrialkoxysilanes can be used, not only as the esterifying agent, but also as the base for the palladium-catalyzed process, and that TFA is not needed (Eq. 7). Representative cross-couplings conducted with this system (method C) are shown in Table 2. It appears that the aminosilicate serves the dual purpose of esterification and of base in the palladium-catalyzed process. Of course, the use of the aminosilicate is not appropriate with nitrogen-containing heterocycles, since competing protonation of the heterocycles occurs and extraction is therefore problematic.



(7)



(8)

We also found that palladium on carbon can be used successfully with dppp as the ligand for this cross-coupling (Eq. 8). Thus the aminosilicate method provides a straightforward approach to the synthesis of various H-arylphosphinate esters.

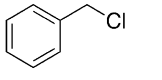
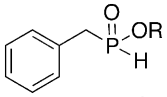
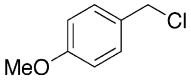
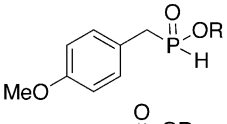
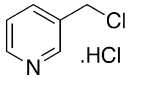
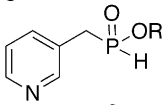
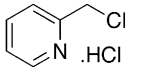
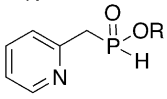
2.3. Cross-coupling of benzylic- and heterobenzylic chlorides

Benzylic and heterobenzylic chlorides can also be used as coupling partners (Table 3). However with these substrates, the best ligand is now dppf.[8] For the pyridine-containing substrates, an additional equivalent of base is also employed to deprotonate the commercially available hydrochlorides. The reason for the low isolated yields observed with the chloromethyl pyridines (entries 3 & 4) is somewhat unclear. Changing the base from Et_3N to *i*-Pr_2NEt does not improve the yield so that quaternarization with the electrophile is not a likely explanation. Some possible reasons for the observed yields include: (a) dealkylation of the ester by the base followed by inefficient re-esterification (see Section 2.2.1. and Scheme 1); and (b) the high polarity of the products and their facile hydrolysis during purification by chromatography. Additionally, in the case of entry 3, an unusual amount of disubstitution is also observed in the crude mixture (singlet, δ 49 ppm, ~20%). Disubstitution generally does not take place to a significant extent (<5%) with other substrates. In spite of these limitations, the direct cross-coupling is probably the best synthetic method available currently to prepare these kinds of benzylic H-phosphinates. For example, Froestl et al. reported on the inability to prepare the product in entry 4 via esterification of the corresponding H-phosphinic acid.[13]

2.4. Cross-coupling of alkenyl halides

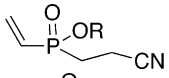
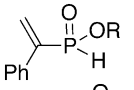
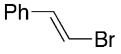
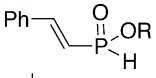
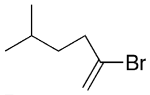
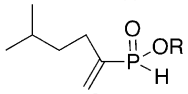
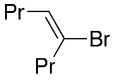
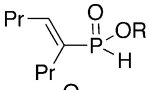
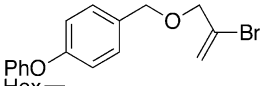
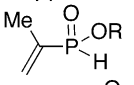
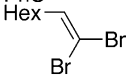
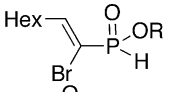
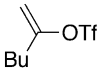
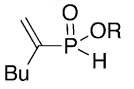
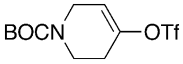
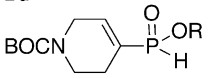
We have also investigated the cross-coupling of alkenyl halides and triflates. The results are summarized in Table 4. Alkenyl-H-phosphinates can be prepared by palladium-catalyzed hydrophosphinylation of alkynes with alkyl phosphinates.[14,15] However, the regiocontrol for the formation of linear versus the branched alkenyl-H-phosphinates isomers is generally about 3 to 1, even though the branched isomers can be obtained with high selectivity. Thus, the present cross-coupling allows access to a variety of alkenyl-substituted compounds with complete regio- and stereocontrol. Vinyl bromide couples in high yield (~80% NMR yield), but the isolated yield is low (ca. 40%) and the product could not be obtained in good purity. We attempted

Table 3. Cross-coupling scope with benzylic chlorides

Entry	Electrophile	H-Phosphinate product	R	Ligand	Isolated yield % (NMR yield %)
1			Bu	dppf dppp	88 (100) (21)
2			Bu	dppf	53 (65)
3			Bu	dppf	46 (60)
4			Bu	dppf	24 (38)

The yields reported are for isolated compounds with satisfactory spectral data (~95% purity). The yield in parentheses is determined by ^{31}P NMR. Conditions: 3 equiv AHP, 3 equiv, $(RO)_4Si$, DABCO 3 equiv (4 equiv for hydrochlorides), 2 mol% $Pd(OAc)_2$/dppf, CH_3CN, reflux.

Table 4. Cross-coupling scope with alkenyl electrophiles

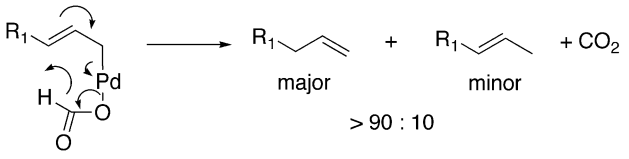
Entry	Electrophile	H-Phosphinate product	R	solvent	Method[a]	Isolated yield %
1			Et	CH_3CN	A	30
2			Bu	THF	B	79
3			Bu	THF	B	95
4			Bu	CH_3CN	B	63
5			Bu	CH_3CN	B	77
6			Bu	CH_3CN	B	57
7			Et	CH_3CN	A	48
8			Bu	CH_3CN	B	58
9			Bu	CH_3CN	B	95

[a] Method A: 2 equiv AHP, 2 equiv $(RO)_3Si(CH_2)_3NH_2$, 2 mol% $Pd(OAc)_2$/dppf [for entry 7, 3 equiv AHP +3 equiv $(RO)_3Si(CH_2)_3NH_2$]; Method B: 3 equiv AHP, 2.1 equiv $(BuO)_4Si$, 1.0 equiv Et_3N, 2 mol% $Pd(OAc)_2$/dppp.

to use a tandem reaction to facilitate product isolation and purification, but the isolated yield remains low (Table 4, entry 1). With vinyl bromide, further optimization is therefore necessary. On the other hand, less polar coupling products can be obtained in satisfactory yields (Table 4, entries 2–5). The cross-coupling and simultaneous reduction (hydrogenolysis) of a substrate containing an allylic ether moiety was observed (entry 6). A 1,1-dibromoolefin was also studied, and in this case the reaction takes place stereospecifically to yield substitution of the bromine atom in the E-configuration (entry 7). Alkenyl triflates can also be coupled successfully (entries 8 and 9). This study is the first to show the successful cross-coupling of alkenyl electrophiles with alkyl phosphinates. This approach presents some advantages over our previously reported coupling with AHP since the products do not need to be esterified in a separate step.[7b]

2.5. Reactions of allylic electrophiles

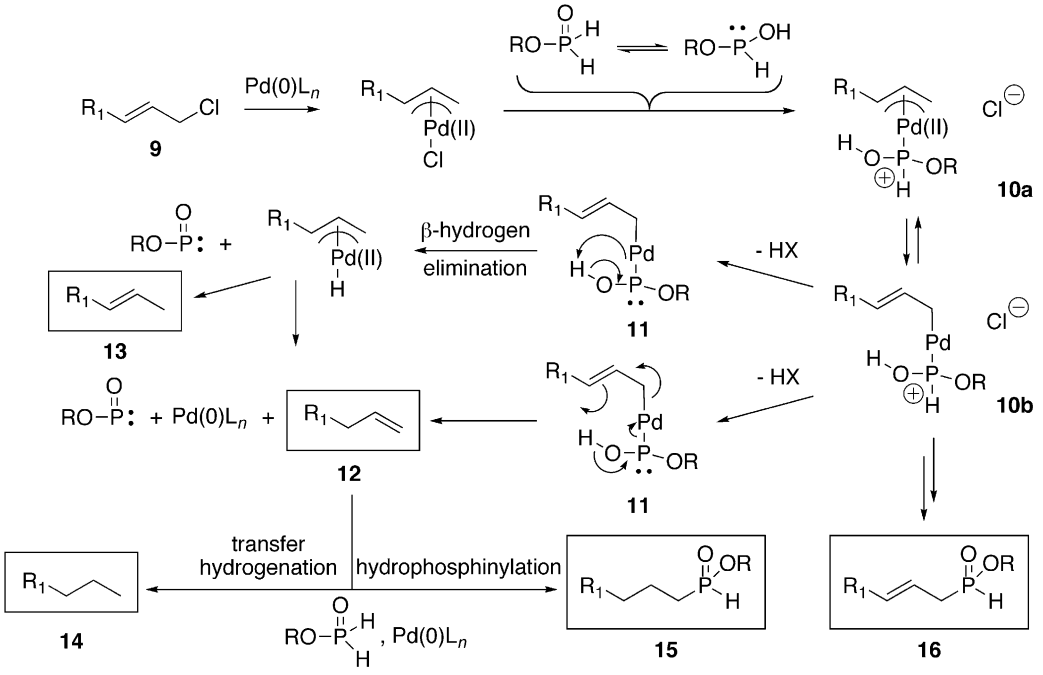
The cross-coupling of allylic substrates was examined next. In spite of much experimentation, a general and high yielding procedure was not found. Allylic H-phosphinic acids have been prepared using the Arbuzov-like reaction of $(TMSO)_2PH$ (BTSP), but disubstitution is usually a significant side reaction, and the handling of BTSP is problematic.[16] We have found that allylic H-phosphinate esters are best prepared from alkyl phosphinates via a direct nucleophilic displacement under basic conditions.[17] Nonetheless, some interesting results related to catalytic cross-coupling were collected, and these are discussed now.



(9)

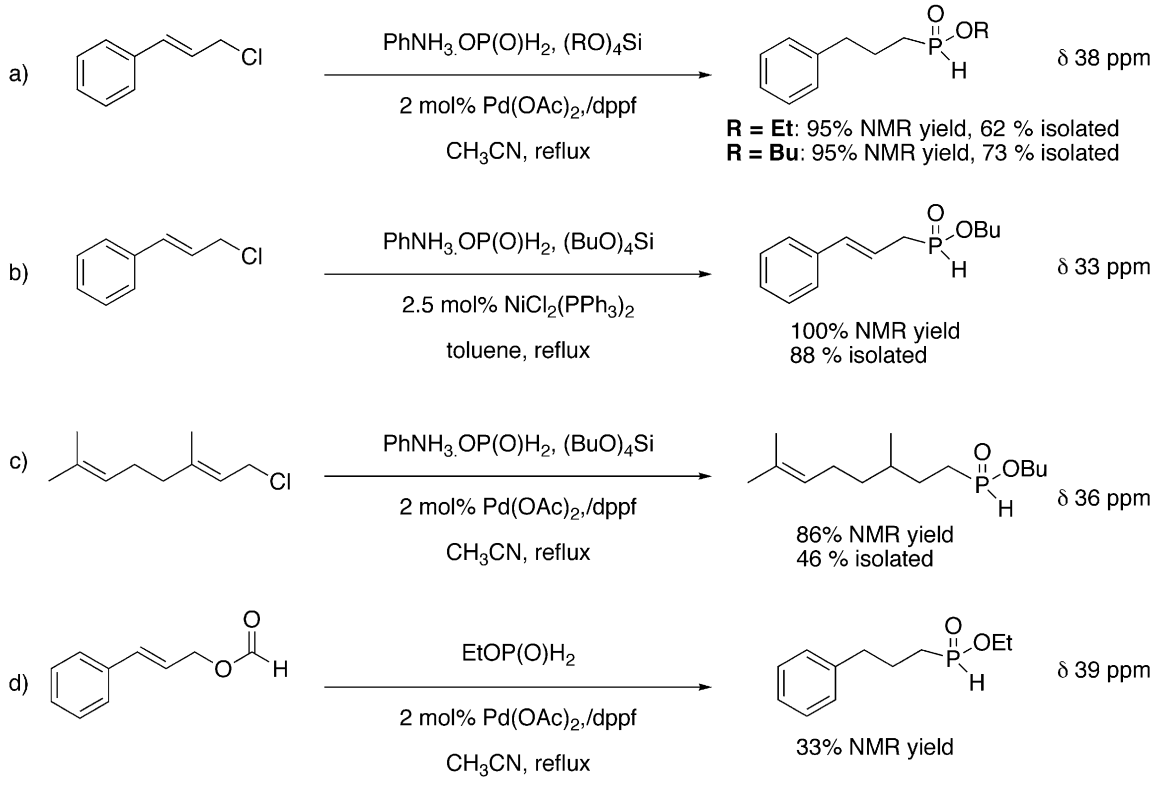
When allyl chloride or bromide was reacted under conditions similar to the ones developed for other electrophiles, no P–C bond formation could be detected. We reasoned that reduction might be taking place instead, in a manner similar to the formate-promoted reduction of allylic electrophiles (Eq. 9).[18] In an attempt at identifying the product of the reaction, we turned our attention to cinnamyl chloride which would give a higher boiling, more easily detected, reduction product. However, with cinnamyl chloride (**9**, R_1=Ph), cross-coupling did take place rather efficiently. The product of the reaction proved to be butyl (3-phenylpropyl)-H-phosphinate (**15**, R_1=Ph), and not the expected cinnamyl-H-phosphinate (**16**, R_1=Ph).

A proposed mechanism to account for the formation of **15** is shown in Scheme 2. Since the reduction of allylic electrophiles is known to take place with formates (Eq. 9),[18] an analogous reductive pathway (**11**→**12**) could occur with the related H-phosphinates if proton transfer or β-hydrogen elimination are faster than reductive elimination from intermediates **10** or **11**. The product of reduction is then the corresponding terminal alkene (again a reaction well precedented with formates), at which point palladium-catalyzed addition[14] of excess alkyl phosphinate can take place (hydrophosphinylation, **12**→**15**). We have



Scheme 2. Mechanistic pathways with allylic electrophiles.

previously discovered the palladium-catalyzed hydrophosphinylation of alkenes, and have shown that it has broad scope and that various ligand (including PPh_3 and dppf) can be employed.[14] A similar reaction would explain the formation of compound **15** from **12**, and the failure of substrates which would give volatile alkenes **12** in the first step. In the reduction with formates (Eq. 9), the β-hydrogen elimination is considered unlikely because the least-substituted alkene always forms with very high regioselectivity.[18] In the case of alkyl phosphinates, regioisomeric alkene **13** could also form, but if it does, hydrophosphinylation of internal alkenes is known to be inefficient[14] and would not lead to any significant P–C bond formation. Experiments using gas chromatographic and ^{31}P NMR analyses were conducted to probe the mechanism further. Monitoring after 35 min, the cinnamyl chloride reaction



Scheme 3. Reactions of allylic electrophiles.

with palladium catalyst (Scheme 3a) reveals, clean and rapid formation of allylbenzene **12** (87%), complete consumption of cinnamyl chloride, and formation of some **15** (13%). No β-methylstyrene **13** can be detected, thus ruling out β-hydrogen elimination as the major pathway (Scheme 2). Evidently, the reductive isomerization (**9**→**12**) is efficient and analogous to formate reduction (Eq. 9). Over time, allylbenzene slowly disappears while product **15** forms (33 and 65%, respectively, after 2.5 h). After 8 h, **15** is formed in nearly quantitative yield (with no detectable **16**), and with only traces of allylbenzene **12** and propylbenzene **14** (1 and 2%, respectively) remaining. This shows that hydrophosphinylation[14] (**12**→**15**) occurs smoothly with negligible competing transfer hydrogenation (**12**→**14**).

Scheme 3 shows some results of the cross-coupling with allylic electrophiles. Interestingly, the use of a nickel catalyst (Scheme 3b) in toluene did give the expected cinnamyl product **16** with little competing reduction to **15** (**16:15** ratio=95:5). This might be due to a more rapid reductive elimination (**10/11**→**16**) versus reductive isomerization (**11**→**12**) in the case of the nickel complex.[19] A GC/NMR monitoring experiment shows the slow disappearance of cinnamyl chloride and the appearance of **16** with only traces of allylbenzene or propylbenzene at any given time. Thus, unlike what was observed with the palladium catalyst formation of **16** takes place directly.

Geranyl chloride also reacted to form the reduced coupling product with $Pd(OAc)_2$/dppf as a catalyst (Scheme 3c). Cinnamyl formate (Scheme 3d) was also reacted under identical conditions with palladium catalysis, in an attempt at probing further our postulated mechanism for cinnamyl chloride. Although the yield is low, the detection of **15** but not **16** indicates that a reduction-hydrophosphinylation pathway is indeed reasonable.

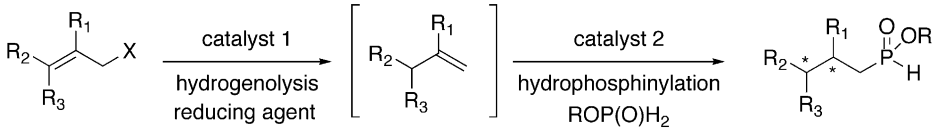
Even if the reactions described here are probably not very useful synthetically, the mechanistic implications are interesting. Alkyl phosphinates can react as formates to promote the hydrogenolysis of allylic compounds, and our independently discovered hydrophosphinylation reaction[14,15] appears to be operative under palladium catalysis. This suggests that a one-pot, two-step process where an allylic electrophile is first hydrogenolyzed,[18] then hydrophosphinylated[14] could be a useful approach to P–C bond formation (Scheme 4) by employing in tandem two known reactions. For example, reaction d in Scheme 3 could possibly be improved using AHP and catalytic Pd_2dba_3/PBu_3/xantphos. Furthermore, asymmetric versions of the first step have already been reported.[20] We are currently examining this puzzling possibility.

The different outcome observed with nickel suggests an avenue for research to develop the cross-coupling of allylic electrophiles, and this will be explored in the near future. However, the best synthetic approach to prepare allylic H-phosphinates from allylic halides remains the base-promoted direct alkylation of alkyl phosphinates in the absence of catalyst.[17,21] The situation is different with other allylic electrophiles (acetate, formate, carbonate) and would justify more work in this area.

3. Conclusions

The palladium-catalyzed cross-coupling reactions of alkyl phosphinates with various electrophiles has been studied, and some mechanistic insights have been provided. A one-pot process was developed which gives moderate to good yields of H-phosphinate esters. This includes a variation employing aminoalkoxysilanes to facilitate the work-up and isolation of the H-phosphinate ester products. The reactions of alkenyl and allylic electrophiles were examined for the first time. Alkenyl halides and triflates are good substrates for the cross-coupling, whereas allylic compounds apparently react in a reduction-hydrophosphinylation sequence. Fortunately, allylic H-phosphinates are accessible through other methods.[17,21] Although our previously reported AHP coupling has a broader scope,[7] the present one-step synthesis of H-phosphinate esters is still quite generally applicable, and is advantageous when H-phosphinic acids cannot be isolated or esterified easily.

The reactions described cover a broad scope of substrates beyond Schwabacher's aryl iodides,[5] and provide a novel access to H-phosphinate esters. Applications to the synthesis of biologically active organophosphorus compounds are in progress. Based on the postulated mechanism of the aryl coupling, the development of a catalytic desymmetrization of alkyl phosphinates for the preparation



X = Hal, O_2CH, OAc, OC(O)OR, OPh, NO_2

catalyst 1: $Cl_2Pd(PPh_3)_2$, Pd_2dba_3/Bu_3P, $Pd(PPh_3)_4$

reducing agent: HCO_2NH_4, $HCO_2H{\cdot}Et_3N$, PMHS, $ROP(O)H_2$

catalyst 2: Pd_2dba_3/xantphos, Pd_2dba_3/dppf

ROP(O)H_2: H_3PO_2, AHP, $AlkOP(O)H_2$

Scheme 4. Possible tandem process.

of P-chiral H-phosphinate esters poses significant challenges for substrates other than aryl iodides.

4. Experimental

General experimental procedures and the preparation of AHP and alkyl phosphinates have been described elsewhere.[7,9,14] The NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra. The yields determined by NMR are accurate within ~10% of the value indicated, and are reproducible. Some experiments with internal standards and gas chromatography also confirmed the validity of the method.[15] In several cases, the isolated yields are very close to the NMR yields. However, isolated yields are often significantly lower which mostly reflects the fact the H-phosphinic esters are typically difficult to purify, rather than some inaccuracy in NMR yield measurements. Chromatography is often complicated by the very polar nature of these compounds, and their relative ease of hydrolysis. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR00954), or by the Mass Spectrometry Facility of the University of South Carolina. Experimental procedures for Table 2

4.1. Experimental procedures for Table 2

Table 2, Method A.[9] *Entry 1*. A solution of anilinium hypophosphite (0.952 g, 6 mmol) and tetrabutoxysilane (1.933 g, 6 mmol) in CH_3CN (12 mL) was refluxed for 2 h, under N_2. After cooling to rt, iodobenzene (0.25 mL, 2 mmol), anhydrous Et_3N (0.30 mL, 2 mmol), and $Cl_2Pd(PPh_3)_2$ (0.025 g, 0.04 mmol), were added successively. The reaction mixture was then refluxed for 5 h. At that point, the black mixture was concentrated under reduced pressure, and the residue partitioned between EtOAc and aq $KHSO_4$. The organic layer was washed successively with saturated aq $NaHCO_3$ (1×), and brine (1×). Drying, concentration, and purification by radial chromatography (4 mm thickness, hexane, EtOAc/hexane 1:1, v/v, EtOAc) afforded butyl phenylphosphinate (0.300 g, 80%).

Table 2 Method B. *Entry 12*. To a solution of 3-bromoquinoline (0.425 g, 2 mmol), $(BuO)_4Si$ (1.923 g, 6 mmol) in DMF (12 mL), were added anilinium hypophosphite (0.955 g, 6 mmol), 1,4-diazabicyclo[2.2.2]octane (0.676 g, 6 mmol), $Pd(OAc)_2$ (0.009 g, 0.04 mmol), 1,3-bis(diphenylphosphino)propane (0.018 g, 0.044 mmol). The resulting mixture was heated at 85 °C for 2 h. The reaction mixture was concentrated in vacuo, the residue was treated with brine (15 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc 7:3, v/v, EtOAc) afforded butyl quinolin-3-yl phosphinate. (0.322 g, 65% yield).

Table 2, Method C. *Entry 8*. To a suspension of anilinum hypophosphite (0.382 g, 2.4 mmol) and 3-aminopropyltriethoxysilane (0.531 g. 2.4 mmol) in CH_3CN (12 mL), was added 2-bromonaphthalene (0.414 g, 2 mmol), $Pd(OAc)_2$ (0.009 g, 0.040 mmol), and 1,3-bis(diphenylphosphino)propane (0.0182 g, 0.044 mmol). The reaction mixture was heated at reflux for 18 h. After cooling to rt, ^{31}P NMR analysis showed the product at 25.8 ppm (90%). The mixture was then diluted with EtOAc and washed successively with aq HCl (1 M). The aq phase was extracted with EtOAc (3×) and the combined organic fractions were washed with saturated aq $NaHCO_3$ (1×) and brine. Drying over $MgSO_4$ and concentration afforded ethyl 2-naphthylphosphinate (0.387 g, 88%).

4.2. Experimental procedures for Table 3

Entry 1. To a solution of benzyl chloride (0.253 g, 2 mmol), $(BuO)_4Si$ (1.923 g, 6 mmol) in CH_3CN (12 mL), were added anilinium hypophosphite (0.955 g, 6 mmol), 1,4-diazabicyclo[2.2.2]octane (0.676 g, 6 mmol), $Pd(OAc)_2$ (0.009 g, 0.04 mmol), 1,1′-bis(diphenylphosphino)ferrocene (0.0266 g, 0.048 mmol). The resulting mixture was heated at reflux for 1 h. The reaction mixture was concentrated in vacuo, the residue was treated with HCl (1 M, 15 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc 7:3, v/v, EtOAc) afforded butyl benzylphosphinate. (0.357 g, 78%) Note: for entries 3 & 4, the difference in workup was that brine was used instead of 1 M HCl above. For entry 4, 10 mmol AHP was used instead of 6 mmol.

4.3. Experimental procedures for Table 4

Table 4, Method A. Preparation of ethyl (vinyl-2-cyanoethyl)phosphinate (entry 1). A mixture of anilinum hypophosphite (0.955 g, 6 mmol), in CH_3CN (12 mL) was placed in a pressure tube. 3-Aminopropyltriethoxysilane (1.328 g, 6 mmol), vinyl bromide (1.0 M in CH_3CN, 3 mL, 3 mmol), $Pd(OAc)_2$ (0.0135 g, 0.06 mmol), and 1,1′-bis(diphenylphosphino)ferrocene (0.0400 g, 0.072 mmol) were then added in that order. The mixture was heated at 85 °C for 6 h. After cooling to rt, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.90 mL, 6 mmol) and acrylonitrile (0.40 mL, 6 mmol) were added in the same reaction tube and the reaction was stirred overnight under nitrogen. After this time, ^{31}P NMR analysis showed the product at 38.3 ppm (72%). The mixture was then diluted with EtOAc and washed successively with aq HCl (1 M). The aq phase was then extracted with EtOAc (3×) and the combined organic fractions were washed with saturated aq $NaHCO_3$ (1×) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, EtOAc to MeOH) afforded the product as a dark yellow oil (0.156 g, 30%).

4.4. Preparation of Ethyl (1-bromo-oct-1-enyl)-phosphinate (entry 7)

To a mixture of anilinum hypophosphite (0.955 g, 6 mmol) and 3-aminopropyltriethoxysilane (1.328 g. 6 mmol) in CH_3CN (12 mL), was added 1,1-dibromo-octene (0.540 g, 2 mmol), $Pd(OAc)_2$ (0.009 g, 0.040 mmol), and 1,1′-bis(diphenylphosphino)ferrocene (0.0270 g, 0.048 mmol). The resulting mixture was heated at reflux for 7 h. The mixture was then diluted with EtOAc and washed successively with aq HCl (1 M). The aq phase was extracted with EtOAc (3×)

and the combined organic fractions were washed with saturated aq $NaHCO_3$ (1×) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, hexanes/EtOAc 5:1, v/v, EtOAc) afforded the product as a light yellow oil (0.272 g, 48%).

Table 4, Method B. Entry 9. A mixture of anilinum hypophosphite (0.955 g, 6 mmol) and $(BuO)_4Si$ (1.346 g, 4.2 mmol) in CH_3CN (12 mL) was heated to reflux for 2 h under nitrogen and then cooled to rt. To the resulting mixture was added *tert*-butyl-1,2,3,6-tetrahydro-4-[(trifluoromethyl)sulfonyloxy]-pyridine-1-carboxylate (0.663 g, 2.0 mmol), anhydrous Et_3N (0.28 mL, 2.0 mmol), $Pd(OAc)_2$ (0.009 g, 0.04 mmol) and 1,3-bis(diphenylphosphino)propane (0.0182 g, 0.044 mmol). The reaction was then refluxed under nitrogen for 8 h. After cooling to rt, ^{31}P NMR analysis showed the product at 26.0 ppm (100%). The mixture was diluted with EtOAc and washed with aq $NaHSO_4$ (1 M). The resulting aqueous phase was extracted with EtOAc (3×) and the combined organic layers were washed with saturated aq $NaHCO_3$ (1×) and brine. Drying over $MgSO_4$ and concentration afforded the crude compound, which was purified by radial chromatography (2 mm thickness, hexanes/EtOAc 3:1, v/v, EtOAc). The product was obtained as a yellow oil (0.576 g, 95%).

4.5. Representative procedure for cross-coupling of allylic substrates

Palladium. Scheme 3a: A mixture of anilinum hypophosphite (0.955 g, 6 mmol) and $(BuO)_4Si$ (1.346 g, 4.2 mmol) in CH_3CN (12 mL) was heated to reflux for 2 h under nitrogen. After cooling to rt, cinnamyl chloride (0.280 mL, 2.0 mmol), $Pd(OAc)_2$ (0.009 g, 0.04 mmol), and 1,3-bis(diphenylphosphino)propane (0.0182 g, 0.044 mmol) were added to the reaction flask and the mixture was heated at reflux under nitrogen for 10 h. At this time, ^{31}P NMR analysis of the reaction mixture showed the product at 39.7 ppm (95%). The mixture was then diluted with EtOAc and washed with aq $NaHSO_4$ (1 M). The resulting aq phase was extracted with EtOAc (3×) and the combined organic fractions were washed with saturated aq $NaHCO_3$ (1×) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, hexanes/EtOAc 5:1, v/v, EtOAc), afforded butyl (3-phenyl-propyl)phosphinate (0.351 g, 73%).

Nickel. Scheme 3b: A mixture of anilinum hypophosphite (0.955 g, 6 mmol) and $(BuO)_4Si$ (1.346 g, 4.2 mmol) in CH_3CN (12 mL) was heated to reflux for 2 h under nitrogen and cooled to rt. Cinnamyl chloride (0.280 mL, 2.0 mmol) and bis(triphenylphosphine)nickel (II) chloride (0.0327 g, 0.050 mmol) were then added to the reaction flask and the mixture was heated at reflux under nitrogen, for 8 h. ^{31}P NMR analysis of the reaction mixture showed the product at 37.1 ppm (100%). The reaction mixture was diluted with EtOAc and washed with aq $NaHSO_4$ (1 M). The resulting aqueous phase was extracted with EtOAc (3×) and the combined organic fractions were washed with saturated aq $NaHCO_3$ (1×) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, hexanes/EtOAc 5:1, v/v, EtOAc) afforded a ~95:5 mixture of butyl (3-phenyl-prop-2-enyl)phosphinate and butyl (3-phenyl-propyl)phosphinate (0.419 g, 88%).

4.5.1. Butyl phenylphosphinate (Table 2, entry 1). ^1H NMR ($CDCl_3$) δ 7.81 (d, $J=7$ Hz, 1H), 7.76 ($J=7$ Hz, 1H), 7.58 (d, $J=562$ Hz, 1H), 7.55–7.6 (m, 1H), 7.45–7.55 (m, 2H), 3.95–4.15 (m, 2H), 1.6–1.8 (m, 2H), 1.35–1.5 (m, 2H), 0.92 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 132.4 (d, $J_{PCCCC}=3$ Hz), 130.3 (d, $J_{PCCC}=12$ Hz), 129.4 (d, $J_{PC}=132$ Hz), 128.1 (d, $J_{PCC}=14$ Hz), 65.1 (d, $J_{POC}=7$ Hz), 31.8 ($J_{POCC}=6$ Hz), 18.2, 12.9; ^{31}P NMR ($CDCl_3$) δ 25.3 (dm, $J_{P\text{-}H}=563$ Hz).

4.5.2. Ethyl phenylphosphinate (Table 2, entry 1). ^1H NMR ($CDCl_3$) δ 7.81 (d, $J=14$ Hz, 1H), 7.79 (d, $J=14$ Hz, 1H), 7.60 (d, $J=563$ Hz, 1H), 7.55–7.60 (m, 1H), 7.50–7.55 (m, 2H), 4.15–4.20 (m, 2H), 1.39 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 133.1 (d, $J_{PCCCC}=3$ Hz), 130.9 (d, $J_{PCCC}=12$ Hz), 130.0 (d, $J_{PC}=132$ Hz), 128.8 (d, $J_{PCC}=14$ Hz), 62.0 (d, $J_{POC}=6$ Hz), 16.4 (d, $J_{POCC}=6$ Hz); ^{31}P NMR ($CDCl_3$) δ 25.7 (dm, $J_{P\text{-}H}=562$ Hz).

4.5.3. Butyl *o*-tolylphosphinate (Table 2, entry 2). ^1H NMR ($CDCl_3$) δ 7.82 (dd, $J=16$, 7 Hz, 1H), 7.64 (d, $J=555$ Hz, 1H), 7.40–7.50 (m, 1H), 7.25–7.35 (m, 2H), 4.05–4.15 (m, 2H), 2.57 (s, 3H), 1.65–1.80 (m, 2H), 1.35–1.50 (m, 2H), 0.93 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 141.1 (d, $J_{PCC}=11$ Hz), 132.9 (d, $J_{PCCCC}=7$ Hz), 131.9 (d, $J_{PCCC}=13$ Hz), 131.1 (d, $J_{PCCC}=12$ Hz), 128.1 (d, $J_{PC}=131$ Hz), 125.8 (d, $J_{PCC}=14$ Hz), 65.8 (d, $J_{POC}=7$ Hz), 32.4 (d, $J_{POCC}=7$ Hz), 19.9 (d, $J_{PCCC}=7$ Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 26.9 (dm, $J_{P\text{-}H}=555$ Hz); HRMS (FAB) calcd for $C_{11}H_{17}O_2P$, $(M+Li)^+$ 219.1126, found 219.1122.

4.5.4. Butyl (3-chlorophenyl)phosphinate (Table 2, entry 3). ^1H NMR ($CDCl_3$) δ 7.77 (d, $J=14$ Hz, 1H), 7.65–7.70 (m, 1H), 7.58 (d, $J=570$ Hz, 1H), 7.55–7.60 (m, 1H), 7.45–7.50 (m, 1H), 4.05–4.15 (m, 2H), 1.70–1.75 (m, 2H), 1.40–1.50 (m, 2H), 0.94 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 135.2 (d, $J_{PCCC}=18$ Hz), 133.2 (d, $J_{PCCCC}=3$ Hz), 132.2 (d, $J_{PC}=130$ Hz), 130.9 (d, $J_{PCC}=13$ Hz), 130.3 (d, $J_{PCCC}=15$ Hz), 129.0 (d, $J_{PCC}=11$ Hz), 66.7 (d, $J_{POC}=7$ Hz), 32.4 (d, $J_{POCC}=6$ Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 23.5 (dm, $J=570$ Hz); HRMS (FAB) calcd for $C_{10}H_{14}ClO_2P$, $(M+Li)^+$ 239.0580, found 239.0586.

4.5.5. Butyl (4-methoxyphenyl)phosphinate (Table 2, entry 4). ^1H NMR ($CDCl_3$) δ 7.70–7.75 (m, 2H), 7.55 (d, $J=561$ Hz, 1H), 7.00–7.05 (m, 2H), 4.05–4.10 (m, 2H), 3.85 (s, 3H), 1.65–1.75 (m, 2H), 1.40–1.45 (m, 2H), 0.93 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.4 (d, $J_{PCCCC}=3$ Hz), 133.0 (d, $J_{PCC}=13$ Hz), 121.1 (d, $J_{PC}=139$ Hz), 114.3 (d, $J_{PCCC}=15$ Hz), 65.4 (d, $J_{POC}=7$ Hz), 55.4, 32.5 (d, $J_{POCC}=6$ Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 25.9 (dm, $J=561$ Hz); HRMS (FAB) calcd for $C_{11}H_{17}O_3P$, $(M+Li)^+$ 235.1075, found 235.1084.

4.5.6. Butyl (4-aminophenyl)phosphinate (Table 2, entry 5). ^1H NMR ($CDCl_3$) δ 7.55 (dd, $J=13$ Hz, $J=8$ Hz, 2H), 7.51 (d, $J=559$ Hz, 1H), 6.73 (dd, $J=9$, 3 Hz, 2H), 3.99–4.1 (m, 4H), 1.67–1.72 (m, 2H), 1.38–1.46 (m, 2H), 0.93 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 151.3

(d, J_{PCCCCC}=3 Hz), 133.1 (d, J_{PCC}=13 Hz, 2C), 117.4 (d, J_{PC}=142 Hz), 114.5 (d, J_{PCCC}=15 Hz, 2C), 65.4 (d, J_{POC}=6 Hz), 32.7 (d. J_{POCC}=7 Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$) δ 27.1 (dm, J=559 Hz).

4.5.7. Butyl [(4-*tert*-butoxycarbonylamino)phenyl]phosphinate (Table 2, entry 6). ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.70–7.75 (m, 2H), 7.60–7.65 (m, 2H), 7.56 (d, J=564 Hz), 4.05–4.10 (m, 2H), 1.65–1.75 (m, 2H), 1.50 (s, 9H), 1.35–1.45 (m, 2H), 0.92 (t, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ 152.6, 143.6 (d, J_{PCCCC}=3 Hz), 132.2 (d, J_{PCC}=13 Hz), 123 (d, J_{PC}=138 Hz), 118.0 (d, J_{PCCC}=14 Hz), 80.9, 65.5 (d, J_{POC}=7 Hz), 32.4 (d, J_{POCC}=6 Hz), 28.3, 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 26.1 (dm, J=565 Hz); HRMS (FAB) calcd for $C_{15}H_{24}NO_4P$, $(M+Li)^+$ 320.1603, found 320.1610.

4.5.8. Butyl 1-naphthylphosphinate (Table 2, entry 7). ^{1}H NMR ($CDCl_3$) δ 8.43 (d, J=8 Hz, 1H), 8.11 (dd, J=7, 1 Hz, 1H), 8.05 (dd, J=7, 4 Hz, 1H), 7.91 (d, J=563 Hz, 1H), 7.90 (d, J=8 Hz, 1H), 7.50–7.65 (m, 3H), 4.05–4.20 (m, 2H), 1.60–1.75 (m, 2H), 1.30–1.45 (m, 2H), 0.87 (t, J=7 Hz, 3H); ^{13}C NMR (CDCl3) δ 134.1 (d, J_{PCCCC}=3 Hz), 133.6 (d, J_{PCC}=10 Hz), 132.7 (d, J_{PCC}=13 Hz), 132.5, 129.2 (d, J_{PCCC}=2 Hz), 128.0, 126.9, 126.2 (d, J_{PC}=129 Hz), 125.0 (d, J_{PCCCC}=1 Hz), 124.8 (d, J_{PCCC}=11 Hz); ^{31}P NMR ($CDCl_3$) δ 27.1 (dm, J=563 Hz); HRMS (FAB) calcd for $C_{14}H_{17}O_2P$, $(M+Li)^+$ 255.1126, found 255.1138.

4.5.9. Ethyl 2-naphthylphosphinate (Table 2, entry 8). ^{1}H NMR ($CDCl_3$) δ 8.40 (d, J=16 Hz, 1H), 7.95–8.00 (m, 2H), 7.90 (d, J=9 Hz, 1H), 7.72 (d, J=564 Hz, 1H), 7.65–7.80 (m, 1H), 7.60–7.65 (m, 2H); 4.15–4.25 (m, 2H), 1.41 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 135.6 (d, J_{PCCCC}=3 Hz), 133.7 (d, J_{PCCC}=12 Hz), 132.6 (d, J_{PCC}=15 Hz), 129.1 (d, J_{PCCC}=3 Hz), 128.9, 128.8, 128.2, 127.1 (d, J_{PC}=132 Hz), 127.4, 125.4 (d, J_{PCC}=12 Hz), 62.3 (d, J_{POC}=6 Hz), 16.7 (d, J_{POCC}=6 Hz); ^{31}P NMR ($CDCl_3$) δ 25.8 (dm, J=565 Hz).

4.5.10. Butyl (4-cyanophenyl)phosphinate (Table 2, entry 9). ^{1}H NMR ($CDCl_3$) δ 7.90–8.00 (m, 2H), 7.80~7.90 (m, 2H), 7.65 (d, J=574 Hz, 1H), 4.10–4.20 (m, 2H), 1.70–1.80 (m, 2H), 1.40–1.50 (m, 2H), 0.95 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 135.0 (d, J_{PC}=129 Hz), 132.3 (d, J_{PCCC}=14 Hz), 131.6 (d, J_{PCC}=12 Hz), 117.7, 116.7 (d, J_{PCCCC}=3 Hz), 66.5 (d, J_{POC}=7 Hz), 32.4 (d, J_{POCC}=6 Hz), 18.7, 13.5; ^{31}P NMR ($CDCl_3$) δ 22.5 (dm, J=574 Hz); HRMS (FAB) calcd for $C_{11}H_{14}NO_2P$, $(M+Li)^+$ 230.0922, found 230.0917.

4.5.11. Butyl 3-pyridinylphosphinate (Table 2, entry 10). ^{1}H NMR ($CDCl_3$) δ 8.98 (dm, J=7 Hz, 1H), 8.85 (m, 1H), 8.10–8.20 (m, 1H), 7.45–7.50 (m, 1H), 7.69 (d, J=573 Hz, 1H), 4.15–4.20 (m, 2H), 1.70–1.80 (m, 2H), 1.40–1.50 (m, 2H), 0.96 (t, J=7 Hz, 3H); ^{13}C NMR (CDCl3) δ 153.7 (d, J_{PCCNC}=2 Hz), 151.8 (d, J_{PCC}=14 Hz), 139.0 (d, J_{PCC}=10 Hz), 126.2 (d, J_{PC}=131 Hz), 123.7 (d, J_{PCCC}=10 Hz), 66.4 (d, J_{POC}=7 Hz), 32.4 (d, J_{POCC}=7 Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 22.0 (dm, J=573 Hz).

4.5.12. Butyl 2-thienylphosphinate (Table 2, entry 11). ^{1}H NMR ($CDCl_3$) δ 7.75–7.80 (m, 1H), 7.70–7.75 (m, 1H), 7.72 (d, J=593 Hz, 1H), 7.25–7.30 (m, 1H), 4.10–4.20 (m, 2H), 1.70–1.80 (m, 2H), 1.40–1.50 (m, 2H), 0.95 (t, J=8 Hz, 3H); ^{13}C NMR (CDCl3) δ 136.7 (d, J_{PCC}=13 Hz), 134.5 (d, J_{PCSC}=6 Hz), 130.2 (d, J_{PC}=145 Hz), 128.5 (d, J_{PCCC}=16 Hz), 65.8 (d, J_{POC}=6 Hz), 32.4 (d, J_{POCC}=7 Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 16.3 (dm, J=593 Hz); HRMS (FAB) calcd for $C_8H_{13}O_2PS$, $(M+Li)^+$ 211.0534, found 211.0531.

4.5.13. Butyl 3-quinolinylphosphinate (Table 2, entry 12). ^{1}H NMR ($CDCl_3$) δ 9.15 (dd, J=5, 2 Hz, 1H), 8.71 (d, J=15 Hz, 1H), 8.19 (d, J=9 Hz, 1H), 7.95 (d, J=8 Hz, 1H), 7.85–7.90 (m, 1H), 7.82 (d, J=573 Hz, 1H), 7.65–7.70 (m, 1H), 4.15–4.25 (m, 2H), 1.75–1.85 (m, 2H), 1.40–1.55 (m, 2H), 0.96 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 149.7, 149.6, 142.1 (d, J_{PCC}=10 Hz), 132.3, 129.6, 128.8, 127.9, 126.7 (d, J_{PCC}=12 Hz), 123.0 (d, J_{PC}=131 Hz), 66.4 (d, J_{POC}=7 Hz), 32.5 (d, J_{POCC}=6 Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 25.9 (dm, J=561 Hz); HRMS (FAB) calcd for $C_{13}H_{16}NO_2P$, $(M+Li)^+$ 256.1079, found 256.1072.

4.5.14. Butyl 4-isoquinolinylphosphinate (Table 2, entry 13). ^{1}H NMR ($CDCl_3$) δ 9.44 (d, J=2 Hz, 1H), 8.98 (d, J=11 Hz, 1H), 8.46 (d, J=9 Hz, 1H), 8.09 (d, J=8 Hz, 1H), 7.98 (d, J=570 Hz, 1H), 7.85–7.90 (m, 1H), 7.70–7.80 (m, 1H), 4.15–4.25 (m, 2H), 1.70–1.80 (m, 2H), 1.40–1.50 (m, 2H), 0.92 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 157.7 (d, J_{PCCNC}=9 Hz), 147.8 (d, J_{PCC}=16 Hz), 134.8 (d, J_{PCC}=9 Hz), 132.3, 128.8, 128.3, 128.0 (d, J_{PCCC}=8 Hz), 124.2 (d, J_{PCCC}=6 Hz), 119.9 (d, J_{PC}=121 Hz), 66.3 (d, J_{POC}=6 Hz), 32.4 (d, J_{POCC}=6 Hz), 18.8, 13.5; ^{31}P NMR ($CDCl_3$) δ 24.3 (dm, J=570 Hz); HRMS (FAB) calcd for $C_{13}H_{16}NO_2P$, $(M+Li)^+$ 256.1079, found 256.1086.

4.5.15. Butyl benzylphosphinate (Table 3, entry 1).[22] ^{1}H NMR ($CDCl_3$) δ 7.20–7.35 (m, 5H), 7.03 (d, J=544 Hz, 1H), 3.90–4.10 (m, 2H), 3.19 (d, J=18 Hz, 2H), 1.55–1.65 (m, 2H), 1.25–1.40 (m, 2H), 0.89 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 129.9, 129.8 (d, J_{PCCC}=7 Hz), 128.9 (d, J_{PCCCC}=3 Hz), 127.7 (d, J_{PCCCCC}=4 Hz), 66.4 (d, J_{POC}=7 Hz), 37.0 (d, J_{PC}=89 Hz), 32.3 (d, J_{POCC}=6 Hz), 18.7, 13.5; ^{31}P NMR ($CDCl_3$) δ 37.9 (dm, J=545 Hz); HRMS (FAB) calcd for $C_{11}H_{17}O_2P$, $(M+Li)^+$ 219.1126, found 219.1125.

4.5.16. Butyl (4-methoxybenzyl)phosphinate (Table 3, entry 2). ^{1}H NMR ($CDCl_3$) δ 7.15 (dd, J=9 Hz, J=3 Hz, 2H), 7.0 (d, J=542 Hz, 1H), 6.87 (d, J=8 Hz, 2H), 3.9–4.15 (m, 2H), 3.8 (s, 3H), 3.14 (d, J=18 Hz, 2H), 1.58–1.68 (m, 2H), 1.28–1.42 (m, 2H), 0.91 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.0 (d, J_{PCCCCC}=4 Hz), 131.0 (d, J_{PCCC}=6 Hz, 2C), 121.8 (d, J_{PCC}=8 Hz), 114.6 (d, J_{PCCCC}=3 Hz, 2C), 66.7 (d, J_{POC}=7 Hz), 55.5, 36.2 (d, J_{PC}=90 Hz), 32.6 (d, J_{POCC}=6 Hz), 18.9, 13.8; ^{31}P NMR ($CDCl_3$) δ 40.2 (dm, J=542 Hz); HRMS (EI^+) calcd for $C_{12}H_{19}O_3P$, $(M)^+$ 242.1072, found 242.1069.

4.5.17. Butyl (pyridin-3-yl-methyl)phosphinate (Table 3, entry 3). ^{1}H NMR ($CDCl_3$) δ 8.50–8.55 (m, 2H), 7.60–7.65 (m, 1H), 7.25–7.35 (m, 1H), 7.12 (d, J=548 Hz, 1H), 4.00–4.15 (m, 2H), 3.20 (d, J=18 Hz, 2H), 1.60–1.70 (m, 2H), 1.30–1.40 (m, 2H), 0.92 (t, J=7 Hz, 3H); ^{13}C NMR

(CDCl3) δ 150.6 (d, $J_{PCCC}=7$ Hz), 148.7 (d, $J_{PCCCNC}=4$ Hz), 137.3 (d, $J_{PCCC}=6$ Hz), 126.1 (d, $J_{PCC}=7$ Hz), 123.7, 66.8 (d, $J_{POC}=7$ Hz), 34.2 (d, $J_{PC}=89$ Hz), 32.3 (d, $J_{POCC}=6$ Hz), 18.7, 13.5; ^{31}P NMR ($CDCl_3$) δ 35.1, (dm, $J=547$ Hz); HRMS (FAB) calcd for $C_{10}H_{16}NO_2P$, $(M+Li)^+$ 220.1079, found 220.1131.

4.5.18. Butyl (pyridin-2-yl-methyl)phosphinate (Table 3, entry 4). ^{1}H NMR ($CDCl_3$) δ 7.20–7.25 (m, 2H), 7.19 (d, $J=548$ Hz, 1H), 6.75–6.85 (m, 1H), 6.69 (d, $J=8$ Hz, 1H), 4.05–4.20 (m, 2H), 3.57 (dm, $J=10$ Hz, 2H), 1.65–1.75 (m, 2H), 1.35–1.45 (m, 2H), 0.95 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 147.1 (d, $J_{PCC}=9$ Hz), 129.7, 119.2, 113.7, 113.5, 67.1 (d, $J_{POC}=7$ Hz), 42.8 (d, $J_{PC}=105$ Hz), 32.6 (d, $J_{POCC}=6$ Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$) δ 33.3 (dm, $J=548$ Hz).

4.5.19. Ethyl (vinyl-2-cyanoethyl)phosphinate (Table 4, entry 1). ^{1}H NMR ($CDCl_3$) δ 6.03–6.5 (m, 3H), 3.96–4.16 (m, 2H), 2.6–2.71 (m, 2H), 2.0–2.2 (m, 2H), 1.35 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.4, 127.9 (d, $J_{PC}=121$ Hz), 118.6, 61.4 (d, $J_{POC}=6$ Hz), 29.9, 25.2 (d, $J_{PC}=101$ Hz), 16.7 (d, $J_{POCC}=6$ Hz); ^{31}P NMR ($CDCl_3$) δ 38.3 (s); HRMS (ES^+) calcd for $C_7H_{12}NO_2P$, $(M+H)^+$ 172.0527, found 172.0529.

4.5.20. Butyl (1-phenyl-vinyl)phosphinate (Table 4, entry 2).[14] ^{1}H NMR ($CDCl_3$) δ 7.35 (d, $J=563$ Hz, 1H), 7.48–7.52 (m, 2H), 7.35–7.38 (m, 3H), 6.27 (d, $J=46$ Hz, 1H), 6.21 (d, $J=25$ Hz, 1H), 4.01–4.08 (m, 2H), 1.6–1.66 (m, 2H), 1.3–1.58 (m, 2H), 0.88 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 141.7 (d, $J_{PC}=119$ Hz), 135.2 (d, $J_{PCC}=12$ Hz), 130.1 (d, $J_{PCC}=13$ Hz), 128.7 (3C), 127.0 (d, $J_{PCCC}=6$ Hz, 2C), 65.9 (d, $J_{POC}=7$ Hz), 32.3 (d, $J_{POCC}=6$ Hz), 18.7, 13.5; ^{31}P NMR ($CDCl_3$) δ 28.7 (dqt, $J=563$, 25, 8 Hz); HRMS (EI^+) calcd for $C_{12}H_{17}O_2P$, $(M)^+$ 224.0966, found 224.0967.

4.5.21. Butyl (*trans*-styryl)phosphinate (Table 4, entry 3).[23] ^{1}H NMR ($CDCl_3$) δ 7.33 (d, $J=560$ Hz, 1H), 7.3–7.58 (m, 5H), 6.4 (d, $J=18$ Hz, 1H), 6.37 (d, $J=22$ Hz, 1H), 4.06–4.15 (m, 2H), 1.67–1.75 (m, 2H), 1.4–1.48 (m, 2H), 0.95 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 149.7 (d, $J_{PCCC}=7$ Hz), 134.5 (d, $J_{PCC}=21$ Hz), 130.6, 129.0 (2C), 127.9 (2C), 116.3 (d, $J_{PC}=133$ Hz), 65.7 (d, $J_{POC}=6$ Hz), 32.5 (d, $J_{POCC}=6$ Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 25.8 (dtt, $J=560$, 23, 8 Hz); HRMS (EI^+) calcd for $C_{12}H_{17}O_2P$, $(M)^+$ 224.0966, found 224.0963.

4.5.22. Butyl [1-(3-methyl-butyl)vinyl]phosphinate (Table 4, entry 4). ^{1}H NMR ($CDCl_3$) δ 7.1 (d, $J=547$ Hz, 1H), 5.94 (d, $J=25$ Hz, 1H), 5.84 (d, $J=49$ Hz, 1H), 3.95–4.1 (m, 2H), 2.2–2.35 (m, 2H), 1.5–1.7 (m, 3H), 1.35–1.44 (m, 4H), 0.85–0.95 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 142.5 (d, $J_{PC}=118$ Hz), 128.5 (d, $J_{PCC}=14$ Hz), 66.1 (d, $J_{POC}=7$ Hz), 37.2 (d, $J_{PCC}=5$ Hz), 32.7 (d, $J_{POCC}=6$ Hz), 28.7 (d, $J_{PCCC}=12$ Hz), 27.9, 22.6, 22.5, 19.0, 13.8; ^{31}P NMR ($CDCl_3$) δ 31.6 (dm, $J=547$ Hz).

4.5.23. Butyl (1-propyl-pent-1-enyl)phosphinate (Table 4, entry 5). ^{1}H NMR ($CDCl_3$) δ 6.98 (d, $J=542$ Hz, 1H), 6.37 (dt, $J=33$, 7 Hz, 1H), 3.88–4.0 (m, 2H), 2.0–2.2 (m, 4H), 1.55–1.63 (m, 2H), 1.3–1.45 (m, 6H), 0.87 (t, $J=7$ Hz, 9H); ^{13}C NMR ($CDCl_3$) δ 147.1 (d, $J_{PCC}=14$ Hz), 131.9 (d, $J_{PC}=124$ Hz), 65.7 (d, $J_{POC}=7$ Hz), 32.6 (d, $J_{POCC}=7$ Hz), 30.5 (d, $J_{PCC}=18$ Hz), 28.4 (d, $J_{PCCC}=12$ Hz), 22.6, 21.9, 18.9, 14.2, 13.9, 13.7; ^{31}P NMR ($CDCl_3$) δ 33.5 (dm, $J=542$ Hz); HRMS (EI^+) calcd for $C_{12}H_{25}O_2P$, $(M)^+$ 232.1592, found 232.1590.

4.5.24. Butyl (1-methyl-vinyl)phosphinate (Table 4, entry 6). ^{1}H NMR ($CDCl_3$) δ 7.09 (d, $J=549$ Hz, 1H), 5.79–6.0 (m, 2H), 3.97–4.14 (m, 2H), 1.96 (d, $J=14$ Hz, 3H), 1.62–1.75 (m, 2H), 1.35–1.5 (m, 2H), 0.95 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 129.8 (d, $J_{PCC}=14$ Hz), 66.0 (d, $J_{POC}=13$ Hz), 32.7 (d, $J_{POCC}=6$ Hz), 19.0, 17.1 (d, $J_{POCCC}=13$ Hz), 13.8; ^{31}P NMR ($CDCl_3$) δ 30.5 (dm, $J=549$ Hz).

4.5.25. Ethyl (1-bromo-oct-1-enyl)phosphinate (Table 4, entry 7). ^{1}H NMR ($CDCl_3$) δ 6.97 (d, $J=601$ Hz, 1H), 7.16–7.3 (m, 1H), 4.07–4.2 (m, 2H), 2.37 (qd, $J=7$, 3 Hz, 2H), 1.41–1.56 (m, 2H), 1.39 (t, $J=7$ Hz, 3H), 1.23–1.35 (m, 6H), 0.89 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 150.9 (d, $J_{PCC}=13$ Hz), 114.9 (d, $J_{PC}=136$ Hz), 62.4 (d, $J_{POC}=7$ Hz), 32.1 (d, $J_{PCCC}=11$ Hz), 31.7, 29.1, 27.6, 22.7, 16.5 (d, $J_{POCC}=7$ Hz), 14.3; ^{31}P NMR ($CDCl_3$) δ 20.9 (ddd, $J=602$, 14, 9 Hz); HRMS (ES^+) calcd for $C_{10}H_{20}BrO_2P$, $(M+H)^+$ 283.0463, found 283.0456.

4.5.26. Butyl (1-butyl-vinyl)phosphinate (Table 4, entry 8). ^{1}H NMR ($CDCl_3$) δ 7.13 (d, $J=547$ Hz, 1H), 5.97 (d, $J=25$ Hz, 1H), 5.86 (d, $J=44$ Hz, 1H), 4.0–4.16 (m, 2H), 2.15–2.3 (m, 2H), 1.1–2.06 (m, 8H), 0.9–0.97 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 142.0 (d, $J_{PC}=118$ Hz), 128.5 (d, $J_{PCC}=13$ Hz), 65.8 (d, $J_{POC}=7$ Hz), 32.4 (d, $J_{POCC}=6$ Hz), 30.4 (d, $J_{PCC}=12$ Hz), 30.0 (d, $J_{PCCC}=5$ Hz), 22.3, 18.8, 13.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 30.9 (dm, $J=547$ Hz); HRMS (ES^+) calcd for $C_{10}H_{21}O_2P$, $(M+H)^+$ 205.1357, found 205.1360.

4.5.27. Butyl (1-carboxylic acid-*tert*-butyl ester-1,2,3,6-tetrahydro-pyridin-4-yl)phosphinate (Table 4, entry 9). ^{1}H NMR ($CDCl_3$) δ 7.07 (d, $J=552$ Hz, 1H), 6.62–6.75 (m, 1H), 4.0–4.13 (m, 4H), 3.45–3.6 (m, 2H), 2.2–2.4 (m, 2H), 1.64–1.74 (m, 2H), 1.47 (s, 9H), 1.36–1.48 (m, 2H), 0.95 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 154.7, 139.8 (d, $J_{PCC}=11$ Hz), 129.8 (d, $J_{PC}=56$ Hz), 80.4, 66.2 (d, $J_{POC}=7$ Hz), 43.7 (br), 39.4 (br), 32.6 (d, $J_{POCC}=6$ Hz), 28.6 (3C), 23.5 (d, $J_{PCC}=10$ Hz), 18.9, 13.8; ^{31}P NMR ($CDCl_3$) δ 25.99, 26.6 (dm, $J=552$ Hz); HRMS (EI^+) calcd for $C_{14}H_{26}NO_4P$, $(M)^+$ 303.1599, found 303.1601.

4.5.28. Butyl (3-phenyl-propyl)phosphinate (Scheme 3a, R=Bu). ^{1}H NMR ($CDCl_3$) δ 7.0 (d, $J=528$ Hz, 1H), 7.15–7.31 (m, 5H), 3.9–4.15 (m, 2H), 2.72 (t, $J=7$ Hz, 2H), 1.57–2.0 (m, 6H), 1.26–1.46 (m, 2H), 0.93 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 140.9, 128.7 (4C), 126.5, 66.3 (d, $J_{POC}=7$ Hz), 36.4 (d, $J_{PCC}=16$ Hz), 32.5 (d, $J_{POCC}=6$ Hz), 28.3 (d, $J_{PC}=94$ Hz), 22.6 (d, $J_{PCCC}=3$ Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$) δ 39.9 (dm, $J=528$ Hz); HRMS (EI^+) calcd for $C_{13}H_{21}O_2P$, $(M)^+$ 240.1279, found 240.1275.

4.5.29. Ethyl (3-phenyl-propyl)phosphinate (Scheme 3a, R=Et). ^{1}H NMR ($CDCl_3$) δ 7.06 (d, $J=530$ Hz, 1H),

7.15–7.31 (m, 5H), 3.98–4.23 (m, 2H), 2.71 (t, $J=7$ Hz, 2H), 1.72–2.0 (m, 4H), 1.34 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 140.9, 128.74 (4C), 126.5, 62.6 (d, $J_{POC}=7$ Hz), 36.5 (d, $J_{PCC}=16$ Hz), 28.3 (d, $J_{PC}=94$ Hz), 22.6 (d, $J_{PCCC}=3$ Hz), 16.5 (d, $J_{POCC}=6$ Hz); ^{31}P NMR ($CDCl_3$) δ 39.7 (d, $J=530$ Hz).

4.5.30. Butyl (3-phenyl-prop-2-enyl)phosphinate (Scheme 3b). ^{1}H NMR ($CDCl_3$) δ 7.06 (d, $J=543$ Hz, 1H), 7.23–7.38 (m, 5H), 6.06–6.17 (m, 1H), 6.55 (dd, $J=16$, 6 Hz, 1H), 4.0–4.2 (m, 2H), 2.82 (dd, $J=19$, 8 Hz, 2H), 1.65–1.74 (m, 2H), 1.36–1.48 (m, 2H), 0.94 (t, $J=7$ Hz, 3H); ^{13} C NMR ($CDCl_3$) δ 136.6, 136.1 (d, $J_{PCCC}=14$ Hz), 128.7 (2C), 128.0, 126.4 (2C), 116.9 (d, $J_{PCC}=10$ Hz), 66.5 (d, $J_{POC}=7$ Hz), 34.7 (d, $J_{PC}=90$ Hz), 32.6 (d, $J_{POCC}=6$ Hz), 18.9, 13.8; ^{31}P NMR ($CDCl_3$) δ 37.1 (dt, $J=543$ Hz, $J=7$ Hz); HRMS (EI^+) calcd for $C_{13}H_{19}O_2P$, $(M)^+$ 238.1123, found 238.1126.

4.5.31. Butyl (3,7-dimethyl-oct-6-enyl)phosphinate (Scheme 3c). Mixture of stereoisomers: ^{1}H NMR ($CDCl_3$) δ 7.1 (d, $J=528$ Hz, 1H), 5.08 (t, $J=7$ Hz, 1H), 3.94–4.17 (m, 2H), 1.91–2.08 (m, 2H), 1.1–1.84 (m, 17H), 0.86–0.97 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 131.7, 124.6, 66.3 (d, $J_{POC}=7$ Hz), 65.7 (d, $J_{POC}=6$ Hz), 36.6, 33.1 (d, $J_{PCCC}=16$ Hz), 32.6 (d, $J_{POCC}=6$ Hz), 27.5 (d, $J_{PCC}=3$ Hz), 26.5 (d, $J_{PC}=94$ Hz), 25.9, 25.5 19.0 (d, $J=6$ Hz), 17.8, 13.8, 13.7; ^{31}P NMR ($CDCl_3$) δ 41.35, 41.33 (d, $J=528$ Hz); HRMS (EI^+) calcd for $C_{14}H_{29}O_2P$, $(M)^+$ 260.1905, found 260.1904.

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Supplementary data

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References and notes

1. Reviews: (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (b) Barañano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287. See also references cited in: (c) Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327. (d) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (e) Al-Masum, M.; Kumaraswamy, G.; Livinghouse, T. *J. Org. Chem.* **2000**, *65*, 4776. (f) Oshidi, T.; Imamoto, T. *J. Am. Chem. Soc.* **1992**, *114*, 3975.
2. For examples of transition metal catalyzed P–C bond formation via cross-coupling: (a) Martorell, G.; Garcías, X.; Janura, M.; Saá, J. M. *J. Org. Chem.* **1998**, *63*, 3463. (b) Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, *55*, 5033. (c) Tunney, S. E.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 748. (d) Xu, Y.; Zhang, J. *Synthesis* **1984**, 778. (e) Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1983**, 377. (f) Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1984**, 781. (g) Xu, Y.; Li, Z. *Synthesis* **1986**, 240. (h) Xu, Y.; Xia, J.; Guo, H. *Synthesis* **1986**, 691. (i) Xu, Y.; Zhang, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1606. (j) Xu, Y.; Wej, H.; Zhang, J.; Huang, G. *Tetrahedron Lett.* **1989**, *30*, 949. (k) Tavs, P.; Wetkamp, H. *Tetrahedron* **1970**, *26*, 5529. (l) Kazankova, M. A.; Trostyanskaya, I. G.; Lutsenko, S. V.; Beletskaya, I. P. *Tetrahedron Lett.* **1999**, *40*, 569. (m) Kurtz, L.; Lee, G.; Morgans, D., Jr.; Waldyke, M. J.; Ward, T. *Tetrahedron Lett.* **1990**, *31*, 6321. (n) Zhong, P.; Huang, X.; Xiong, Z.-X. *Synlett* **1999**, *6*, 721. (o) Fiaud, J.-C. *J. Chem. Soc., Chem. Commun.* **1983**, 1055. (p) Malet, R.; Moreno-Manas, M.; Pleixats, R. *Synth. Commun.* **1992**, *22*, 2219. (q) Bennett, S. N. L.; Hall, R. G. *J. Chem. Soc. Trans. 1* **1995**, 1145. (r) Imamoto, T.; Oshiki, T.; Onozawa, T.; Matsuo, M.; Hikosaka, T.; Yanagawa, M. *Heteroatom Chem.* **1992**, *3*, 563. (s) Al-Masum, M.; Kumuraswamy, G.; Livinghouse, T. *J. Org. Chem.* **2000**, *65*, 4776. (t) Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, *55*, 5033. (u) Kwong, F. Y.; Chan, K. S. *Chem. Commun.* **2000**, 1069. (v) Maffei, M.; Buono, G. *Phosphorus, Sulfur, Silicon* **1993**, *79*, 297. (w) Beletskaya, I. P.; Kazankova, M. A. *Russ. J. Org. Chem.* **2002**, *38*, 1391. (x) Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315.
3. (a) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1980**, *21*, 3595. (b) Hirao, T.; Masunaga, T.; Yamada, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909.
4. For references on the catalytic transfer hydrogenation with hypophosphorous derivatives, see: (a) Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567. (b) Johnstone, R. A. W.; Wilby, A. H.; Entwistle, A. I. *Chem. Rev.* **1985**, *85*, 129. (c) Boyer, S. K.; Bach, J.; McKenna, J.; Jagdmann, E., Jr. *J. Org. Chem.* **1985**, *50*, 3408. (d) Johnstone, R. A. W.; Wilby, A. H. *Tetrahedron* **1981**, *37*, 3667. (e) Sala, R.; Doria, G.; Passarotti, C. *Tetrahedron Lett.* **1984**, *25*, 4565. (f) Khai, B. T.; Arcelli, A. *J. Org. Chem.* **1989**, *54*, 949. (g) Brigas, A. F.; Johnstone, R. A. W. *Tetrahedron* **1992**, *48*, 7735. (h) Marques, C. A.; Selva, M.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 529. (i) Khai, B. T.; Arcelli, A. *Chem. Ber.* **1993**, *126*, 2265.
5. (a) Lei, H.; Stoakes, M. S.; Schwabacher, A. W. *Synthesis* **1992**, 1255. (b) Schwabacher, A. W.; Stefanescu, A. D. *Tetrahedron Lett.* **1996**, *37*, 425. (c) Schwabacher, A. W.; Zhang, S.; Davy, W. *J. Am. Chem. Soc.* **1993**, *115*, 6995. (d) Lei, H.; Stoakes, M. S.; Herath, K. P. B.; Lee, J.; Schwabacher, A. W. *J. Org. Chem.* **1994**, *59*, 4206.
6. Holt, D. A.; Erb, J. M. *Tetrahedron Lett.* **1989**, *30*, 5393.
7. (a) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510. (b) Dumond, Y. R.; Montchamp, J.-L. *J. Organomet. Chem.* **2002**, *653*, 252.
8. Huang, Z.; Bravo-Altamirano, K.; Montchamp, J.-L. *Comptes Rendus Chimie* **2004**, *7/8–9*, 763.
9. Deprèle, S.; Montchamp, J.-L. *J. Organomet. Chem.* **2002**, *643–644*, 154.
10. Fitch, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 61.
11. Dumond, Y. R.; Baker, R. L.; Montchamp, J.-L. *Org. Lett.* **2000**, *2*, 3341.
12. Diazoalkanes: (a) Tokutake, N.; Hiratake, J.; Katoh, M.; Irie, T.; Kato, H.; Oda, J. *Bioorg. Med. Chem.* **1998**, *6*, 1935. (b) Lloyd, J.; Schmidt, J. B.; Hunt, J. T.; Barrish, J. C.; Little,

D. K.; Tymiak, A. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1323. (c) Martin, M. T.; Angeles, T. S.; Sugasawara, R.; Aman, N. I.; Napper, A. D.; Darsley, M. J.; Sanchez, R. I.; Booth, P.; Titmas, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 6508. (d) Baillie, A. C.; Cornell, C. L.; Wright, B. J.; Wright, K. *Tetrahedron Lett.* **1992**, *33*, 5133. Carbodiimides+ROH: (e) Karanewsky, D. S.; Badia, M. C. *Tetrahedron Lett.* **1986**, *27*, 1751. (f) Sampson, N. A.; Bartlett, P. A. *J. Org. Chem.* **1988**, *53*, 4500. (g) Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Loots, M. J.; Perri, M. G.; Petrillo, E. W., Jr.; Powell, J. R. *J. Med. Chem.* **1988**, *31*, 204. (h) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385. (i) Chen, S.; Coward, J. K. *J. Org. Chem.* **1998**, *63*, 502. (j) Qiao, L.; Nan, F.; Kunkel, M.; Gallegos, A.; Powis, G.; Kozikowski, A. P. *J. Med. Chem.* **1998**, *41*, 3303. (k) Willems, H. A. M.; Veeneman, G. H.; Westerduin, P. *Tetrahedron Lett.* **1992**, *33*, 2075. $P(OAlk)_3$: (l) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652. (m) Elepina, L. T.; Balakhontseva, V. N.; Nifant'ev, E. E. *J. Gen. Chem. USSR* **1973**, *43*, 1795. $(AlkO)_2SO_2$: (n) Hatt, H. H. *J. Chem. Soc.* **1933**, 776. PCl_5: (o) Natchev, I. A. *Liebigs Ann. Chem.* **1988**, 861. PyBOP/*i*-Pr_2NEt: (p) Chen, S.; Lin, C.-H.; Walsh, C. T.; Coward, J. K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 505. (q) See also Ref. 13.

13. Froestl, W.; Mickel, S. J.; von Sprecher, G.; Diel, P. J.; Hall, R. G.; Maier, L.; Strub, D.; Melillo, V.; Baumann, P. A.; Bernasconi, R.; Gentsch, C.; Hauser, K.; Jaekel, J.; Karlsson, G.; Klebs, K.; Maitre, L.; Marescaux, C.; Pozza, M. F.; Schmutz, M.; Steinmann, M. W.; van Riezen, H.; Vassout, A.; Mondadori, C.; Olpe, H.-R.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3313.
14. Deprèle, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9386.
15. Montchamp, J. L. *J. Organomet. Chem.* **2005**, *690*, 2388.
16. (a) Boyd, E. A.; Regan, A. C.; James, K. *Tetrahedron Lett.* **1994**, *35*, 4223. (b) Boyd, E. A.; Corless, M.; James, K.; Regan, A. C. *Tetrahedron Lett.* **1990**, *31*, 2933. (c) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2119.
17. Abrunhosa-Thomas, I.; Montchamp, J.-L., unpublished results.
18. (a) Tsuji, J. Palladium Reagents and Catalysts: Innovations in Organic Synthesis; Wiley: New York, 2002; pp 366–379. (b) Inomata, K.; Kinoshita, H. In Negishi, E., Ed.; Handbook of Organopalladium Chemistry for Organic Synthesis; Wiley: New York, 2002; Vol. 2; Chapter V.2.3.1.
19. Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857.
20. (a) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354. (b) Hayashi, T.; Iwamura, H.; Naito, M.; Matsumoto, Y.; Uozumi, Y.; Miki, M.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 775.
21. Gallagher, M. J.; Ranasinghe, M. G.; Jenkins, I. D. *Phosphorus, Sulfur, Silicon* **1996**, *115*, 255.
22. Kabatschnik, M. I.; Tsvetkov, E. N.; Chang, C.-Y. *Dokl. Chem.* **1959**, *124–129*, 309.
23. Levin, Y. A.; Galeev, V. S. *J. Gen. Chem. USSR* **1967**, *37*, 2604.

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Practical application of new catalytic methods: a concise synthesis of a potent PDE IV inhibitor

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This paper is dedicated to the memory of Jackie Smitrovich, a dear friend and talented colleague.

Abstract—An efficient synthesis of a potent PDE IV inhibitor **1** is described. The synthesis is highlighted by two practical and efficient catalytic reactions: a highly selective catalytic palladium mediated carbonylation of the pyridine side chain and an efficient palladium-catalyzed Suzuki–Miyaura coupling of a chloropyridine-*N*-oxide.

1. Introduction

Phosphodiesterase IV inhibitors have generated interest as potential pharmaceutical targets for the intervention of various detrimental inflammatory responses including colitis, rheumatoid arthritis, asthma and chronic obstructive pulmonary disease.[1] Phosphodiesterase enzymes are responsible for the inactivation of cyclic AMP (cAMP) which in turn effects neutrophil activation. During many of the non-infectious human diseases described above, the recruitment of neutrophils plays a crucial role in the development of tissue damage. Since the neutrophil activation is dependent upon cAMP protein kinase A, inhibitors of PDE IV can enhance intracellular cAMP and decrease inflammatory cell activation. Several other mechanisms may contribute to the action of PDE IV inhibitors including inhibition of tumor necrosis factor (TNFα) release, increase in interleukin (IL)-1 release and suppression of T-lymphocyte function. Early PDE IV inhibitors such as rolipram, suffer from side effects such as nausea and vomiting which restrict their use as therapeutic agents. Second generation compounds with a reduced side effect liability such as Ariflo® have been identified. Efforts to identify potent selective inhibitors of PDE IV with the goal of identifying a therapeutic agent which may be efficacious in the treatment of rheumatoid arthritis, asthma and chronic obstructive pulmonary disease are on-going throughout the pharmaceutical industry.

Compound **1** was identified as a potent PDE IV inhibitor and a promising development candidate for clinical trials. As a result, we required a concise, scalable synthesis to prepare kilogram quantities of **1**. The retrosynthetic analysis of **1** is outlined in Scheme 1. Formation of the biphenyl ring junction was envisioned as the key late-stage step, bringing together two highly functionalized intermediates (**2** and **3**) using cross-coupling chemistry. Formation of the requisite naphthyridone **2** was anticipated to arise from an extension of previous chemistry in these labs for the synthesis of naphthyridones.[2] This strategy benefits from having the boronic acid included as a part of the readily available starting material, 3-aminophenyl boronic acid, and thus eliminates a potentially delicate cryogenic step for installation of this functional group on a highly functionalized intermediate late in the synthesis. Synthesis of the 2,5-disubstituted pyridine-*N*-oxide **3** was planned to arise from the readily available 2,5-dihalopyridine, and would require a practical and selective differentiation of the two halide groups.

This retrosynthetic strategy has formed the basis of a concise and practical synthesis of the PDE IV inhibitor **1**, as disclosed herein. The manuscript is divided into four major sections: (1) optimization of the naphthyridone synthesis, (2) defining a new synthesis of the functionalized pyridine-*N*-oxide partner involving a novel catalytic carbonylation reaction, (3) development of

Keywords: Naphthyridone; Pyridine; Suzuki–Miyaura coupling; Carbonylation; *N*-Oxide.
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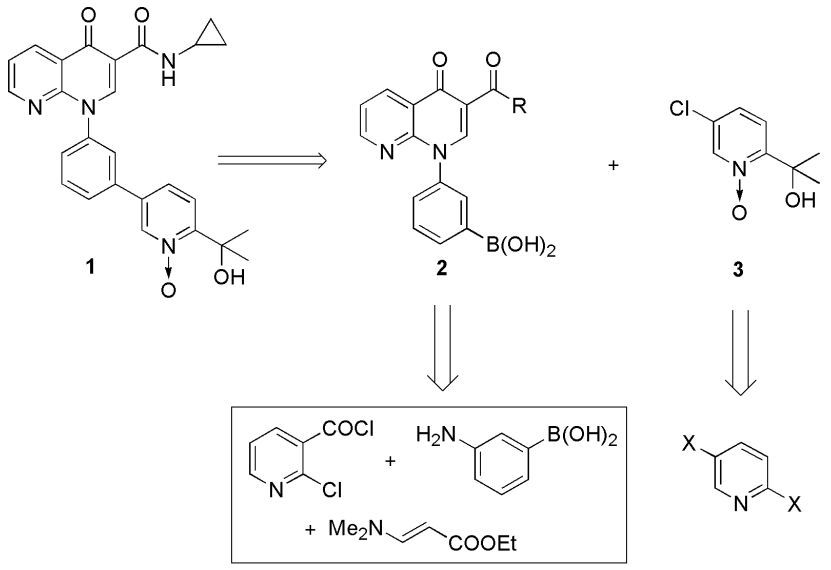


Scheme 1.

the challenging and unprecedented Suzuki–Miyaura coupling of a substituted chloro-pyridine-*N*-oxide, and (4) installation of the cyclopropyl amide and completion of the synthesis.

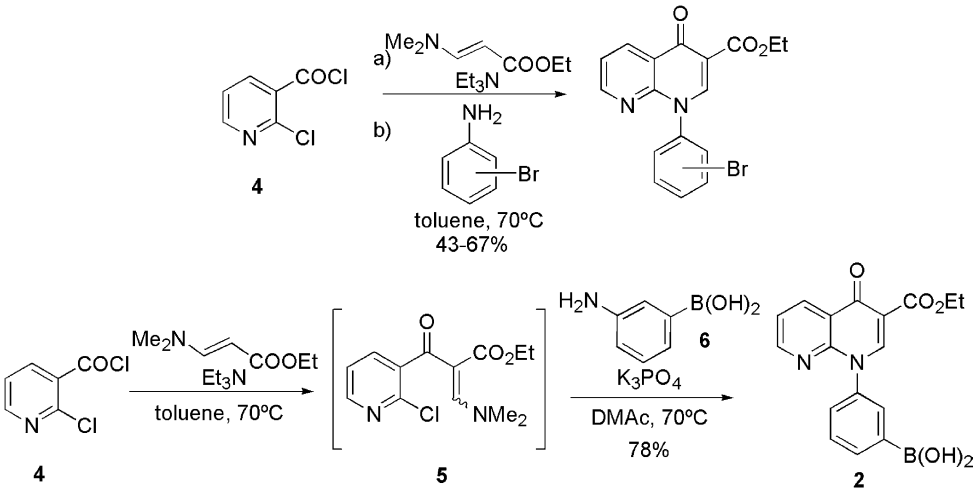
1.1. Naphthyridone synthesis

Naphthyridone formation is typically achieved in three separate and tedious steps.[3] We developed a new one-pot process which is both convenient for varying substitution, and provided pure material in good yield by direct crystallization of the product from the crude reaction mixture (Scheme 2).[2] This procedure works very well to generate halo- or alkyl-substituted naphthyridones.

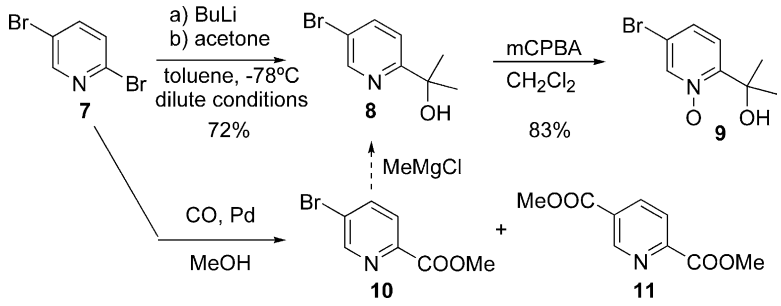
From this experience with naphthyridones, we adapted our procedure to accommodate the boronic acid moiety required for the subsequent Suzuki–Miyaura coupling reaction. When we applied our one-pot protocol to the synthesis of the desired naphthyridone boronic acid, however, we experienced crystallization and isolation difficulties. These problems were eliminated by simply removing the triethylamine HCl salt formed in the first reaction by filtration into a second pot, followed by a solvent switch into the more polar solvent dimethylacetamide, and then addition of the aminophenylboronic acid and base to complete the cyclization. Thus naphthyridonephenylboronic acid **2** was synthesized directly in two pots via a through-process in 78% yield, thereby eliminating the need to install an appropriate functional group later for the cross-coupling.

1.2. Synthesis of the functionalized pyridine—selective carbonylation of 2,5-dichloropyridine

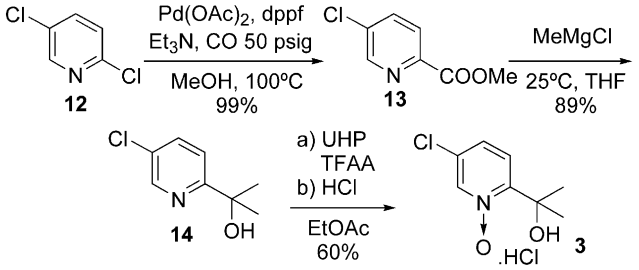
With our boronic acid coupling partner in hand, we next surveyed methods to make the substituted bromopyridine-*N*-oxide substrate. There are a number of relevant reports in the literature, including one from these laboratories describing the selective lithiation of 2,5-dibromopyridine.[4] Initially we used this selective lithiation/alkylation to introduce the dimethylcarbinol onto the 2-position of the pyridine, followed by *N*-oxidation with *m*CPBA (Scheme 3).



Scheme 2. One-pot method for creation of 1,8-naphthyridin-4ones.



Scheme 3.



Scheme 4.

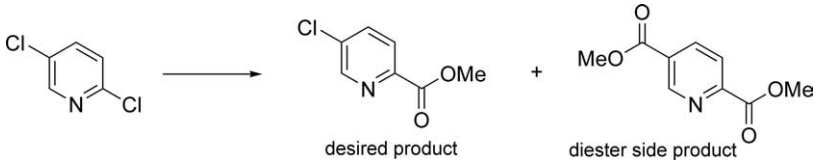
Owing to the low volume productivity and the requirement for cryogenic conditions for lithiation selectivity, we sought a more efficient route to the carbinolpyridine **9**.

We decided to next explore a selective metal catalyzed carbonylation route. We repeated a reported preparation of methyl 5-bromo-carboxypyridine from 2,5-dibromopyridine, and noted formation of >30% diester **11** along with the desired monocarbonylated product.[5] Screening with >30 different catalysts failed to show satisfactory improvement. Initial carbonylation is selective for the 2-position: no 2-bromo-5-carboxypyridine was detected. However, once the desired 2-carboxypyridine is formed, the bromide in the 5-position becomes activated and is susceptible to the carbonylation conditions. Separation of the monoester product from the diester product and the starting dibromopyridine is tedious. Song and Yee[6] have reported an interesting two step solution to the problem, however we desired a more direct, efficient solution. We decided to investigate the selective carbonylation of 2,5-dichloropyridine **12** (Scheme 4).

Selective carbonylation of dichloropyridines has been reported with varying degrees of success.[7] Typically high pressures (up to 100 bar CO) and temperatures (>100 °C) have been used to produce the mono-carbonylated product. Advances have been reported by Bessard and Crettaz, the Beller group, and most recently by our group.[8]

Catalyst screening was undertaken to identify optimal selective carbonylation conditions to convert **12** to **13** (Table 1). The choice of ligand and base were the most important variables investigated. Use of monodentate ligands gave either little reaction (Entry 4), or very poor selectivity (Entries 1 and 3). Use of bidentate ligands typically increased the reaction rate, but again, gave poor selectivity (Entry 5). Base was also important for reaction conversion: sodium acetate was less effective than amine bases (entry 2 and 9). The bidentate dppf ligand provided both good reaction rate as well as good selectivity (entry 9). Selectivity was further improved by limitation of triethylamine to just 1.01 equiv to help prevent over-carbonylation (entry 10). Catalyst loading of 0.2 mol% was optimal, giving the most reproducible results upon scale up. The carbonylation reaction is extremely efficient, performed

Table 1. Optimization of mono-carbonylation of 2,5-dichloropyridine



Entry	Catalyst	mol%	Solvent	Base	equiv	CO (psig)	°C	h	% Product	% Diester	% St. mat.
1	$PdCl_2(PPh_3)_2$	10	MeOH	Et_3N	1.2	725	140	8	69	17	14
2	$Pd(OAc)_2$ + dppf	10	EtOH	NaOAc	3.0	220	120	3	0	0	100
3	$PdCl_2(PPh_3)_2$	5	MeOH	Et_3N	1.1	100	100	8	75	25	0
4	$PdCl_2[P(fur)_3]_2$	5	MeOH	Et_3N	1.1	100	100	8	6	0	88
5	$PdCl_2$(BINAP)	5	MeOH	Et_3N	1.1	100	100	8	50	50	0
6	$PdCl_2$(dppp)	5	MeOH	Et_3N	1.1	100	100	8	79	21	0
7	$Pd(OAc)_2$ + dppf	5	MeOH	Et_3N	1.1	100	100	8	73	26	1
8	$PdCl_2$(dppf)	5	MeOH	Et_3N	1.1	100	100	8	78	22	0
9	$Pd(OAc)_2$ + dppf	0.2	MeOH	Et_3N	1.1	50	80	6	91	1.5	7.5
10	$Pd(OAc)_2$ + dppf	0.2	MeOH	Et_3N	1.01	50	100	7	98	1	1

under relatively mild conditions, and extremely productive as only four volumes of methanol solvent were used. The yield of **13** was excellent, and the diester side product was <0.5% HPLC area percent. Unlike the bromide analogue **10**, however, isolation of **13** initially proved problematic: **13** possesses significant solubility in every solvent tested, from hexanes to water! After much experimentation, optimal recovery could be realized by precipitation from a methanol–brine mixture which allowed isolation of the desired **13** in 92–95% yield.

With mono-ester **13** in hand, conversion to the carbinol **14** was studied next. Intermediate **14** was generated by addition of 2.5 equiv methyl Grignard reagent. Inverse addition of the substrate to a solution of the Grignard reagent was necessary to insure completion of the reaction. The resulting product **14** is an oil and was not isolated, but was carried directly through into the *N*-oxidation step. Oxidation was sluggish with *m*CPBA conditions, even when using a large excess of *m*CPBA. Sharpless MTO conditions were not any better. The oxidation was best achieved using the urea hydrogen peroxide/trifluoroacetic acid anhydride reagent as reported by Caron.[9] Performing the oxidation in ethyl acetate allowed isolation of the product as the HCl salt in greater than 99% purity, which proved best for handling and storing, as well as purification of the fully functionalized coupling partner **3**.

1.3. Suzuki–Miyaura cross-coupling

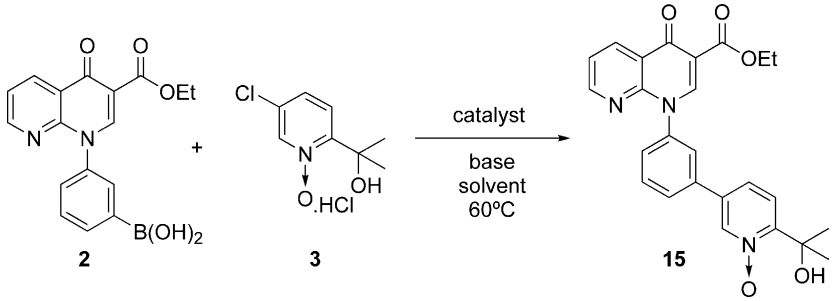
The Suzuki–Miyaura coupling between the boronic acid **2** and the chloride salt **3** failed using typical Suzuki–Miyaura conditions, (Table 2, entries 1 and 2) however, desired product was formed with the use of the Fu ligand tri-*t*-butylphosphine (entry 6).[10] The ratio of palladium to ligand was crucial to the success of the coupling (entries 3, 4 vs 6). The typical 2:1 ratio of tri-*t*-butylphosphine to palladium failed to produce any product at all. Lowering the ratio to 1:1 produced a much more active catalyst. We found it convenient to mix the palladium reagent with the ligand, and add the catalyst solution to the substrate solution under inert atmosphere. We abandoned the use of $Pd_2(dba)_3$ as the palladium source, as it was difficult to remove the dibenzylidineacetone from the batch downstream. Use of the π-allyl palladium chloride dimer reagent consistently produced excellent results. The purity of the chloride substrate **3** was also important to success of the coupling: using **3** as the free base produced inconsistent results, and the reaction rarely proceeded to completion. Isolation of **3** as the HCl salt from the *N*-oxidation step typically provided the chloride in >99.8% purity, which performed reliably in the coupling step. Choice of solvent and base were also critical for success of the reaction. The reaction proceeded only in polar coordinating solvents such as dimethylacetamide and dimethylformamide, and the presence of water was found to accelerate the reaction. Several bases examined caused extensive deborination of **2**, particularly K_3PO_4 (entry 6). The most effective base was found to be potassium carbonate. Under these conditions, **15** was consistently produced in 80–90% yield. Importantly, no deoxygenation of the *N*-oxide was ever detected.

1.4. Installation of the cyclopropyl amide and completion of the synthesis

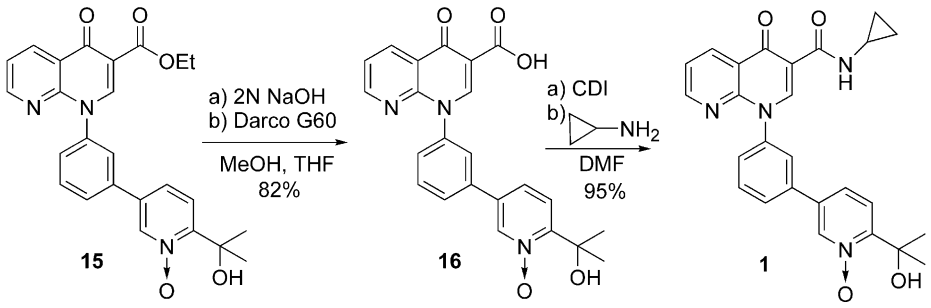
The coupled product **15** was transformed into **1** by hydrolysis to the acid **16** and subsequent amide formation. Hydrolysis was uneventful. Residual palladium was removed at this point by stirring with 100 wt% Darco G-60, followed by isolation of pristine **16**. CDI mediated amide formation was achieved in 95% yield to produce the desired target **1** (Scheme 5).

In conclusion, we have synthesized the potent PDE IV clinical candidate **1** in four linear steps, plus three steps required for the construction of the substituted chloropyridine-*N*-oxide coupling partner. The synthesis is efficient and scalable for processing kilogram quantities. A through-

Table 2. Optimization of coupling



Entry	Catalyst	mol%	L/Pd	Solvent(s)	Base	% Prod.	% Deborinated
1	$Pd(OAc)_2$/dppf	5	1/1	DMF/H_2O	K_2CO_3	0	0
2	POPd catalyst	5	2/1	DMAc/H_2O	K_2CO_3	0	0
3	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	5/20	2/1	MeOH	K_2CO_3	0	0
4	Pd[P(*t*-Bu)$_3$]	5	2/1	DMF/H_2O	K_2CO_3	0	0
5	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	5/10	1/1	dry DMF	Cs_2CO_3	0	0
6	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	3/6	1/1	DMAc/H_2O	K_3PO_4	54	45
7	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	20/40	1/1	DMF/H_2O	K_2CO_3	50	10
8	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	2.5/5	1/1	DMF/H_2O	K_2CO_3	70	20
9	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	5/10	1/1	DMF/H_2O	Cs_2CO_3	77	5
10	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	5/10	1/1	DMAc/H_2O	K_2CO_3	92	<2



Scheme 5. Amide formation.

process synthesis of the naphthyridone core, a highly selective carbonylation of the functionalized chloropyridine-*N*-oxide, and an unprecedented Suzuki–Miyaura coupling of a chloropyridine-*N*-oxide were developed.

2. Experimental

2.1. General methods

NMR and ^{13}C NMR were recorded at ambient temperature on a Bruker DPX 400 at a frequency of 400.13 and 100.61 MHz, respectively. The chemical shifts are reported in ppm relative to residual $CHCl_3$ ($\delta=7.27$) for proton and $CDCl_3$ ($\delta=77.0$) for carbon unless otherwise indicated. The data are reported as follows: proton multiplicities (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, and app=apparent), coupling constants, and integration. Microanalyses were performed by Quantitative Technologies, Inc. Melting points are reported uncorrected. Flash chromatography was performed using the indicated solvent system on EM Reagents silica gel (SiO_2) 60 (230–400 mesh). Materials. Solvents and triethylamine were used as received. All reagents used were commercially available.

2.1.1. Ethyl-1-(phenyl-3-boronic acid)-1,4-dihydro[1,8]-naphthyridin-4-one-3-carboxylate (2). A 50 L round bottom flask was equipped with an overhead stirrer, nitrogen blanket, and thermocouple/steam regulator. Toluene 20 L was added to the vessel. *K*F of toluene must be <200 ppm. Triethylamine 3.2 L (22.8 mol) was added in one portion while stirring. Next, ethyl dimethylacrylate 2.6 kg (18.2 mol) was charged to the vessel, followed by 2-chloronicotinoyl chloride 2.0 kg (11.4 mol) added as a solid. The reaction was heated to 70 °C and aged until completion-approx. 5 h. LC samples were quenched with *n*-propylamine, and consumption of starting material is complete when less then 3% LCAP of *n*-propyl-2-chloronicotin-amide remains. The reaction mixture was allowed to cool to ambient temperature and filtered to remove the triethylamine hydrochloride salt that formed during the reaction. The vessel/line and filter pot were rinsed with toluene 10 L. The toluene solution was switched under reduced pressure ($T_{int}<30$ °C) to DMAc 10 L and carried forward into next flask as a solution in DMAc. A 100 L round bottom was equipped with an overhead stirrer, nitrogen inlet and condenser. The step 1 intermediate solution in DMAc 10 L was added. DMAc 10 L was used as vessel and line rinses and added to the round bottom bringing the final volume of DMAc to 20 L. Potassium phosphate tribasic 4.86 kg (22.8 mol) was added, followed by immediate addition of 3-aminophenylboronic acid–HCl 1.68 kg (9.7 mol). Caution—mild exotherm ~10 °C upon addition of 3-aminophenylboronic acid–HCl. Reaction mixture was heated to 70 °C and aged until reaction was complete—typically 12–18 h. LC samples are quenched with *n*-propylamine, and consumption of SM is complete when less then 3% LCAP of 3-aminophenylboronic acid remains. The reaction mixture was allowed to cool to ambient temperature, and ~20 L of 1 N HCl was added over ~2 h until pH=5–6. Water was added to adjust ratio of aqueous/DMAc to ~2:1. Caution—slight exotherm upon addition of aqueous HCl. Keep $T_{int}<35$ °C with cooling bath. Mother liquor losses are typically 2–3%. Batch was immediately filtered at room temperature and washed with ~5 L of 2:1 water/DMAc. Multiple 5 L slurry washes with water were performed to remove DMAc. Batch was dried overnight on filter pot under partial vacuum with nitrogen sweep. Yield 2.58 kg, 78% yield over two steps; uncorrected. Collected as an off-white solid. Mp 273 °C. ^1H NMR DMSO-d_6 δ 2.50 (t, $J=7.1$ Hz, 3H), 4.22 (q, $J=7.1$ Hz, 2H), 7.55 (t, $J=7.6$ Hz, 1H), 7.57 (dd, $J=8.0$, 4.4 Hz, 1H), 7.61 (ddd, $J=7.6$, 2.0, 1.2 Hz, 1H), 7.86 (d, $J=1.2$ Hz, 1H), 7.93 (dt, $J=7.6$, 1.2 Hz, 1H), 8.27 (br s, 2H), 8.61 (dd, $J=8.0$, 2.0 Hz, 1H), 8.63 (s, 1H), 8.68 (dd, $J=4.4$, 2.0 Hz, 1H). ^{13}C NMR DMSO-d_6 δ 14.6, 60.5, 112.0, 121.9, 122.7, 128.9, 129.9, 133.1, 134.9, 136.3, 136.4 (br s, *C*-$B(OH)_2$), 140.3, 149.8, 150.4, 153.2, 164.3, 174.1. Hi-Res MS calcd for $C_{17}H_{15}BN_2O_5$: 338.1189 (M+H). Found: 338.1188 (M+H).

2.1.2. Methyl 5-chloro-2-carboxypyridine (13). A 10 L bottle was charged with 2,5-dichloropyridine 2.0 kg (13.51 mol), palladium acetate 6.08 g (0.03 mol, 0.2 mol%), dppf 30.0 g (0.05 mol, 0.4 mol%), and triethylamine 1.9 L (13.6 mol) in methanol 6 L. The bottle was stirred then contents transferred to a five gallon stainless steel stirred reaction vessel (Kla=1.42 @ 40% fill and 1000 rpm) via vacuum. Bottle was rinsed with another 2 L methanol, and the rinse was added to reaction vessel by the same method. Vessel was tested for leaks using nitrogen, then purged with nitrogen three times and carbon monoxide three times. The vessel was pressurized to 50 psig with carbon monoxide and heated to a temperature of 100 °C. The agitation rate was 1000 rpm. The reaction was thus allowed to progress for 11 h, then allowed to cool to room temp and sampled. Reaction was judged to be complete when 3% LCAP or less of starting material remained. Batch was transferred to a 50 L round bottom flask equipped with a thermocouple and stir paddle. Flask was connected to a

batch concentrator and concentration begun at 25–30 in Hg of applied vacuum. Intermittent heating of batch was applied to maintain temp. at 30–35 °C. Concentration was discontinued when copious precipitate was noted. HPLC assay of batch was 350 mg/mL. Saturated brine 20 L was added via addition funnel over 1 h. Batch was aged with gentle stirring overnight. In morning, a methanol/ice bath was applied to cool batch to −5 °C for 1.5 h. Solids were collected by filtration and rinsed with 5 L brine twice, then dried under nitrogen tent overnight to give 3.47 kg of product intimately mixed with sodium chloride: 57 wt%, 1.98 kg of product in the isolated solids, 99% yield, ML losses 0.41%. The product can be stored at this point if desired. Mp 57 °C. NMR ^{1}H δ: 3.87 (s, 3H), 7.69 (dd, J= 8.4, 2.4 Hz, 1H), 7.95 (d, J=8.4 Hz, 1H), 8.54 (d, J= 2.4 Hz, 1H). NMR ^{13}C δ: 52.8, 125.8, 135.7, 136.6, 145.7, 148.6, 164.6. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.99 (s, 3H), 4.04 (s, 3H), 8.20 (dd, J=8.2, 0.8 Hz, 1H), 8.42 (dd, J=8.2, 2.1 Hz, 1H), 9.30 (dd, J=2.0, 0.7 Hz, 1H). ^{13}C NMR δ 49.0, 49.5, 120.9, 124.9, 134.6, 147.0, 147.1, 161.1, 161.2. Anal. calcd for $C_9H_8F_3NO_3$: C, 49.00; H, 3.52; N, 8.16. Found: C, 49.01; H, 3.44; N, 8.03.

2.1.3. 3-Chloro-2-(dimethylcarbinol)-pyridine (14). Solid mixture of methyl 5-chloro-2-carboxypyridine 3.47 kg at 57wt% with sodium chloride, and tetrahydrofuran 16 L were charged to a 50 L round bottom flask equipped with stir paddle. Batch was stirred for one hour. Batch was sampled for K_f. Water content must be 1000 μg/0.5 mL or less to proceed to Grignard reaction. Assay was 122 mg/g of THF solution, 1.97 kg 5-chloro-2-carboxypyridine in 16.06 kg of solution. A 100 L round bottom flask was flushed with nitrogen, fitted with thermocouple, overhead stir paddle, and dropping funnel. The flask was charged with a 3 M solution of methylmagnesium chloride 9.7 L (29.1 mol) and stirring begun. The flask was packed in an ice bath. When temperature reached 5 °C, the solution of 5-chloro-2-carboxypyridine in THF was added by dropping funnel. Rate of addition was controlled to keep temperature below 30 °C, averaging between 20 and 25 °C. After addition was complete, reaction was aged for 30–45 min longer and assayed. Reaction was quenched by addition of ethyl acetate 800 mL followed by methanol 800 mL, again not allowing temperature to rise above 30 °C. pH was adjusted with 2 N hydrochloric acid solution to pH=4–5 (~12 L) (note: pH must not exceed 4, else some product is lost in water layer). Acidic reaction solution was extracted with ethyl acetate 9 L. Organic layer was extracted once with 1 N hydrochloric acid solution 40 L, and again with 1 N hydrochloric acid solution 20 L (note: product is now in aqueous layer; two extractions are necessary for good yield). Combined aqueous layers were adjusted with 10 N sodium hydroxide to pH=8 (~4 L) (note: an oily layer was noted to separate out on top). The basic aqueous layer was extracted once with ethyl acetate 10 L, dried by batch concentration to until K_f<1000 ppm. Final concentration was 200 mg/mL of product. Aliquot of product solution was concentrated to a colorless oil and purified further by column chromatography on silica gel with 5–10% ethyl acetate in hexanes for characterization purposes. NMR ^{1}H δ: 1.53 (s, 6H), 4.44 (br s, 1H), 7.35 (dd, J=8.4, 0.7 Hz, 1H), 7.66 (dd, J=8.4, 2.4 Hz, 1H), 8.46 (dd, J=2.3, 0.6 Hz, 1H). NMR ^{13}C δ: 30.5, 71.9, 119.5, 130.1, 136.6, 146.4, 164.4. Hi-Res MS calcd for $C_8H_{10}ClNO$: 172.0529 (M+H). Found: 172.0530 (M+H).

2.1.4. 3-Chloro-2-(1-hydroxy-1-methylethyl)-pyridine-*N*-oxide HCl salt (3). A 50 L round bottom flask was flushed with nitrogen, fitted with thermocouple, overhead stir paddle, and dropping funnel. The flask was charged with urea–hydrogen peroxide 1.39 L (14.5 mol) and ethyl acetate 5 L and stirring begun. The flask was packed in an ice bath. When temperature reached −10 °C, TFAA 2.0 L (14.5 mol) was added slowly. Rate of addition was controlled to keep temperature below 10 °C. Reaction was cooled back down to −10 °C and solution of alcohol 1.55 kg (9.0 mol) in ethyl acetate 5 L was added via dropping funnel over 1 h. After addition was complete, reaction was allowed to warm to ambient temperature and aged for one hour longer, assayed then cooled to −5 °C. Reaction was quenched by 40% $Na_2S_2O3.5H_2O$ aqueous solution 2.9 L. The organic layer was separated from the aqueous layer. Hydrochloric acid 1.8 N in IPA solution 2 L was added to the organic layer over 45 min. Batch was allowed to warm to ambient temperature, then filtered to remove urea salts. Filtrate was concentrated to 7 L volume, followed by addition of hydrochloric acid 1.8 N in isopropyl acetate 5 L. Batch was filtered again, sampled, then seeded. Product crystals formed and batch was cooled to −10 °C to finish precipitation. Product salt was collected by filtration, rinsed with ethyl acetate and dried in vacuum oven at ambient temperature. 1.11 kg, 57% yield in 99% purity. Aliquot of organic layer before HCl addition was concentrated to a colorless oil and purified further by column chromatography on silica gel with 5–10% ethyl acetate in hexanes for characterization purposes. NMR ^{1}H δ: 1.64 (s, 6H), 6.99 (br s, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.36 (dd, J= 8.4, 1.6 Hz, 1H), 8.28 (d, J=1.6 Hz, 1H). NMR ^{13}C δ: 27.2, 71.4, 122.7, 128.0, 131.6, 139.7, 153.4. Anal. calcd for $C_8H_{10}ClNO_2$.1/2 HCl: C, 46.68; H, 5.14; N, 6.80. Found: C, 46.48; H, 5.13; N, 6.88.

2.1.5. Ethyl 1-{3-[6-(1-hydroxy-1-methylethyl)-1-oxido-pyridin-3-yl]phenyl}-1,4-dihydro[1,8]naphthyridin-4-one-3-carboxylate (15). A 100 L round bottom flask was flushed with nitrogen, fitted with thermocouple, overhead stir paddle, and solid addition funnel. The flask was charged with chloro-alcohol. HCl 0.9 kg (4.0 mol) and 2.7 L water and stirring begun. The flask was packed in an ice bath. When temperature reached 10 °C, solid potassium carbonate 1.32 kg (9.6 mol) was added by solid addition funnel. Rate of addition was controlled to keep temperature below 20 °C and minimize gas evolution. After addition was complete, half of a pre-mixed solution of 2.7 L water in 17.5 L DMAc was added slowly to keep temp below 25 °C (heat of mixing of water and DMAc is significant). Solid naphthyridone-phenylboronic acid 1.3 kg (3.8 mol) was added and remaining half of water/DMAc solution added. Slurry was sparged with nitrogen for minimum of 1 h. Pi-allyl palladium chloride dimer 70.0 g (0.2 mol, 5 mol%) was charged into a separate 5 L flask, DMAc 2.25 L added and stirred to produce a yellow solution. Nitrogen was sparged through for a minimum of 1 h. A 10 wt% (0.33 M) solution of tri-*t*-butylphosphine 1.2 L (0.4 mol, 10 mol%) was added without exposure to air. (Note: L/Pd ratio must be 1:1. More ligand shuts the reaction down completely.) Solution was

stirred for 30 min turning a deep golden color. This catalyst solution was added to the reaction solution without exposure to air. Reaction solution was heated to 60 °C for 6 h. As completion neared, product began to precipitate out, even at 60 °C. Reaction should be assayed after 4 h, or if reaction becomes thick with product precipitate before that time. When boronic acid was consumed, reaction was allowed to cool to room temperature and poured into 55 L water to complete product precipitation. This gray slurry was filtered and solids were collected. Filter cake was washed with another 55 L water, then dried under partial vacuum at 40–50 °C overnight, until constant weight, to give 1.51 kg, 80% yield. NMR ^{1}H δ: 1.72 (t, J=7.1 Hz, 3H), 4.41 (q, J=7.1 Hz, 2H), 7.45 (dd, J=7.6, 4.4 Hz, 1H), 7.47 (d, J=8.8 Hz, 1H), 7.57(dt, J=6.4, 2.0 Hz, 1H), 7.60 (dd, J=8.4, 2.0 Hz, 1H), 7.65–7.68 (m, 1H), 7.71–7.77 (m, 2H), 8.53 (d, J=2.0 Hz, 1H), 8.64 (dd, J=4.4, 2.0 Hz, 1H), 8.73 (s, 1H), 8.84 (dd, J=8.0, 2.0 Hz, 1H). NMR ^{13}C δ: 14.3, 27.3, 61.2, 71.5, 113.0, 121.5, 122.8, 123.2, 126.13, 126.14, 127.6, 128.1, 130.8, 136.4, 136.9, 137.0, 138.8, 141.2, 149.1, 149.9, 152.5, 153.8, 164.8, 174.6. Hi-Res MS calcd for $C_{25}H_{23}N_3O_5$: 446.1716 (M+H). Found: 446.1708 (M+H).

2.1.6. 1-{3-[6-(1-Hydroxy-1-methylethyl)-1-oxidopyridin-3-yl]phenyl}-1,4-dihydro[1,8]naphthyridin-4-one-3-carboxylate (16). A 72 L round bottom flask was flushed with nitrogen, fitted with thermocouple, overhead stir paddle, and addition funnel. The flask was charged with ester compound 0.96 kg (2.15 mol), THF 10 L, and methanol 10 L, followed by 2 N aqueous sodium hydroxide 10 L. Reaction was allowed to stir overnight at room temperature. Reaction was adjusted to pH 8 by addition of 1.4 L concentrated hydrochloric acid. Darco G-60 0.96 kg (100 wt%) was added and resulting mixture was allowed to stir for 2 h. The mixture was filtered through Solka Floc to remove Darco resin. Concentrated hydrochloric acid was added to the filtrate to adjust to pH 3. White precipitate was collected by filtration. The filter cake was dried in a vacuum oven at 40–50 °C under nitrogen stream until constant weight to give 0.65 kg white solids, 72% yield. Mp 163 °C. NMR ^{1}H (DMSO-d_6) δ: 1.59 (s, 6H), 7.70–7.74 (m, 4H), 7.85 (dd, J=8.4, 1.8 Hz, 1H), 7.97–8.00 (m, 1H), 8.11 (br s, 1H), 8.75 (d, J=1.8 Hz, 1H), 8.80 (dd,, J=8.0, 1.9 Hz, 1H), 8.87 (dd, J=4.5, 1.9 Hz, 1H), 9.03 (s, 1H). NMR ^{13}C (DMSO-d_6) δ: 27.1, 71.5, 109.4, 120.7, 123.1, 123.8, 126.0, 126.0, 128.2, 128.8, 130.4, 135.9, 136.0, 136.5, 138.6, 141.0, 150.4, 150.8, 154.2, 154.9, 165.5, 179.2. Anal. calcd for $C_{23}H_{19}N_3O_5.2H_2O$ (dihydrate): C, 60.92; H, 5.11; N, 9.27. Found: C, 60.61; H, 4.74; N, 9.11.

2.1.7. Cyclopropyl-1-{3-[6-(1-hydroxy-1-methylethyl)-1-oxidopyridin-3-yl]phenyl}-1,4-dihydro[1,8]naphthyridin-4-one-3-carboxamide (1). A 100 L cylindrical flask was flushed with nitrogen, fitted with an addition funnel. The flask was charged with the naphthyridone acid derivative followed by DMF 28 L and carbonyldiimidazole 1.4 kg (4.9 mol). Reaction was allowed to stir until acid was consumed. Cyclopropylamine 5.9 L (48.9 mol) was added and reaction stirred overnight. Water was added to milky reaction mixture and temperature was noted to rise to 38 °C. The mixture was allowed to cool to room temperature, then filtered and washed with ethanol 20 L to collect white solids. The filter cake was dried under a nitrogen stream until constant weight to give 1.24 kg white solids, 82% yield. The white solids were suspended in 60 L dry ethanol in a 100 L cylindrical flask. The mixture was heated to reflux, then allowed to cool to room temperature. The solids were collected by filtration, washed with 5 L ethanol, and dried in a vacuum oven at 40 °C under a nitrogen stream until constant weight to give 1.20 kg white solids, 96% recovery. Mp 271 °C. NMR ^{1}H δ: 0.66–0.70 (m, 2H), 0.84–0.89 (m, 2H), 1.72 (s, 6H), 2.97–2.03 (m, 1H), 7.45–7.60 (overlapping multiplets, 4H), 7.64 (s, 1H), 7.72–7.76 (m, 2H), 8.53 (d, J=4.3 Hz, 1H), 8.83 (d, J=8.0 Hz, 1H), 9.05 (s, 1H), 9.76 (s, 1H). NMR ^{13}C δ: 6.5, 22.4, 27.3, 71.5, 113.5, 121.4, 122.1, 122.7, 126.11, 126.14, 127.7, 128.0, 130.7, 136.3, 136.5, 136.9, 138.8, 141.2, 148.0, 149.8, 153.0, 153.7, 165.1, 177.1. Anal. calcd for $C_{26}H_{24}N_4O_4 \cdot 1/2$ EtOH (hemi-ethanol adduct): C, 67.63; H, 5.68; N, 11.68. Found: C, 67.69; H, 5.28; N, 12.16.

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References and notes

1. (a) Souness, J. E.; Foster, M. *Drugs* **1998**, *1*, 541–553. (b) Dyke, H.; Montana, J. *Expert Opin. Invest. Drugs* **1999**, *8*, 1301–1325.
2. Springfield, S. A.; Marcantonio, K.; Ceglia, S.; Albaneze-Walker, J.; Dormer, P. G.; Nelson, T. D.; Murry, J. A. *J. Org. Chem.* **2003**, *68*, 4598–4599.
3. For a review, see: (a) Stanforth, S. P. In *Comprehensive Heterocyclic Chemistry II*, *527*; Elsevier Science: New York, 1996; pp 527–559. (b) Jacquet, J-P. ; Bouzard, D.; Di Cesare, P.; Dolnic, N.; Massoudi, M.; Remuzon, P. *Heterocycles* **1992**, *34*12, 2301. (c) Jacquet, J.-P.; Bouzard, D.; Di Cesare, P.; Dolnic, N.; Massoudi, M.; Remuzon, P. *Heterocycles* **1992**, *34*12, 2301. (d) Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Gracey, E. H.; Pernet, A. G. *J. Med. Chem.* **1986**, *29*, 2363. (e) Yoon, S. J.; Chung, Y. H.; Lee, C. W.; Oh, Y. S.; Choi, D. R.; Kim, N. D.; Lim, J. K.; Jin, Y. H.; Lee, D. K.; Lee, W. Y. *J. Heterocycl. Chem.* **1997**, *34*, 1021. (f) Chu, D. T. W.; Claiborne, A. K. *J. Heterocycl. Chem.* **1990**, *27*, 1191.
4. Wang, X.; Rabbat, P.; O'Shea, P.; Tillyer, R.; Grabowski, E.J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 4335–4338.
5. Chambers, R. J.; Marfat, A. *Syn. Commun.* **1997**, *27*, 515–520.
6. Song, J. J.; Yee, N. K. *J. Org. Chem.* **2001**, *66*, 605–608.
7. (a) Head, R. A.; Ibbotson, A. *Tetrahedron Lett.* **1984**, *25*, 5939–5942. (b) Scalone, M.; Vogt, P. EP 385210 A2, **1990**. (c) Najiba, D.; Carpentier, J.-F.; Castanet, Y.; Biot, C.; Brocard, J.; Mortreux, A. *Tetrahedron Lett.* **1999**, *40*, 3719–3722.
8. (a) Bessard, Y.; Crettaz, R. *Heterocycles* **1999**, *51*, 2589–2602. (b) Beller, M.; Magerlein, W.; Indolese, A.; Fischer, C. *Synthesis* **2001**, 1098–1109. (c) Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P. G.; Murry, J. A. *Org. Lett.* **2004**, *6*, 2097–2100.
9. Caron, S.; Do, N. M.; Sieser, J. E. *Tetrahedron Lett.* **2000**, *41*, 2299–2302.
10. Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.

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Remote steric effect on the regioselectivity of Sharpless asymmetric dihydroxylation

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Abstract—Studies on the regioselectivities for the Sharpless asymmetric dihydroxylation (AD) of conjugated dienoates, trienoates, dienones and dienamides are described. Excellent regioselectivities were obtained in straight chain dienoates, all trienoates, ketones and amides. The remote branched *iso*-propyl and *tert*-butyl groups of dienoates greatly lowered the normally excellent regiocontrol. This observation is rationalized in terms of substrate conformational changes, and the steric interaction between the branched methyl group of *iso*-propyl or *tert*-butyl groups and the ethyl group on the $(DHQD)_2PHAL$ ligand.

The Sharpless asymmetric dihydroxylation reaction has proven to be one of the most powerful reactions for asymmetric synthesis.[1] Over the years we and others[1] have found the selective use of the asymmetric dihydroxylation (AD) of polyenes to be a powerful tool for total synthesis.[2–4] In particular, we have found the AD reaction of vinylfurans,[2] dieneoates[3] and trienoates[4] provides excellent starting materials for natural product synthesis.

Not surprisingly, Sharpless has extensively studied the AD reaction of polyenes[5,6] and found the osmium quinuclidine ligand systems appear to react preferentially with the more electron rich double bond of a polyene π-system. This is best exemplified by the asymmetric dihydroxylation of 2,4-dienoates to give regioisomeric diols (**1** to **2** or **3**, Scheme 1). In general, Sharpless has found these reactions occur to give preferentially the conjugated 2-enoate-4,5-diol **2** over the unconjugated 4-enoate-2,3-diol **3**. An exception to this excellent control was seen when the dienoates were substituted in the 5-position with a phenyl ring as in **1b**. Thus, when **1a** was exposed to the Sharpless AD-mix-β conditions a greater than 20 to 1 ratio of **2a** to **3a** was produced. In contrast, when **1b** was exposed to the AD-mix-β conditions only a 5:1 ratio of **2b** to **3b** resulted. Sharpless suggested that this lowering of regioselectivity was a result of the fact that the dihydroxylation reaction tends to avoid the breaking of conjugation.[5]

Recently, we developed several effective routes to various natural products using a three-step asymmetric hydration of the γ,δ-double bond of dienoates[7] and the ε,ϕ-double bond of trienoates.[4] Key to this transformation is the regioselective dihydroxylation of dienoates and trienoates. An interesting observation occurred in the course of our use of this asymmetric hydration procedure for the total synthesis of the bioactive colletodiol class of natural products **4a–c** (Scheme 2).[4] Specifically, we found an alternative case where a loss of regioselectivity occurred in the Sharpless dihydroxylation process (Scheme 3).

In the course of this synthetic investigation, it was found as expected that only the γ,δ-unsaturated double bond underwent dihydroxylation for the methyl and ethyl dienoates **10b** and **10c**, providing triols **11b** and **11c** as the only regioisomers (Scheme 3). This expected high regiocontrol was unaffected by a bulky TBS-group on the distal oxygen as in **10d**. When the TBS-ether **10d** was reacted with the AD-mix-β system diol **11d** was formed as a single regioisomer. In contrast, when the ester was changed to the sterically demanding *t*-butyl group (**10a**) the dihydroxylation became unselective. Thus exposing **10a** to the typical AD-mix-β conditions resulted in a 1:1 ratio of the products **11a** and **12a**.

In the previous regioselectivity studies by Sharpless the observed selectivities were rationalized by a combination of electronic and steric effects;[5,6] however, no such remote substituent effect has been reported. Therefore, to better delineate the origins of this peculiar phenomenon, we decided to further investigate this remote steric effect with several dienoates, dienones and dienamides. This was done

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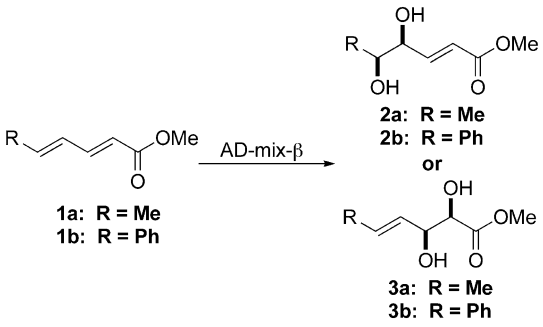
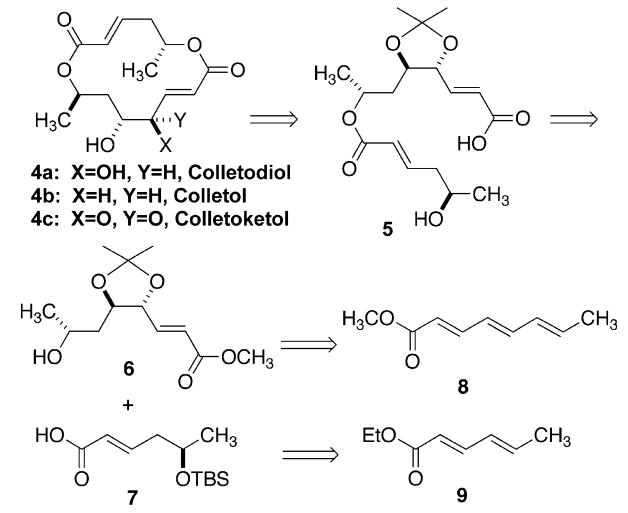


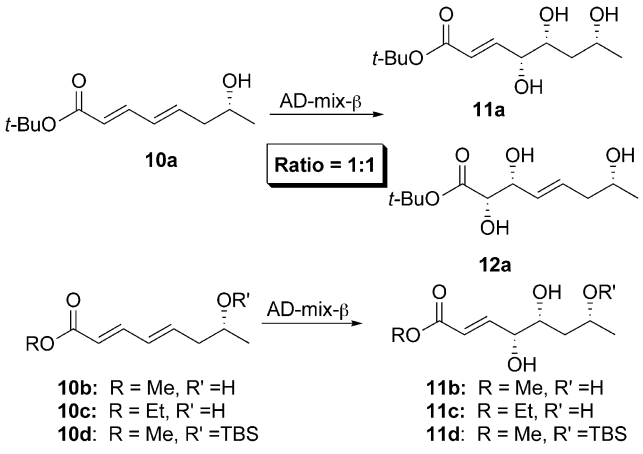
Scheme 1. Regioselectivity of the Sharpless dihydroxylation.

with the hope of gaining a better understanding of the dihydroxylation mechanism and thus more reliably delivering these valuable synthetic intermediates.

Because the methyl and *t*-butyl esters impose a similar electronic effect on the dienoates, we theorized that the above observation (**10a** to **11a/12a**) results from a steric effect on the conformation. That is to say, the larger *t*-butyl group may have caused the ester carbonyl to turn out of plane/conjugation with the diene and thus become less electron withdrawing. If this assumption were true the same effect should be seen with other esters, not to mention other dienes substituted with electron withdrawing groups. To probe the steric contribution of this conformational effect, we have chosen to study ethyl, *iso*-propyl and *tert*-butyl dienoates. We also chose to study the Weinreb amide and methyl ketone. For instance in the case of the Weinreb amides, they should exist exclusively in one planar conformation. To investigate the steric effect due to the ester oxygen atom, we have chosen the thiol ethyl ester dienoate **13f**. To distinguish between steric effects on conformation and electronic withdrawing effects, we chose to study methyl, ethyl and *tert*-butyl trienoates (**19a–c**), because we believed the conformational effects should be identical for the trienoate substrates as the dienoates. Knowing that the phenyl group lowers the regioselectivity,[5] we chose to study dienes with both methyl and phenyl substitution at the δ-position. This substitution should allow us to modulate the inherent substrate selectivity, and thereby give us a tunable probe to variably test this distant substituent effect on regioselectivity.



Scheme 2. Colletodiol retrosynthesis.

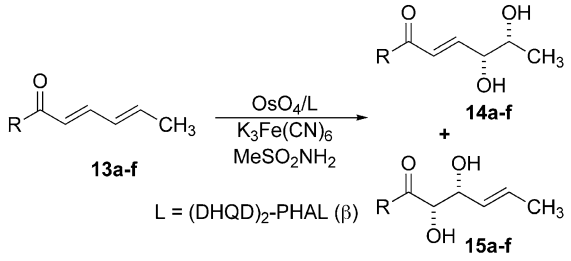


Scheme 3. Unusual regioselectivity for *t*-butyl esters.

1. Results and discussion

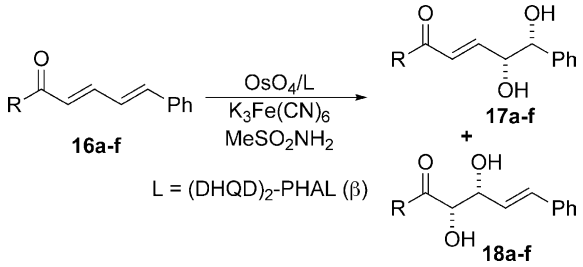
All the dienes and trienes were exposed to slight variations of the Sharpless AD conditions, using both the $(DHQ)_2$-PHAL (AD-mix-α) and $(DHQD)_2$PHAL (AD-mix-β) ligands.[8] For the dienoates (**13a–c**, **16a–c**) the typical

Table 1. AD of 5-methyl substituted dienes using $(DHQD)_2$PHAL



SM	R	Yield	Ratio (**14**/**15**)	%ee **14**	%ee **15**
13a	OEt	78	>20:1	92	n.a.
13b	O*i*-Pr	45	9:2	72	96
13c	O*t*-Bu	76	6:1	76	n.a.
13d	N(OMe)Me	82	>20:1	75	n.a.
13e	Me	68	>20:1	69	n.a.
13f	SMe	38	>20:1	92	n.a.

Table 2. AD of 5-phenyl substituted dienes using $(DHQD)_2PHAL$



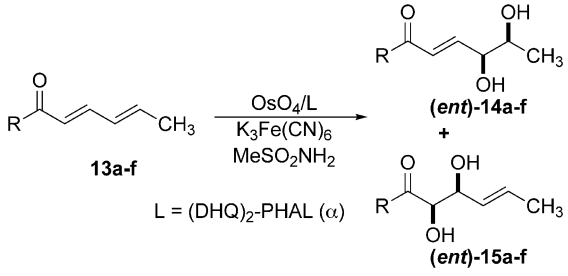
SM	R	Yield	Ratio (**17**/**18**)	%ee **17**	%ee **18**
16a	OEt	76	5:1	99	n.a.
16b	O*i*-Pr	50	7:3	91	98
16c	O*t*-Bu	62	5:3	91	99
16d	N(OMe)Me	85	>20:1	99	n.a.
16e	Me	68	~10:1	98	n.a.
16f	SMe	31	3.7:1	99	99

reaction conditions involved exposure of the substrates to 1–5 mol% ligand, 3 equiv $K_3Fe(CN)_6$, 3 equiv K_2CO_3, 1 equiv $MeSO_2NH_2$, and 1–5 mol% OsO_4 in 1:1 *t*-butyl alcohol/ H_2O at 0 °C. The other substrates, dienamide **13d/16d**, dineone **13e/16e** and dienethioester **13f/16f** were much less reactive and required 10% OsO_4 and 11% ligand at room temperature to give satisfactory yields of diol products. The absolute configurations of diol products were determined either by conversion to known compounds, or by the Mosher method.[9] For some minor products the assignments were based upon the Sharpless mnemonic.[1] The ratio of the regioisomers was determined by analysis of the crude ^1H NMR and isolation of the purified products. The enantioselectivities were determined by HPLC (Chiralcel OD column, 1–8% *i*-PrOH in hexane, 0.8–1.0 mL/min). The minor regioisomers, **15e** and **18e**, were unstable to the reaction conditions and underwent a retro-aldol reaction to give cinnamaldehyde, integration of which in the crude ^1H NMR was used to determine the regioselectivities.

The results for the 5-methyl substituted diene substrates using the $(DHQD)_2PHAL$ are summarized in Table 1. As expected, the more electron rich distal double bond of each substrate was the more reactive one and thus the major dihydroxylation products were **14a–f**. When one looks at the series of esters **13a–c**, a clear trend can be seen between increase in steric bulk of the ester substituent and a decrease in regioselectivity. Interestingly, the less reactive substrates **13d–f** all reacted to give essentially one regioisomer **14d–f**. This came as a surprise as it was expected that the amide substrate **13d** would have a similar conformation as the hindered esters **13b** and **13c**, and thus have a similar loss of regiocontrol.

The results for the 5-phenyl substituted diene substrates **16a–f** using the $(DHQD)_2PHAL$ ligand system are summarized in Table 2. As expected, in all six cases **17a–f** were the major dihydroxylation products formed. Not surprisingly, the products from the phenyl-substituted dienes **16a–f** afforded products with higher enantiomeric excess.[5] Similarly, we were not surprised to see an across the board decrease in regioselectivity, with the bulky esters **16b** and **16c** having product ratio in the range of 2:1. While the phenyl substituted thioester **16f** did have a detectable amount of the regioisomer **18f** (~4:1), we were, once again, surprised to see the high selectivities for both the amide (**16d**) and ketone (**16e**) substrates.

Table 3. AD of 5-methyl substituted dienes using $(DHQ)_2PHAL$



SM	R	Yield	Ratio (**14**/**15**)	%ee (*ent*)-**14**	%ee (*ent*)-**15**
13a	OEt	71	>20:1	80	n.a.
13b	O*i*-Pr	59	16:1	79	96
13c	O*t*-Bu	57	>20:1	85	n.a.
13d	N(OMe)Me	76	>20:1	75	n.a.
13e	Me	71	>20:1	65	n.a.
13f	SMe	24	>20:1	71	n.a.

The results for the 5-methyl substituted diene substrates **13a–f** with the $(DHQ)_2PHAL$ ligand system were summarized in Table 3. Interestingly, this remote steric effect on regioselectivity disappears when the $(DHQD)_2PHAL$ ligand was switched to the pseudo-enantiomeric ligand $(DHQ)_2$-PHAL. To our surprise, all six substrates **13a–f** reacted under the dihydroxylation conditions using the $(DHQ)_2$-PHAL ligand to give (*ent*)-**14a–f** for all practical purposes as a single regioisomer, with the *iso*-propyl ester having the lowest selectivity that being at the barely detectable level of 16:1.

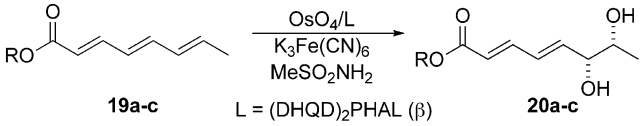
The results for the 5-phenyl substituted diene substrates **16a–f** using the $(DHQ)_2PHAL$ are summarized in Table 4. Once again, the effect of the phenyl groups lowering regioselectivity can be seen. As in Table 3, the improvement in regioselectivity for the $(DHQ)_2PHAL$ ligand system over the $(DHQD)_2PHAL$ ligand system could be seen; albeit, the difference in regioselectivity was observed to a much smaller extent. For example, the *t*-butyl ester **16c** reacted under the $(DHQD)_2PHAL$ reaction condition to give a 5:3 ratio of **17c** to **18c** (Table 2). In contrast, **16c** reacted under the $(DHQ)_2PHAL$ reaction condition to give a 2:1 ratio of (*ent*)-**17c** to (*ent*)-**18c** (Table 4). Although this change is small, the trend is consistent throughout the whole series.

The final evidence against our hypothesis that the decrease of regiocontrol is a result of steric effect on conformation came from our study of trienoates **19a–c** (Table 5). Regardless of ligand system good yields were obtained for the AD reaction of methyl, ethyl and *tert*-butyl trienoates. Similarly, excellent regiocontrol was observed (i.e., only the distal double bond underwent a dihydroxylation forming diols **20a–c**). As our initial hypothesis predicted that these trienoates **19a–c** should have similar conformational populations and electronic polarization as the dienoates **13a–c** and thus similar regioselectivities in the dihydroxylation reaction, an alternative explanation was needed (vide infra).

Our revised hypothesis, for the origins of this unusual remote steric effect on the regioselectivity of the AD reaction on dienoates, came from two observations. The decrease in regiocontrol only appears when the substituent has branching (i.e., *i*-propyl and *t*-butyl esters and not amides) and the effect significantly differs depending on which ligand system is used (i.e., a 9:2 ratio for **13b** with $(DHQD)_2PHAL$ and a 16:1 ratio for (*ent*)-**13b** with $(DHQ)_2PHAL$). Thus the origins of this phenomenon must be the result of a steric interaction between the branched substitutent and the stereogenic ethyl group that makes $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ diastereomers and not enantiomers. This steric interaction must be significantly greater in the $(DHQD)_2PHAL$/Os/dienoate complex than the $(DHQ)_2PHAL$/Os/dienoate complex.

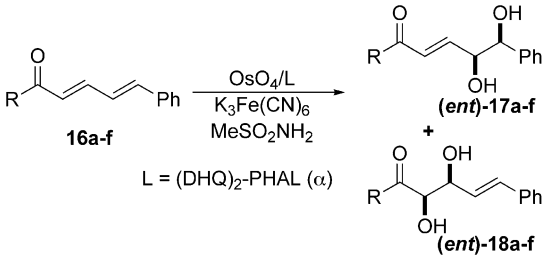
Finally it should be noted that these studies of the AD reaction on the dienone **16e** were complicated by an isolation problem. This problem introduced some uncertainty to the measurement of regioselectivity. Isolation of the minor regioisomer **18e** for the AD reaction of phenyl substituted dienone **16e** proved problematic due to base sensitivity. Upon the typical base wash (2 N KOH) to remove $MeSO_2NH_2$ from the reaction mixture, it was noted that the minor regioisomer **18e** underwent a retro-aldol reaction to give cinnamaldehyde **21** (Scheme 4). Buffering the reaction mixture with $NaHCO_3$ and skipping the base-washing can significantly reduce this retro-aldol reaction, however, a degree of uncertainty in our ability of measure the ratio of **17e** to **18e** still remains. Because of our concerns about the retro-aldol reactions, we skipped the base-washing step for both the methyl and phenyl substituted dienones **13e** and **16e**. The crude ^1H NMR spectra for these reactions were examined for both the minor regioisomers as well as the retro-aldol products cinnamaldehyde and crotonaldehyde.

Table 5. AD of 7-methyl substituted trienes using $(DHQD)_2PHAL$

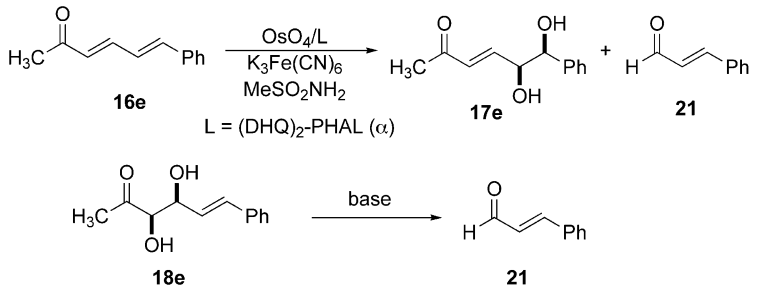


	R	Ratio	Yield	%ee **20**
19a	Me	>20:1	82	96
19b	Et	>20:1	96	99
19c	*t*-Bu	>20:1	78	96

Table 4. AD of 5-phenyl substituted dienes using $(DHQ)_2PHAL$



SM	R	Yield	Ratio (**17**/**18**)	%ee (*ent*)-**17**	%ee (*ent*)-**18**
16a	OEt	73	6.5:1	99	n.a.
16b	O*i*-Pr	60	9:2	45	99
16c	O*t*-Bu	36	2:1	87	93
16d	N(OMe)Me	61	>20:1	98	n.a.
16e	Me	60	~10:1	93	n.a.
16f	SMe	31	7.8:1	99	98



Scheme 4. Isolation of base sensitive substrates.

While skipping the base washing allowed for the isolation of diols **14e** and **17e**, this new procedure did not afford pure material. To properly gauge the yield of the reaction we found it easier to convert the crude diol products to diacetates **22** and **23** (Ac_2O/Py/DMAP). Interestingly, the base sensitive diol products were easily regenerated from the purified diacetate products upon exposure to Et_3N in CH_3OH. No indication of retro-aldol products was observed under these mildly basic reaction conditions. While no regioisomers were detected, having pure diol in hand allowed for analysis of crude ^1H NMR (Scheme 5).

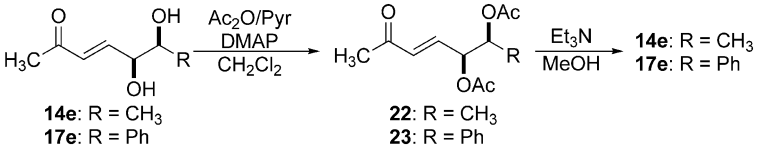
In summary, the regioselectivities for the AD reaction of dienoates, dienones, dienamides and trienoates were studied. In general, excellent regioselectivities were found in the ketone and amide cases. The unbranched esters (methyl, ethyl) gave diol products with good regiocontrol. In contrast, branched esters (*iso*-propyl, *tert*-butyl) gave diol products with poor regiocontrol. This branching steric effect can lower regiocontrol by the same magnitude as Sharpless' previous noted 'disruption of conjugation' phenomena. This can be explained by a steric interaction between the methyls on the *iso*-propyl or *tert*-butyl groups, and the ethyl group on the $(DHQD)_2PHAL$ ligand. This is consistent with the $(DHQ)_2PHAL$ ligand giving higher regiocontrol. This branched methyl group/ligand interaction is removed by adding an extra double bond as in the trienoates. Detailed computational and synthetic studies are ongoing to further support this new hypothesis.

2. Experimental

2.1. . General methods

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Varian VXR-200 (200 MHz), Varian VXR-300 (300 MHz) or Varian VXR-500 (500 MHz) spectrometers. Chemical shifts are reported relative to internal tetramethylsilane (δ0.00 ppm) or residual solvent signal. Infrared (IR) spectra were obtained on a Prospect MIDAC FT-IR spectrometer. Optical rotations were measured with a Jasco DIP-370 digital polarimeter in the solvent specified. Flash column chromatography was performed on ICN reagent 60 (60–200 mesh) silica gel. Analytical thin-layer chromatography was performed with pre-coated glass-backed plates (Whatman K6F 60 Å, F_{254}) and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or potassium permanganate stain. R_f values are obtained by elution in the stated solvent ratios (v/v). High resolution mass spectrometric data analysis was performed by the University of Minnesota Mass Spectrometry Laboratory. Ether and THF were distilled from benzophenone and sodium metal. Methylene chloride, benzene and triethylamine were distilled from calcium hydride. Unless otherwise noted, solvents were reagent grade and were used without purification. Commercial reagents were used without purification unless otherwise noted. Air- and /or moisture-sensitive reactions were carried out under an atmosphere of nitrogen using oven-dried glassware and standard syringe/septa techniques.

2.1.1. Ethyl (4*S*,5*S*)-4,5-dihydroxy-2-hexenoate ((*ent*)-14a). Into a 250 mL round bottom flask was added 60 mL of *t*-BuOH, 60 mL of water, $K_3Fe(CN)_6$ (41.1 g, 125 mmol), K_2CO_3 (17.24 g, 125 mmol), $MeSO_2NH_2$ (3.39 g, 35.7 mmol), $(DHQ)_2PHAL$ (278 mg, 0.36 mmol), and OsO_4 (45 mg, 0.18 mmol). The mixture was stirred at room temperature for about 15 min and then cooled to 0 °C. To this solution was added dienoate **13a** (5.00 g, 35.7 mmol) and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with saturated aqueous sodium sulfite (40 mL) at room temperature. Ethyl acetate (40 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the organic solvent (2×30 mL). The combined organic layers were washed with 2 N KOH (20 mL) and brine to remove the methanesulfonamide, and dried over anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel (7:3 (v/v) hexanes/EtOAc) afforded 6.182 g (71% yield) of **14a** as a light yellow oil: $[\alpha]_D$ −52.0° (*c* 1.17, EtOH); IR (neat) 3426, 2978, 1695, 1652, 1464, 1369, 1279, 1179, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.92 (dd, J=16.0, 5.5 Hz, 1H), 6.14 (dd, J=15.5, 2 Hz, 1H), 4.20 (q, J=7.5 Hz, 2H), 4.06 (ddd, J=10.25, 4.5, 1.5 Hz, 1H), 3.73 (dq, J=10.5,



Scheme 5. Purification of base sensitive substrates.

6.5 Hz, 1H), 2.89 (br, 1H), 2.59 (br, 1H), 1.29 (t, $J=7.5$ Hz, 3H), 1.24 (d, $J=6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.8, 146.9, 122.6, 75.7, 70.2, 60.7, 19.1, 14.2.

2.1.2. Ethyl (4*R*,5*R*)-4,5-dihydroxy-2-hexenoate (14a). Into a 250 mL round bottom flask was added 60 mL of *t*-BuOH, 60 mL of water, $K_3Fe(CN)_6$ (41.1 g, 125 mmol), K_2CO_3 (17.24 g, 125 mmol), $MeSO_2NH_2$ (3.39 g, 35.7 mmol), $(DHQD)_2$-PHAL (278 mg, 0.36 mmol), and OsO_4 (45 mg, 0.18 mmol). The mixture was stirred at room temperature for about 15 minutes and then cooled to 0 °C. To this solution was added dienoate **13a** (5.00 g, 35.7 mmol) and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with saturated aqueous sodium sulfite (40 mL) at room temperature. Ethyl acetate (40 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the organic solvent (2×30 mL). The combined organic layers were washed with 2 N KOH (20 mL) and brine to remove the methanesulfonamide, and dried over anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel (7:3 (v/v) hexanes/EtOAc) afforded 4.53 g (73% yield) of **14a** as a light yellow oil: $[\alpha]_D$ 56° (*c* 1.0, EtOH); IR (neat) 3426, 2978, 1695, 1652, 1464, 1369, 1279, 1179, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.92 (dd, $J=16.0$, 5.5 Hz, 1H), 6.14 (dd, $J=15.5$, 2 Hz, 1H), 4.20 (q, $J=7.5$ Hz, 2H), 4.06 (ddd, $J=10.25$, 4.5, 1.5 Hz, 1H), 3.73 (dq, $J=10.5$, 6.5 Hz, 1H), 2.89 (br, 1H), 2.59 (br, 1H), 1.29 (t, $J=7.5$ Hz, 3H), 1.24 (d, $J=6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.8, 146.9, 122.6, 75.7, 70.2, 60.7, 19.1, 14.2.

2.1.3. Ethyl (4*S*,5*S*)-4,5-dihydroxy-5-phenyl-2-pentenoate ((*ent*)-17a). Into a 250 mL round bottom flask was added 40 mL of *t*-BuOH, 40 mL of water, $K_3Fe(CN)_6$ (18.75 g, 57 mmol), K_2CO_3 (7.87 g, 57 mmol), $MeSO_2NH_2$ (1.81 g, 19 mmol), $(DHQ)_2$-PHAL (296 mg, 0.38 mmol), and OsO_4 (48 mg, 0.19 mmol). The mixture was stirred at room temperature for about 15 minutes and then cooled to 0 °C. To this solution was added dienoate **16a** (3.85 g, 19 mmol) and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with satd aqueous sodium sulfite (30 mL) at room temperature. Ethyl acetate (40 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the organic solvent (2×30 mL). The combined organic layers were washed with 2 N KOH (20 mL) and brine to remove the methanesulfonamide, and dried over anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel (7:3 (v/v) hexanes/EtOAc) afforded 0.96 g (73% yield) of (*ent*)-**17a** as a clear oil: $[\alpha]_D$ −48.7° (*c* 0.97, EtOH); IR (neat) 3426, 3063, 3031, 2983, 2902, 1955, 1888, 1737, 1651, 1495, 1455, 1368, 1279, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 (m, 5H), 6.75 (dd, $J=16$, 4.5 Hz, 1H), 6.10 (dd, $J=15.5$, 1.5 Hz, 1H), 4.57 (d, $J=7$ Hz, 1H), 4.41 (ddd, $J=6.5$, 4.5, 2 Hz, 1H), 4.17 (q, $J=7$ Hz, 2H), 2.55 (br, 2H), 1.26 (t, $J=7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.4, 145.5, 139.7, 128.7, 128.6, 126.7, 122.4, 76.8, 75.3, 60.6, 14.2.

2.1.4. Ethyl (4*S*,5*S*)-4,5-dihydroxy-5-phenyl-2-pentenoate (17a). Into a 250 mL round bottom flask was added 40 mL of *t*-BuOH, 40 mL of water, $K_3Fe(CN)_6$ (18.75 g, 57 mmol), K_2CO_3 (7.87 g, 57 mmol), $MeSO_2NH_2$ (1.81 g, 19 mmol), $(DHQD)_2$-PHAL (296 mg, 0.38 mmol), and OsO_4 (48 mg, 0.19 mmol). The mixture was stirred at room temperature for about 15 min and then cooled to 0 °C. To this solution was added dienoate **16a** (3.84 g, 19 mmol) and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with satd aqueous sodium sulfite (30 mL) at room temperature. Ethyl acetate (40 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the organic solvent (2×30 mL). The combined organic layers were washed with 2 N KOH (20 mL) and brine to remove the methanesulfonamide, and dried over anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel (7:3 (v/v) hexanes/EtOAc) afforded 1.00 g (76% yield) of **17a** as a clear oil: $[\alpha]_D$ +50° (*c* 0.97, EtOH); IR (neat) 3426, 3063, 3031, 2983, 2902, 1955, 1888, 1737, 1651, 1495, 1455, 1368, 1279, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 (m, 5H), 6.75 (dd, $J=16$, 4.5 Hz, 1H), 6.10 (dd, $J=15.5$, 1.5 Hz, 1H), 4.57 (d, $J=7$ Hz, 1H), 4.41 (ddd, $J=6.5$, 4.5, 2 Hz, 1H), 4.17 (q, $J=7$ Hz, 2H), 2.55 (br, 2H), 1.26 (t, $J=7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.4, 145.5, 139.7, 128.7, 128.6, 126.7, 122.4, 76.8, 75.3, 60.6, 14.2.

2.1.5. *i*-Propyl (4*S*,5*S*)-4,5-dihydroxy-2-hexenoate (*ent*)-14b(*S*,*S*) and *i*-propyl (2*R*,3*S*)-2,3-dihydroxy-5-phenyl-4-hexenoate (*ent*)-15b(*R*,*S*). To a 25 mL round bottom flask was added 1:1 *tert*-butyl alcohol (5 mL)/water (5 mL), $K_3Fe(CN)_6$ (780 mg, 2.4 mmol), K_2CO_3 (327 mg, 2.4 mmol), $CH_3SO_2NH_2$ (75 mg, 0.8 mmol), $(DHQ)_2$-PHAL (36.9 mg, 6 mol%), OsO_4 (10.0 mg, 5 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **13b** (122 mg, 0.8 mmol) and the reaction was stirred vigorously at room temperature overnight. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4, and concentrated to afford the crude mixture of regioisomers ((*ent*)-**14b**/(*ent*)-**15b**=94:6 by ^{1}H NMR). Flash chromatography on silica gel (2:1 (v/v) hexane/EtOAc) provided regioisomer (*ent*)-**14b** (78 mg, 52.8% yield, 79% ee) and (*ent*)-**15b** (9 mg, 6.1% yield, 96% ee), both as colorless oil. For *i*-propyl (4*S*,5*S*)-4,5-dihydroxy-2-hexenoate (*ent*)-**14b**: $R_f=0.05$ (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ −51.0° (*c* 1.03, EtOH); IR (neat, cm^{-1}) 3411, 2982, 1700, 1659, 1375, 1283, 1181, 985; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.89 (dd, $J=15.6$, 5.1 Hz, 1H), 6.10 (dd, $J=15.6$, 1.5 Hz, 1H), 5.05 (septet, $J=6.3$ Hz, 1H), 4.04 (ddd, $J=5.7$, 5.4, 1.5 Hz, 1H), 3.71 (dq, $J=6.6$, 6.0 Hz, 1H), 3.00 (br, 2H), 1.26 (d, $J=6.9$ Hz, 6H), 1.23 (d, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.1, 146.4, 122.9, 75.7, 70.3, 68.2, 21.8, 19.1; HRMS (CI) Calcd for $[C_9H_{16}O_4+NH_4]^+$: 206.1392, Found: 206.1389. The enantiomeric excess of compound (*ent*)-**14b** was determined by HPLC analysis (Chiralcel OD column), using 3% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *S*,*S*=17.8; *R*,*R*=21.3.

2.1.6. *i*-Propyl (2*R*,3*S*)-2,3-dihydroxy-4-hexenoate (*ent*)-15b(*R*,*S*). R_f=0.15 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ −45° (*c* 1.00, EtOH); IR (neat, cm^{-1}) 3505, 2919, 2852, 1722, 1674, 1346, 1290, 1107; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.82 (ddq, *J*=15.0, 6.5, 1.5 Hz, 1H), 5.63 (ddq, *J*=15.3, 6.5, 1.5 Hz, 1H), 5.14 (dseptet, *J*=6.5, 2.4 Hz, 1H), 4.33 (ddd, *J*=6.5, 5.7, 1.5 Hz, 1H), 4.09 (dd, *J*=5.4, 3.0 Hz, 1H), 3.13 (br, 1H), 2.23 (br, 1H), 1.74 (dd, *J*=6.5, 1.5 Hz, 3H), 1.31 (dd, *J*=6.0, 5.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.5, 129.4, 129.2, 73.8, 73.5, 70.2, 21.79, 21.77, 17.8; HRMS (CI) Calcd for $[C_9H_{16}O_4+NH_4]^+$: 206.1392, Found: 206.1390. The enantiomeric excess of compound (*ent*)-**15b** was determined by HPLC analysis (Chiralcel OD column), using 3% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*S*=16.9; *S*,*R*=18.9.

2.1.7. *i*-Propyl (4*R*,5*R*)-4,5-dihydroxy-2-hexenoate 14b(*R*,*R*) and *i*-propyl (2*S*,3*R*)-2,3-dihydroxy-5-phenyl-4-hexenoate 15b(*S*,*R*). To a 25 mL round bottom flask was added 1:1 *tert*-butyl alcohol (5 mL)/water (5 mL), $K_3Fe(CN)_6$ (767 mg, 2.4 mmol), K_2CO_3 (322 mg, 2.4 mmol), $CH_3SO_2NH_2$ (74 mg, 0.8 mmol), $(DHQD)_2$-PHAL (36.3 mg, 6 mol%), OsO_4 (9.9 mg, 5 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **13b** (120 mg, 0.8 mmol) and the reaction was stirred vigorously at room temperature overnight. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4, and concentrated to afford the crude mixture of regioisomers (**14b**/**15b**)=82:18 by ^1H NMR). Flash chromatography on silica gel (2:1 (v/v) hexane/EtOAc) provided regioisomer **14b** (56 mg, 38.4% yield, 72% ee) and **15b** (9 mg, 6.4% yield, 96% ee), both as colorless oil. For *i*-propyl (4*R*,5*R*)-4,5-dihydroxy-2-hexenoate (**14b**(*R*,*R*)): R_f=0.08 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ +56.0° (*c* 1.05, EtOH); IR (neat, cm^{-1}) 3411, 2982, 1700, 1659, 1375, 1283, 1181, 985; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.88 (dd, *J*=15.5, 5.5 Hz, 1H), 6.08 (dd, *J*=16.0, 1.5 Hz, 1H), 5.04 (septet, *J*=6.0 Hz, 1H), 4.02 (ddd, *J*=5.5, 5.0, 1.5 Hz, 1H), 3.70 (dq, *J*=6.5, 6.0 Hz, 1H), 3.25 (br, 2H), 1.25 (d, *J*=6.0 Hz, 6H), 1.21 (d, *J*=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.1, 146.4, 122.9, 75.7, 70.3, 68.2, 21.8, 19.1; HRMS (CI) Calcd for $[C_9H_{16}O_4+NH_4]^+$: 206.1392, Found: 206.1389. The enantiomeric excess of compound **14b**(*R*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 3% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *S*,*S*=17.6; *R*,*R*=21.4.

2.1.8. *i*-Propyl (2*S*,3*R*)-2,3-dihydroxy-4-hexenoate (15b(*S*,*R*)). R_f=0.16 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ +45° (*c* 1.00, EtOH); IR (neat, cm^{-1}) 3505, 2919, 2852, 1722, 1674, 1346, 1290, 1107; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.82 (ddq, *J*=15.0, 6.5, 1.5 Hz, 1H), 5.63 (ddq, *J*=15.5, 6.5, 1.5 Hz, 1H), 5.15 (dseptet, *J*=6.5, 2.5 Hz, 1H), 4.33 (ddd, *J*=6.5, 5.5, 1.5 Hz, 1H), 4.09 (dd, *J*=5.5, 3.0 Hz, 1H), 3.10 (br, 1H), 2.22 (br, 1H), 1.74 (dd, *J*=6.5, 1.5 Hz, 3H), 1.30 (dd, *J*=6.0, 5.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.5, 129.4, 129.2, 73.8, 73.5, 70.2, 21.79, 21.77, 17.8; HRMS (CI) Calcd for $[C_9H_{16}O_4+NH_4]^+$: 206.1392, Found: 206.1389. The enantiomeric excess of compound **15b**(*S*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 3% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*S*=17.4; *S*,*R*=19.8.

2.1.9. *i*-Propyl (4*S*,5*S*)-4,5-dihydroxy-5-phenyl-2-pentenoate ((*ent*)-17b(*S*,*S*)) and *i*-propyl (2*R*,3*S*)-2,3-dihydroxy-5-phenyl-4-pentenoate ((*ent*)-18b(*R*,*S*)). To a 25 mL round bottom flask was added 1:1 *tert*-butyl alcohol (5 mL)/water (5 mL), $K_3Fe(CN)_6$ (877 mg, 2.7 mmol), K_2CO_3 (368 mg, 2.7 mmol), $CH_3SO_2NH_2$ (84 mg, 0.9 mmol), $(DHQ)_2$-PHAL (41.6 mg, 6 mol%), OsO_4 (11.3 mg, 5 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **16b** (192 mg, 0.9 mmol) and the reaction was stirred vigorously at room temperature overnight. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4, and concentrated to afford the crude mixture of regioisomers ((*ent*)-**17b**/(*ent*)-**18b**=82:18 by ^1H NMR). Flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) provided the pure mixture of two regioisomers (133 mg, 60.0% combined yield). The two regioisomers were separated by MPLC (2:1 (v/v) hexane/EtOAc; flow rate: 6 mL/min) to provide (*ent*)-**17b** (95 mg, 42.7% yield, 45% ee) and (*ent*)-**18b** (11 mg, 4.9% yield, 99% ee), both as colorless oil. For *i*-propyl (4*S*,5*S*)-4,5-dihydroxy-5-phenyl-2-pentenoate ((*ent*)-**17b**): R_f=0.17 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ −42.9° (*c* 0.99, EtOH); IR (neat, cm^{-1}) 3437, 2981, 1716, 1659, 1306, 1280, 1176, 1109, 1053; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35 (m, 5H), 6.74 (dd, *J*=15.6, 4.5 Hz, 1H), 6.07 (dd, *J*=15.6, 1.8 Hz, 1H), 5.03 (septet, *J*=6.3 Hz, 1H), 4.54 (d, *J*=6.9 Hz, 1H), 4.38 (ddd, *J*=6.3, 4.5, 1.8 Hz, 1H), 3.61 (br, 2H), 1.25 (dd, *J*=6.0, 2.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.7, 145.4, 139.7, 128.4, 128.1, 126.7, 122.4, 76.8, 75.2, 67.7, 21.7; HRMS (CI) Calcd for $[C_{14}H_{18}O_4+NH_4]^+$: 268.1549, Found: 268.1544. The enantiomeric excess of compound (*ent*)-**17b**(*S*,*S*) was determined by HPLC analysis (Chiralcel OD column), using 8% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *S*,*S*=21.3; *R*,*R*=26.9.

2.1.10. *i*-Propyl (2*R*,3*S*)-2,3-dihydroxy-5-phenyl-4-pentenoate ((*ent*)-18b(*R*,*S*)). R_f=0.17 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ −33.0° (*c* 1.00, EtOH); IR (neat, cm^{-1}) 3458, 2982, 2925, 1730, 1375, 1105, 968, 754, 693; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33 (m, 5H), 6.71 (dd, *J*=15.9, 1.2 Hz, 1H), 6.35 (dd, *J*=15.9, 6.6 Hz, 1H), 5.17 (septet, *J*=6.3 Hz, 1H), 4.57 (d, *J*=3.0 Hz, 1H), 4.22 (dd, *J*=5.7, 3.0 Hz, 1H), 3.19 (br, 1H), 2.43 (br, 1H), 1.30 (dd, *J*=6.3, 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.3, 136.3, 132.5, 128.6, 128.0, 127.5, 126.7, 73.8, 73.6, 70.4, 21.8; HRMS (CI) Calcd for $[C_{14}H_{18}O_4+NH_4]^+$: 268.1549, Found: 268.1541. The enantiomeric excess of compound (*ent*)-**18b**(*R*,*S*) was determined by HPLC analysis (Chiralcel

OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*S*=30.1; *S*,*R*=41.7.

2.1.11. *i*-Propyl (4*R*,5*R*)-4,5-dihydroxy-5-phenyl-2-pentenoate (17b(*R*,*R*)) and *i*-propyl (2*S*,3*R*)-2,3-dihydroxy-5-phenyl-4-pentenoate (18b(*S*,*R*)). To a 25 mL round bottom flask was added 1:1 *tert*-butyl alcohol (5 mL)/H_2O (5 mL), $K_3Fe(CN)_6$ (900 mg, 2.7 mmol), K_2CO_3 (378 mg, 2.7 mmol), $CH_3SO_2NH_2$ (87 mg, 0.9 mmol), $(DHQD)_2$-PHAL (42.6 mg, 6 mol%), OsO_4 (11.6 mg, 5 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **16b** (197 mg, 0.9 mmol) and the reaction was stirred vigorously at room temperature overnight. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4, and concentrated to afford the crude mixture of regioisomers (**17b**/**18b**=77:33 by ^{1}H NMR). Flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) provided the pure mixture of two regioisomers (151 mg, 66.2% combined yield). The two regioisomers were separated by MPLC (2:1 (v/v) hexane/EtOAc; flow rate: 6 mL/min) to provide **17b** (91 mg, 39.9% yield, 91% ee) and **18b** (23 mg, 10.1% yield, 98% ee), both as colorless oil. For *i*-propyl (4*R*,5*R*)-4,5-dihydroxy-5-phenyl-2-pentenoate (**17b**): R_f= 0.26 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ +46.2° (*c* 1.02, EtOH); IR (neat, cm^{-1}) 3437, 2981, 1716, 1659, 1306, 1280, 1176, 1109, 1053; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (m, 5H), 6.72 (dd, *J*=15.5, 4.0 Hz, 1H), 6.06 (dd, *J*= 15.5, 2.0 Hz, 1H), 5.02 (septet, *J*=6.0 Hz, 1H), 4.54 (d, *J*= 6.5 Hz, 1H), 4.37 (ddd, *J*=6.5, 4.5, 2.0 Hz, 1H), 2.89 (br, 2H), 1.23 (dd, *J*=5.5, 3.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.7, 145.4, 139.7, 128.4, 128.1, 126.7, 122.4, 76.8, 75.2, 67.7, 21.7; HRMS (CI) Calcd for $[C_{14}H_{18}O_4+NH_4]^+$: 268.1549, Found: 268.1544. The enantiomeric excess of compound **17b**(*R*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 8% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *S*,*S*=21.7; *R*,*R*=26.8.

2.1.12. *i*-Propyl (2*S*,3*R*)-2,3-dihydroxy-5-phenyl-4-pentenoate (18b(*S*,*R*)). R_f=0.26 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ +36.0° (*c* 1.00, EtOH); IR (neat, cm^{-1}) 3458, 2982, 2925, 1730, 1375, 1105, 968, 754, 693; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 5H), 6.72 (dd, *J*=16.0, 1.0 Hz, 1H), 6.35 (dd, *J*=16.0, 6.5 Hz, 1H), 5.17 (septet, *J*=6.5 Hz, 1H), 4.58 (d, *J*=3.5 Hz, 1H), 4.22 (dd, *J*=6.0, 3.0 Hz, 1H), 3.21 (br, 1H), 2.44 (br, 1H), 1.30 (dd, *J*=10.5, 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.3, 136.3, 132.5, 128.6, 128.0, 127.5, 126.7, 73.8, 73.6, 70.4, 21.8; HRMS (CI) Calcd for $[C_{14}H_{18}O_4+NH_4]^+$: 268.1549, Found: 268.1541. The enantiomeric excess of compound **18b**(*S*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*S*=32.3; *S*,*R*=42.2.

2.1.13. *t*-Butyl (4*S*,5*S*)-4,5-dihydroxy-5-phenyl-2-pentenoate ((*ent*)-17c(*S*,*S*)) and *t*-butyl (2*R*,3*S*)-2,3-dihydroxy-5-phenyl-4-pentenoate ((*ent*)-18c(*R*,*S*)). To a 25 mL round bottom flask was added 1:1 *tert*-butyl alcohol (5 mL)/water (5 mL), $K_3Fe(CN)_6$ (1.80 g, 5.5 mmol), K_2CO_3 (756 mg, 5.5 mmol), $CH_3SO_2NH_2$ (174 mg, 1.8 mmol), $(DHQ)_2$-PHAL (39.7 mg, 2.8 mol%), OsO_4 (7.0 mg, 1.5 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **16c** (420 mg, 1.8 mmol) and the reaction was stirred vigorously at 0 °C overnight. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction and the suspension was warmed to room temperature while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4, and concentrated to afford the crude mixture of regioisomers ((*ent*)-**17c**(*S*,*S*)/(*ent*)-**18c**(*R*,*S*)=2:1 by ^{1}H NMR). Flash chromatography on silica gel (15:1–3:1 (v/v) hexane/EtOAc) provided regioisomer (*ent*)-**17c** (131 mg, 27.2% yield, 87% ee) and (*ent*)-**18c** (42 mg, 8.7% yield, 93% ee), both as off-white solids. For *t*-Butyl (4*S*,5*S*)-4,5-dihydroxy-5-phenyl-2-pentenoate ((*ent*)-**17c**(*S*,*S*)): R_f= 0.12 (4:1 (v/v) hexane/EtOAc); mp: 68–70 °C; $[\alpha]_D^{25}$ −43.3° (*c* 1.04, EtOH); IR (neat, cm^{-1}) 3550, 2987, 1717, 1456, 1370, 1319, 1157, 1052, 982; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38 (m, 5H), 6.68 (dd, *J*=15.6, 4.2 Hz, 1H), 6.05 (dd, *J*=15.6, 1.8 Hz, 1H), 4.59 (d, *J*=6.6 Hz, 1H), 4.42 (ddd, *J*=6.6, 4.5, 1.5 Hz, 1H), 2.57 (br, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.7, 144.3, 139.8, 128.7, 128.5, 126.8, 124.2, 80.7, 77.0, 75.4, 28.1; HRMS (CI) Calcd for $[C_{15}H_{20}O_4+NH_4]^+$: 282.1705, Found: 282.1703. The enantiomeric excess of compound (*ent*)-**17c**(*S*,*S*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *S*,*S*=20.2; *R*,*R*=29.9.

2.1.14. *t*-Butyl (2*R*,3*S*)-2,3-dihydroxy-5-phenyl-4-pentenoate ((*ent*)-18c(*R*,*S*)). R_f=0.19 (4:1 (v/v) hexane/EtOAc); mp: 116–119 °C; $[\alpha]_D^{25}$ −47.1° (*c* 1.01, EtOH); IR (neat, cm^{-1}) 3447, 2977, 1735, 1655, 1369, 1161, 968; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (m, 5H), 6.71 (dd, *J*= 16.0, 1.0 Hz, 1H), 6.34 (dd, *J*=16.0, 6.0 Hz, 1H), 4.53 (ddd, *J*=6.5, 3.0, 1.0 Hz, 1H), 4.14 (d, *J*=3.5 Hz, 1H), 3.16 (br, 1H), 2.36 (br, 1H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, 136.4, 132.3, 128.7, 128.0, 127.8, 126.7, 83.6, 73.9, 73.8, 28.1; HRMS (CI) Calcd for $[C_{15}H_{20}O_4+NH_4]^+$: 282.1705, Found: 282.1705. The enantiomeric excess of compound (*ent*)-**18c**(*R*,*S*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*S*=20.6; *S*,*R*=31.1.

2.1.15. *t*-Butyl (4*R*,5*R*)-4,5-dihydroxy-5-phenyl-2-pentenoate (17c(*R*,*R*)) and *t*-butyl (2*S*,3*R*)-2,3-dihydroxy-5-phenyl-4-pentenoate (18c(*S*,*R*)). To a 25 mL round bottom flask was added 1:1 *tert*-butyl alcohol (5 mL)/water (5 mL), $K_3Fe(CN)_6$ (1.72 g, 5.2 mmol), K_2CO_3 (720 mg, 5.2 mmol), $CH_3SO_2NH_2$ (165 mg, 1.7 mmol), $(DHQD)_2$-PHAL (27.1 mg, 2 mol%), OsO_4 (4.4 mg, 1 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **16c** (400 mg, 1.7 mmol) and the reaction was stirred vigorously at 0 °C overnight. Satd aqueous sodium

sulfite (5 mL) was added to quench the reaction and the suspension was warmed to room temperature while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine to remove the methanesulfonamide, dried over anhydrous Na_2SO_4, and concentrated to afford the crude mixture of regioisomers (**17c**/**18c**)=5:3 by ^{1}H NMR). Flash chromatography on silica gel (15:1–3:1 (v/v) hexane/EtOAc) provided regioisomer **17c**(*R*,*R*) (178 mg, 38.7% yield, 91% ee) and **18c**(*S*,*R*) (104 mg, 22.7% yield, 99% ee), both as off-white solids. For *t*-Butyl (4*R*,5*R*)-4,5-dihydroxy-5-phenyl-2-pentenoate (**17c**(*R*,*R*)): R_f=0.19 (4:1 (v/v) hexane/EtOAc); mp: 66–67 °C; $[\alpha]_D^{25}$ +45.6° (*c* 1.07, EtOH); IR (neat, cm^{-1}) 3435, 2978, 1711, 1701, 1660, 1373, 1315, 1153, 1052; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38 (m, 5H), 6.68 (dd, *J*=15.6, 4.5 Hz, 1H), 6.05 (dd, *J*=15.6, 1.8 Hz, 1H), 4.59 (d, *J*=6.6 Hz, 1H), 4.41 (ddd, *J*=5.4, 4.5, 1.8 Hz, 1H), 2.57 (br, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.7, 144.4, 139.8, 128.7, 128.5, 126.8, 124.2, 80.7, 77.0, 75.4, 28.1; HRMS (CI) Calcd for $[C_{15}H_{20}O_4+NH_4]^+$: 282.1705, Found: 282.1710. The enantiomeric excess of compound **17c**(*R*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *S*,*S*=19.7; *R*,*R*=30.2.

2.1.16. *t*-Butyl (2*S*,3*R*)-2,3-dihydroxy-5-phenyl-4-pentenoate (18c(*S*,*R*)). R_f=0.25 (4:1 (v/v) hexane/EtOAc); mp: 115–117 °C; $[\alpha]_D^{25}$ +48.4° (*c* 1.07, EtOH); IR (neat, cm^{-1}) 3447, 2988, 1734, 1652, 1373, 1276, 1086; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (m, 5H), 6.71 (dd, *J*=15.6, 1.2 Hz, 1H), 6.34 (dd, *J*=15.9, 6.3 Hz, 1H), 4.53 (ddd, *J*=6.6, 3.0, 1.2 Hz, 1H), 4.14 (d, *J*=3.3 Hz, 1H), 3.15 (br, 1H), 2.35 (br, 1H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, 136.4, 132.3, 128.7, 128.0, 127.8, 126.7, 83.6, 73.9, 73.8, 28.1; HRMS (CI) Calcd for $[C_{15}H_{20}O_4+NH_4]^+$: 282.1705, Found: 282.1708. The enantiomeric excess of compound **18c**(*S*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*S*=21.3; *S*,*R*=30.8.

2.1.17. S-ethyl (4*S*,5*S*)-4,5-dihydroxy-2-hexenoate ((*ent*)-14f(*S*,*S*)). To a 25 mL round bottom flask was added 3 mL *tert*-butyl alcohol, 5 mL water, $K_3Fe(CN)_6$ (714 mg, 2.2 mmol), K_2CO_3 (300 mg, 2.2 mmol), $CH_3SO_2NH_2$ (69 mg, 0.7 mmol), $(DHQ)_2$-PHAL (62.1 mg, 11 mol%), OsO_4 (18.4 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **13f** (113 mg, 0.7 mmol) and the reaction was stirred vigorously at room temperature for 36 h. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4. After removal of the solvents in vacuo, the crude product was purified by flash chromatography on silica gel (2:1 (v/v) hexane/EtOAc) to obtain (*ent*)-**14f**(*S*,*S*) (32 mg, 23.5% yield, 78% ee), a light yellow oil, as the only product: R_f=0.14 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ −43.0° (*c* 1.04, EtOH); IR (neat, cm^{-1}) 3467, 2977, 2933, 2877, 1666, 1634, 1061, 978; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.83 (dd, *J*=15.5, 5.0 Hz, 1H), 6.42 (dd, *J*=15.5, 1.5 Hz, 1H), 4.06 (ddd, *J*=6.0, 5.0, 2.0 Hz, 1H), 3.72 (dq, *J*=6.5, 6.0 Hz, 1H), 2.96 (q, *J*=7.0 Hz, 2H), 2.63 (br, 2H), 1.28 (t, *J*=7.5 Hz, 3H), 1.25 (d, *J*=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.5, 142.2, 129.0, 75.5, 70.3, 23.4, 19.1, 14.6; HRMS (CI) Calcd for $[C_8H_{14}O_3S+NH_4]^+$: 208.1007, Found: 208.1015. The enantiomeric excess of compound (*ent*)-**14f**(*S*,*S*) was determined by HPLC analysis (Chiralcel OD column), using 8% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=21.7; *S*,*S*=24.2.

2.1.18. S-ethyl (4*R*,5*R*)-4,5-dihydroxy-2-hexenoate (14f(*R*,*R*)). To a 25 mL round bottom flask was added 2 mL *tert*-butyl alcohol, 10 mL water, $K_3Fe(CN)_6$ (1.22 g, 3.7 mmol), K_2CO_3 (513 mg, 3.7 mmol), $NaHCO_3$ (312 mg, 3.7 mmol), $CH_3SO_2NH_2$ (118 mg, 1.2 mmol), $(DHQD)_2$-PHAL (106 mg, 11 mol%), OsO_4 (31.4 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **13f** (193 mg, 1.2 mmol) and the reaction was stirred vigorously at room temperature for 20 h. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4. After removal of the solvents in vacuo, the crude product was purified by flash chromatography on silica gel (2:1 (v/v) hexane/EtOAc) to obtain 23 mg **13f** (11.9% starting material recovered) and **14f**(*R*,*R*) (78 mg, 37.7% yield, 92% ee), a light yellow oil, as the only product: R_f=0.19 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ +59.6° (*c* 1.06, EtOH); IR (neat, cm^{-1}) 3467, 2977, 2933, 2877, 1666, 1634, 1061, 978; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.84 (dd, *J*=16.0, 5.0 Hz, 1H), 6.44 (dd, *J*=15.5, 1.5 Hz, 1H), 4.09 (dddd, *J*=6.0, 5.0, 4.5, 1.5 Hz, 1H), 3.75 (ddq, *J*=6.5, 6.0, 4..5 Hz, 1H), 2.97 (q, *J*=7.5 Hz, 2H), 2.44 (br, 1H), 2.11 (br, 1H), 1.30 (t, *J*=7.5 Hz, 3H), 1.27 (d, *J*=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.5, 142.2, 129.0, 75.5, 70.3, 23.4, 19.1, 14.6; HRMS (CI) Calcd for $[C_8H_{14}O_3S+NH_4]^+$: 208.1007, Found: 208.1015. The enantiomeric excess of compound **14f**(*R*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 8% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=22.9; *S*,*S*=26.2.

2.1.19. S-ethyl (4*S*,5*S*)-4,5-dihydroxy-5-phenyl-2-pentenoate ((*ent*)-17f(*S*,*S*)) and S-ethyl (2*R*,3*S*)-2,3-dihydroxy-5-phenyl-4-pentenoate ((*ent*)-18f(*R*,*S*)). To a 25 mL round bottom flask was added 5 mL *tert*-butyl alcohol, 10 mL water, $K_3Fe(CN)_6$ (1.47 g, 4.5 mmol), K_2CO_3 (617 mg, 4.5 mmol), $NaHCO_3$ (375 mg, 4.5 mmol), $CH_3SO_2NH_2$ (142 mg, 1.5 mmol), $(DHQ)_2$-PHAL (128 mg, 11 mol%), OsO_4 (37.8 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **16f** (325 mg, 1.5 mmol) and the reaction was stirred vigorously at room temperature for

24 h. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine to remove the methanesulfonamide, dried over anhydrous Na_2SO_4, and concentrated to afford the crude mixture of regioisomers (*ent*)-**17f** and (*ent*)-**18f**. Flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) provided 49 mg **16f** (15.4% starting material recovered), regioisomer (*ent*)-**17f** (109 mg, 29.0% yield, 98.6% ee), as a light yellow oil, and (*ent*)-**18f** (6.6 mg, 1.8% yield, 98% ee), as a off-white solid. For S-ethyl (4*S*,5*S*)-4,5-dihydroxy-5-phenyl-2-pentenoate ((*ent*)-**17f**)): R_f=0.18 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ −43.0° (*c* 1.00, EtOH); IR (neat, cm^{-1}) 3423, 3063, 3032, 2970, 2931, 1666, 1633, 1454, 1113, 1051; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (m, 5H), 6.61 (dd, *J*=15.5, 4.0 Hz, 1H), 6.35 (dd, *J*=15.5, 2.0 Hz, 1H), 4.52 (d, *J*=6.5 Hz, 1H), 4.37 (ddd, *J*=7.0, 4.5, 2.0 Hz, 1H), 3.22 (br, 2H), 2.90 (q, *J*=7.5 Hz, 2H), 1.24 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.4, 141.3, 139.6, 128.8, 128.7, 128.5, 126.8, 77.1, 75.3, 23.3, 14.6; HRMS (CI) Cacld for $[C_{13}H_{16}O_3S+NH_4]^+$: 270.1164, Found: 270.1171. The enantiomeric excess of compound (*ent*)-**17f**(*S*,*S*) was determined by HPLC analysis (Chiralcel OD column), using 2% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=39.4, *S*,*S*=41.8.

2.1.20. S-ethyl (2*R*,3*S*)-2,3-dihydroxy-5-phenyl-4-pentenoate ((*ent*)-18f(*R*,*S*)). R_f=0.25 (4:1 (v/v) hexane/EtOAc); mp: 126–128 °C; $[\alpha]_D^{25}$ +64.3° (*c* 0.98, EtOH); IR (neat, cm^{-1}) 3414, 3038, 2927, 2872, 1648, 1448, 1413, 1106, 1069, 963; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37 (m, 5H), 6.74 (d, *J*=16.0 Hz, 1H), 6.33 (dd, *J*=16.5, 6.5 Hz, 1H), 4.72 (dd, *J*=6.0, 6.0 Hz, 1H), 4.28 (dd, *J*=7.5, 3.0 Hz, 1H), 3.30 (br, 1H), 2.98 (dq, *J*=7.5, 3.0 Hz, 2H), 2.34 (br, 1H), 1.30 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.3, 133.0, 128.6, 128.2, 128.1, 127.0, 126.7, 80.0, 73.7, 23.2, 14.5; HRMS (CI) Cacld for $[C_{13}H_{16}O_3S+NH_4]^+$: 270.1164, Found: 270.1166. The enantiomeric excess of compound (*ent*)-**18f**(*R*,*S*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*S*=54.3, *S*,*R*=67.5.

2.1.21. S-ethyl (4*R*,5*R*)-4,5-dihydroxy-5-phenyl-2-pentenoate (17f(*R*,*R*)) and S-ethyl (2*S*,3*R*)-2,3-dihydroxy-5-phenyl-4-pentenoate (18f(*S*,*R*)). To a 25 mL round bottom flask was added 5 mL *tert*-butyl alcohol, 10 mL water, $K_3Fe(CN)_6$ (1.43 g, 4.4 mmol), K_2CO_3 (602 mg, 4.4 mmol), $NaHCO_3$ (366 mg, 4.4 mmol), $CH_3SO_2NH_2$ (138 mg, 1.5 mmol), $(DHQD)_2$-PHAL (125 mg, 11 mol%), OsO_4 (36.9 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **16f** (317 mg, 1.5 mmol) and the reaction was stirred vigorously at room temperature for 24 h. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine to remove the methanesulfonamide, dried over anhydrous Na_2SO_4, and concentrated to afford the crude mixture of regioisomers **17f**(*R*,*R*) and **18f**(*S*,*R*). Flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) provided 49 mg **5** (15.4% starting material recovered), regioisomer **17f**(*R*,*R*) (96.3 mg, 26.3% yield, 98.7% ee), as a light yellow oil, and **18f**(*S*,*R*) (18.3 mg, 5.0% yield, 99% ee), as a off-white solid. For S-ethyl (4*R*,5*R*)-4,5-dihydroxy-5-phenyl-2-pentenoate (**17f**(*R*,*R*)): R_f=0.11 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ +49.7° (*c* 1.01, EtOH); IR (neat, cm^{-1}) 3423, 3063, 3032, 2970, 2931, 1666, 1633, 1454, 1113, 1051; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.38 (m, 5H), 6.65 (dd, *J*=15.0, 4.5 Hz, 1H), 6.40 (dd, *J*=15.0, 2.0 Hz, 1H), 4.59 (d, *J*=6.5 Hz, 1H), 4.44 (ddd, *J*=7.0, 4.5, 2.0 Hz, 1H), 2.94 (q, *J*=7.5 Hz, 2H), 2.66 (br, 1H), 1.57 (br, 1H), 1.27 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.4, 141.3, 139.6, 128.8, 128.7, 128.5, 126.8, 77.1, 75.3, 23.3, 14.6; HRMS (CI) Cacld for $[C_{13}H_{16}O_3S+NH_4]^+$: 270.1164, Found: 270.1171. The enantiomeric excess of compound **17f**(*R*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 2% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=36.7, *S*,*S*=40.4.

2.1.22. S-ethyl (2*S*,3*R*)-2,3-dihydroxy-5-phenyl-4-pentenoate (18f(*S*,*R*)). R_f=0.16 (4:1 (v/v) hexane/EtOAc); mp: 133–134 °C; $[\alpha]_D^{25}$ −69.1° (*c* 0.99, EtOH); IR (neat, cm^{-1}) 3414, 3038, 2927, 2872, 1648, 1448, 1413, 1106, 1069, 963; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (m, 5H), 6.74 (d, *J*=15.5 Hz, 1H), 6.33 (dd, *J*=16.0, 6.5 Hz, 1H), 4.73 (dd, *J*=6.0, 6.0 Hz, 1H), 4.28 (dd, *J*=7.5, 2.5 Hz, 1H), 3.28 (d, *J*=7.0 Hz, 1H), 2.98 (dq, *J*=7.5, 3.0 Hz, 2H), 2.31 (d, *J*=6.0 Hz, 1H), 1.30 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.3, 133.0, 128.6, 128.2, 128.1, 127.0, 126.7, 80.0, 73.7, 23.2, 14.5; HRMS (CI) Cacld for $[C_{13}H_{16}O_3S+NH_4]^+$: 270.1164, Found: 270.1166. The enantiomeric excess of compound **18f**(*S*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*S*=54.2, *S*,*R*=62.1.

2.1.23. (4*S*,5*S*)-4,5-Dihydroxy-2-hexenoic acid methoxy-methyl-amide ((*ent*)-14d(*S*,*S*)). To a 25 mL round bottom flask was added 3 mL *tert*-butyl alcohol, 5 mL water, $K_3Fe(CN)_6$ (481 mg, 1.5 mmol), K_2CO_3 (202 mg, 1.5 mmol), $NaHCO_3$ (123 mg, 1.5 mmol), $CH_3SO_2NH_2$ (46 mg, 0.5 mmol), $(DHQ)_2$-PHAL (41.7 mg, 11 mol%), OsO_4 (12.4 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **13d** (69 mg, 0.5 mmol) and the reaction was stirred vigorously at room temperature for 27 h. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4. After removal of the solvents in vacuo, the crude product was purified by flash chromatography on silica gel (1:1 (v/v) hexane/EtOAc–9:1 (v/v) EtOAc/MeOH–1:1 (v/v) EtOAc/MeOH) to obtain (*ent*)-**14d**(*S*,*S*) (64 mg, 76.0% yield, 65% ee), a light yellow oil, as the only product: R_f=0.19 (EtOAc); $[\alpha]_D^{25}$ −40.5° (*c* 1.05, EtOH); IR (neat, cm^{-1}) 3396, 2977, 2937, 1653, 1617,

1419, 1387, 1180, 1117, 1082; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.91 (dd, J=15.6, 5.1 Hz, 1H), 6.69 (d, J=15.6 Hz, 1H), 4.08 (ddd, J=5.7, 5.4, 1.5 Hz, 1H), 3.73 (dq, J=6.3, 6.0 Hz, 1H), 3.71 (s, 3H), 3.24 (s, 3H), 3.12 (br, 2H), 1.22 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.6, 145.9, 119.6, 75.9, 70.3, 61.9, 32.4, 19.0; HRMS (CI) Cacld for $[C_8H_{15}NO_4+NH_4]^+$: 207.1345, Found: 207.1355. The enantiomeric excess of compound (*ent*)-**14d**(*S*,*S*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=34.3, *S*,*S*=37.4.

2.1.24. (4*R*,5*R*)-4,5-Dihydroxy-2-hexenoic acid methoxy-methyl-amide (14d(*R*,*R*)). To a 25 mL round bottom flask was added 3 mL *tert*-butyl alcohol, 5 mL water, $K_3Fe(CN)_6$ (741 mg, 2.3 mmol), K_2CO_3 (311 mg, 2.3 mmol), $NaHCO_3$ (189 mg, 2.3 mmol), $CH_3SO_2NH_2$ (71 mg, 0.75 mmol), $(DHQD)_2$-PHAL (64.4 mg, 11 mol%), OsO_4 (19.1 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **13d** (117 mg, 0.75 mmol) and the reaction was stirred vigorously at room temperature for 24 h. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4. After removal of the solvents in vacuo, the crude product was purified by flash chromatography on silica gel (1:1 (v/v) hexane/EtOAc–9:1 (v/v) EtOAc/MeOH–1:1 (v/v) EtOAc/MeOH) to obtain **14d**(*R*,*R*) (116 mg, 81.7% yield, 75% ee), a light yellow oil, as the only product: R_f=0.16 (EtOAc); $[\alpha]_D^{25}$ +46.9° (*c* 1.18, EtOH); IR (neat, cm^{-1}) 3396, 2977, 2937, 1653, 1617, 1419, 1387, 1180, 1117, 1082; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.85 (dd, J=15.3, 5.1 Hz, 1H), 6.61 (d, J=15.3 Hz, 1H), 4.00 (ddd, J=5.7, 5.4, 1.5 Hz, 1H), 3.99 (br, 2H), 3.63 (s, 3H), 3.63 (dq, dq, J=6.6, 6.3 Hz, 1H), 3.16 (s, 3H), 1.13 (d, J=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.6, 146.0, 119.4, 76.0, 70.4, 61.9, 32.4, 18.9; HRMS (CI) Cacld for $[C_8H_{15}O_4N+NH_4]^+$: 207.1345, Found: 207.1363. The enantiomeric excess of compound **14d**(*R*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=33.3, *S*,*S*=38.4.

2.1.25. (4*S*,5*S*)-4,5-Dihydroxy-5-phenyl-2-pentenoic acid methoxy-methyl-amide ((*ent*)-17d(*S*,*S*)). To a 25 mL round bottom flask was added 3 mL *tert*-butyl alcohol, 5 mL water, $K_3Fe(CN)_6$ (554 mg, 1.7 mmol), K_2CO_3 (233 mg, 1.7 mmol), $NaHCO_3$ (141 mg, 1.7 mmol), $CH_3SO_2NH_2$ (53 mg, 0.6 mmol), $(DHQ)_2$-PHAL (48.1 mg, 11 mol%), OsO_4 (14.3 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **7** (122 mg, 0.6 mmol) and the reaction was stirred vigorously at room temperature for 25 h. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4. After removal of the solvents in vacuo, the crude product was purified by flash chromatography on silica gel (1:1 (v/v) hexane/EtOAc–9:1 (v/v) EtOAc/MeOH) to obtain (*ent*)-**17d**(*S*,*S*) (86 mg, 61.2% yield, 98% ee), a light yellow oil, as the only product: R_f=0.38 (EtOAc); $[\alpha]_D^{25}$ −40.3° (*c* 1.00, EtOH); IR (neat, cm^{-1}) 3410, 2984, 2939, 1663, 1621, 1388, 1195, 1052, 1002; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31 (m, 5H), 6.74 (dd, J=15.3, 4.8 Hz, 1H), 6.51 (d, J=15.6 Hz, 1H), 4.52 (d, J=6.9 Hz, 1H), 4.36 (dd, J=6.6, 4.8 Hz, 1H), 3.60 (br, 2H), 3.53 (s, 3H), 3.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 144.9, 140.1, 128.5, 128.2, 127.1, 119.9, 77.0, 76.0, 61.8, 43.2; HRMS (CI) Cacld for $[C_{13}H_{17}NO_4+NH_4]^+$: 269.1501, Found: 269.1523. The enantiomeric excess of compound (*ent*)-**17d**(*S*,*S*) was determined by HPLC analysis (Chiralcel OD column), using 8% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=28.4, *S*,*S*=31.0.

2.1.26. (4*R*,5*R*)-4,5-Dihydroxy-5-phenyl-2-pentenoic acid methoxy-methyl-amide (17d(*R*,*R*)). To a 25 mL round bottom flask was added 3 mL *tert*-butyl alcohol, 5 mL water, $K_3Fe(CN)_6$ (575 mg, 1.7 mmol), K_2CO_3 (241 mg, 1.7 mmol), $NaHCO_3$ (147 mg, 1.7 mmol), $CH_3SO_2NH_2$ (55 mg, 0.6 mmol), $(DHQD)_2$-PHAL (50.0 mg, 11 mol%), OsO_4 (14.8 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **16d** (127 mg, 0.6 mmol) and the reaction was stirred vigorously at room temperature for 25 h. Satd aqueous sodium sulfite (5 mL) was added to quench the reaction while stirring vigorously. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 2 N KOH (10 mL) and brine (10 mL) to remove the methanesulfonamide, dried over anhydrous Na_2SO_4. After removal of the solvents in vacuo, the crude product was purified by flash chromatography on silica gel (1:1 (v/v) hexane/EtOAc–9:1 (v/v) EtOAc/MeOH) to obtain **17d**(*R*,*R*) (86 mg, 85.3% yield, 99.97% ee), a light yellow oil, as the only product: R_f=0.47 (EtOAc); $[\alpha]_D^{25}$ +41.8° (*c* 0.99, EtOH); IR (neat, cm^{-1}) 3401, 2939, 1663, 1621, 1454, 1195, 1119, 1052, 1001; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 (m, 5H), 6.76 (dd, J=15.6, 4.8 Hz, 1H), 6.55 (d, J=15.6 Hz, 1H), 4.55 (d, J=6.9 Hz, 1H), 4.39 (dd, J=6.3, 5.1 Hz, 1H), 3.56 (s, 3H), 3.35 (br, 2H), 3.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 144.9, 140.1, 128.5, 128.1, 127.1, 119.8, 77.0, 76.0, 61.8, 32.4; HRMS (CI) Cacld for $[C_{13}H_{17}O_4N+NH_4]^+$: 269.1501, Found: 269.1507. The enantiomeric excess of compound **17d**(*R*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 8% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=26.9, *S*,*S*=32.3.

2.1.27. (5*S*,6*S*)-5,6-Dihydroxy-3-en-2-heptanone ((*ent*)-14e(*S*,*S*)). To a 25 mL round bottom flask was added 3 mL *tert*-butyl alcohol, 5 mL water, $K_3Fe(CN)_6$ (1.07 g, 3.3 mmol), K_2CO_3 (451 mg, 3.3 mmol), $NaHCO_3$ (274 mg, 3.3 mmol), $CH_3SO_2NH_2$ (103 mg, 1.1 mmol), $(DHQ)_2$-PHAL (93.2 mg, 11 mol%), OsO_4 (27.6 mg, 10 mol%). The mixture was stirred at room temperature until both

phases were clear, and then cooled to 0 °C. To this solution was added dienoate **13e** (118 mg, 1.1 mmol) and the reaction was stirred vigorously at room temperature for 30 h. For workup, no Na_2SO_3 was added. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). Due to the fact that the product would decompose in the presence of base, no base wash was used. Only satd NaCl wash was performed to the combined organic layers, followed by drying over anhydrous Na_2SO_4. After removal of the solvents in vacuo, the crude product was purified by flash chromatography on silica gel (hexane/EtOAc 2:1 (v/v)–1:1 (v/v), then EtOAc) to obtain a light yellow oil (*ent*)-**14e**(*S*,*S*), together with unseparatable $CH_3SO_2NH_2$ (after subtracting the $CH_3SO_2NH_2$ from ^{1}H NMR, the mass of (*ent*)-**14e**(*S*,*S*) was 72 mg, 46.9% yield, 71% ee): R_f=0.36 (EtOAc); $[\alpha]_D$ −57.3° (*c* 0.75, EtOH); IR (neat, cm^{-1}) 3407, 2984, 2931, 1671, 1642, 1367, 1123, 1080, 988; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.75 (dd, *J*=15.9, 5.1 Hz, 1H), 6.34 (dd *J*=15.9, 1.5 Hz, 1H), 4.06 (ddd, *J*=6.0, 4.8, 1.5 Hz, 1H), 3.72 (dq, *J*=6.3, 6.0 Hz, 1H), 3.23 (br, 2H), 2.26 (s, 3H), 1.21 (d, *J*=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.1, 145.9, 131.0, 75.6, 70.3, 27.6, 19.2; HRMS (CI) Cacld for $[C_7H_{12}O_3+NH_4]^+$: 162.1130, Found: 162.1137. The enantiomeric excess of compound (*ent*)-**14e**(*S*,*S*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=25.8, *S*,*S*=28.9.

2.1.28. (5*R*,6*R*)-5,6-Dihydroxy-3-en-2-heptanone (14e(*R*,*R*)). To a 25 mL round bottom flask was added 3 mL *tert*-butyl alcohol, 5 mL water, $K_3Fe(CN)_6$ (1.07 g, 3.3 mmol), K_2CO_3 (451 mg, 3.3 mmol), $NaHCO_3$ (274 mg, 3.3 mmol), $CH_3SO_2NH_2$ (103 mg, 1.1 mmol), $(DHQD)_2$-PHAL (93.2 mg, 11 mol%), OsO_4 (27.6 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **13e** (120 mg, 1.1 mmol) and the reaction was stirred vigorously at room temperature for 27 h. For workup, no Na_2SO_3 was added. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). Due to the fact that the product would decompose in the presence of base, no base wash was used. Only satd NaCl wash was performed to the combined organic layers, followed by drying over anhydrous Na_2SO_4. After removal of the solvents in vacuo, the crude product was purified by flash chromatography on silica gel (hexane/EtOAc 2:1 (v/v)–1:1 (v/v), then EtOAc) to obtain a light yellow oil **14e**(*R*,*R*), together with unseparatable $CH_3SO_2NH_2$ (after subtracting the $CH_3SO_2NH_2$ from ^{1}H NMR, the mass of **14e**(*R*,*R*) was 46 mg, 29.4% yield, 71% ee): R_f=0.37 (EtOAc); $[\alpha]_D$ +63.1° (*c* 1.03, EtOH); IR (neat, cm^{-1}) 3407, 2984, 2931, 1671, 1642, 1367, 1123, 1080, 988; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.76 (dd, *J*=15.9, 5.1 Hz, 1H), 6.34 (d, *J*=16.2 Hz, 1H), 3.94, (ddd, *J*=6.0, 5.1, 1.5 Hz, 1H), 3.72 (dq, *J*=6.3, 6.0 Hz, 1H), 3.21 (br, 2H), 2.27 (s, 3H), 1.17 (d, *J*=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.2, 145.9, 131.0, 75.6, 70.3, 27.6, 19.2; HRMS (CI) Cacld for $[C_7H_{12}O_3+NH_4]^+$: 162.1130, Found: 162.1137. The enantiomeric excess of compound **14e**(*R*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=25.1, *S*,*S*=28.8.

2.1.29. (5*S*,6*S*)-5,6-Dihydroxy-6-phenyl-3-en-2-hexanone ((*ent*)-17e(*S*,*S*)) and (3*R*,4*S*)-3,4-dihydroxy-6-phenyl-5-en-2-hexanone ((*ent*)-18e(*R*,*S*)). To a 25 mL round bottom flask was added 3 mL *tert*-butyl alcohol, 5 mL water, $K_3Fe(CN)_6$ (700 mg, 2.1 mmol), K_2CO_3 (294 mg, 2.1 mmol), $NaHCO_3$ (179 mg, 2.1 mmol), $CH_3SO_2NH_2$ (67 mg, 0.7 mmol), $(DHQ)_2PHAL$ (60.8 mg, 11 mol%), OsO_4 (18.0 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **16e** (125 mg, 0.7 mmol) and the reaction was stirred vigorously at room temperature for 28 h. For workup, no Na_2SO_3 was added. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). Due to the fact that the product would decompose in the presence of base, no base wash was used. The combined oraginc layers were then washed with satd NaCl wash, dried over anhydrous Na_2SO_4 and concentrated to afford the crude mixture of regioisomers ((*ent*)-**17e**(*S*,*S*)/(*ent*)-**18e**(*R*,*S*)=11:1 by ^{1}H NMR). Flash chromatography on silica gel (2:1–1:1 (v/v) hexane/EtOAc) provided regioisomer (*ent*)-**17e**(*S*,*S*) (after subtracting the $CH_3SO_2NH_2$ from ^{1}H NMR, the mass of (*ent*)-**17e**(*S*,*S*) was 79 mg, 53.1% yield, 93% ee) and (*ent*)-**18e**(*R*,*S*) (after subtracting the $CH_3SO_2NH_2$ from ^{1}H NMR, the mass of (*ent*)-**18e**(*R*,*S*) was 5.7 mg, 3.8% yield), both mixed with unseparatable $CH_3SO_2NH_2$. For (5*S*,6*S*)-5,6-dihydroxy-6-phenyl-3-en-2-hexanone ((*ent*)-**17e**(*S*,*S*)): light yellow oil; R_f=0.10 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$=−35.1° (product after protection–deprotection process, *c* 1.08, EtOH); IR (neat, cm^{-1}) 3416, 3010, 2925, 1672, 1646, 1361, 1081; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (m, 5H), 6.54 (dd, *J*=15.0, 4.5 Hz, 1H), 6.28 (dd, *J*=15.5, 1.5 Hz, 1H), 4.54 (d, *J*=6.0 Hz, 1H), 4.40 (ddd, *J*=6.5, 5.0, 1.5 Hz, 1H), 2.75 (br, 2H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.9, 144.8, 139.7, 130.7, 128.7, 128.5, 126.8, 77.1, 75.4, 27.4; HRMS (CI) Cacld for $[C_{12}H_{14}O_3+NH_4]^+$: 224.1287, Found: 224.1277. The enantiomeric excess of compound **9**(*S*,*S*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=40.6, *S*,*S*=42.9.

2.1.30. (5*R*,6*R*)-5,6-Dihydroxy-6-phenyl-3-en-2-hexanone (17e(*R*,*R*)) and (3*S*,4*R*)-3,4-dihydroxy-6-phenyl-5-en-2-hexanone (18e(*S*,*R*)). To a 25 mL round bottom flask was added 3 mL *tert*-butyl alcohol, 5 mL water, $K_3Fe(CN)_6$ (700 mg, 2.1 mmol), K_2CO_3 (294 mg, 2.1 mmol), $NaHCO_3$ (179 mg, 2.1 mmol), $CH_3SO_2NH_2$ (67 mg, 0.7 mmol), $(DHQD)_2PHAL$ (60.8 mg, 11 mol%), OsO_4 (18.0 mg, 10 mol%). The mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. To this solution was added dienoate **16e** (122 mg, 0.7 mmol) and the reaction was stirred vigorously at room temperature for 28 h. For workup, no Na_2SO_3 was added. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3×5 mL). Due to the fact that the product would decompose in the presence of base, no base wash was used. The combined oraginc layers were then

washed with satd NaCl wash, dried over anhydrous Na_2SO_4 and concentrated to afford the crude mixture of regioisomers (**17e**(*R*,*R*)/**18e**(*S*,*R*)=12:1 by ^{1}H NMR). Flash chromatography on silica gel (2:1–1:1 (v/v) hexane/EtOAc) provided regioisomer **17e**(*R*,*R*) (after subtracting the $CH_3SO_2NH_2$ from ^{1}H NMR, the mass of **17e**(*R*,*R*) was 89 mg, 60.6% yield, 98% ee) and **18e**(*S*,*R*) (after subtracting the $CH_3SO_2NH_2$ from ^{1}H NMR, the mass of **18e**(*S*,*R*) was 4.4 mg, 3.0% yield), both mixed with unseparatable $CH_3SO_2NH_2$. For (5*R*,6*R*)-5,6-dihydroxy-6-phenyl-3-en-2-hexanone (**17e**(*R*,*R*)): light yellow oil; R_f=0.56 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}=+34.3°$ (product after protection–deprotection process, *c* 1.08, EtOH); IR (neat, cm^{-1}) 3416, 3010, 2925, 1672, 1646, 1361, 1081; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 (m, 5H), 6.52 (dd, *J*=15.9, 4.5 Hz, 1H), 6.27 (dd, *J*=16.2, 1.5 Hz, 1H), 4.53 (d, *J*=6.9 Hz, 1H), 4.37 (ddd, *J*=6.6, 5.1, 1.5 Hz, 1H), 3.29 (br, 2H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.9, 144.8, 139.7, 130.7, 128.7, 128.5, 126.8, 77.1, 75.4, 27.4; HRMS (CI) Cacld for $[C_{12}H_{14}O_3+NH_4]^+$: 224.1287, Found: 224.1277. The enantiomeric excess of compound **17e**(*R*,*R*) was determined by HPLC analysis (Chiralcel OD column), using 5% *i*PrOH in hexane at 0.8 mL/min. Retention time (min): *R*,*R*=43.8, *S*,*S*=49.2.

2.1.31. Protection of diol (*ent*)-14e(*S*,*S*) to diacetate (5*S*,6*S*)-5,6-diacetate-3-en-2-heptanone ((*ent*)-22(*S*,*S*)). To a solution of (*ent*)-**14e**(*S*,*S*) (51 mg, 0.7 mmol) in CH_2Cl_2 (2 mL) was added excess Ac_2O (0.5 mL, 5.3 mmol), pyridine (1 mL) and a catalytic amount of DMAP (3 mg, 5 mol%). The reaction was stirred for an hour, after which 2 mL of 1 N sodium bisulfate was added to remove excess base. The organic layer was washed with saturated sodium bicarbonate and the aqueous layer was further extracted with ether (3×2 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) to yield the diacetate (*ent*)-**22** (47 mg, 58.2% yield) as a light yellow oil. R_f=0.38 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ −21.2° (*c* 1.11, EtOH); IR (neat, cm^{-1}) 2990, 2941, 1742, 1703, 1679, 1637, 1373, 1222, 1061; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.64 (dd, *J*=16.2, 5.1 Hz, 1H), 6.21 (dd, *J*=15.9, 1.5 Hz, 1H), 5.48 (ddd, *J*=5.1, 5.1, 1.5 Hz, 1H), 5.11 (ddq, *J*=6.3, 6.0, 1.5 Hz, 1H), 2.27 (s, 3H), 2.14 (s, 3H), 2.04 (s, 3H), 1.22 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.5, 170.0, 169.6, 139.8, 131.8, 73.2, 69.6, 27.4, 20.9, 20.7, 15.9; HRMS (CI) Cacld for $[C_{11}H_{16}O_5+NH_4]^+$: 246.1341, Found: 246.1340.

2.1.32. Protection of diol 14e(*S*,*S*) to diacetate (5*S*,6*S*)-5,6-diacetate-3-en-2-heptanone (22(*S*,*S*)). To a solution of **14e**(*S*,*S*) (47 mg, 0.7 mmol) in CH_2Cl_2 (2 mL) was added excess Ac_2O (0.5 mL, 5.3 mmol), pyridine (1 mL) and a catalytic amount of DMAP (3 mg, 5 mol%). The reaction was stirred for an hour, after which 2 mL of 1 N sodium bisulfate was added to remove excess base. The organic layer was washed with saturated sodium bicarbonate and the aqueous layer was further extracted with ether (3×2 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) to yield the diacetate **22** (45 mg, 67.2% yield) as a light yellow oil. R_f=0.29 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ +22.6° (*c* 1.03, EtOH); IR (neat, cm^{-1}) 2990, 2941, 1742, 1703, 1679, 1637, 1373, 1222, 1061; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.63 (dd, *J*=16.2, 5.1 Hz, 1H), 6.20 (dd, *J*=15.9, 1.5 Hz, 1H), 5.48 (ddd, *J*=5.1, 5.1, 1.5 Hz, 1H), 5.11 (dq, *J*=6.3, 6.0 Hz, 1H), 2.26 (s, 3H), 2.13 (s, 3H), 2.04 (s, 3H), 1.22 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.5, 170.0, 169.6, 139.8, 131.8, 73.2, 69.6, 27.4, 20.9, 20.7, 15.9; HRMS (CI) Cacld for $[C_{11}H_{16}O_5+NH_4]^+$: 246.1341, Found: 264.1340.

2.1.33. Deprotection of diacetate (*ent*)-22(*S*,*S*) to diol (5*S*,6*S*)-5,6-diacetate-6-phenyl-3-en-2-hexanone ((*ent*)-14e(*S*,*S*)). To a 5 mL round-bottom flask was added the diacetate (*ent*)-**22**(*S*,*S*) (45 mg, 0.03 mmol), MeOH (1 mL) and NEt_3 (0.1 mL). The reaction was stirred at room temperature for 24 h and concentrated. The diol was purified by flash chromatography on silica gel (2:1 (v/v) hexane/EtOAc) to yield the pure diol (*ent*)-**14e**(*S*,*S*) (22 mg, 77.4% yield) without methanesulfonamide. For the characterization of (*ent*)-**14e**(*S*,*S*), please refer to the previous dihydroxylation reaction of dienoate **13e**.

2.1.34. Deprotection of diacetate 22(*R*,*R*) to diol (5*R*,6*R*)-5,6-diacetate-6-phenyl-3-en-2-hexanone (14e(*R*,*R*)). To a 5 mL round-bottom flask was added the diacetate **22**(*R*,*R*) (40 mg, 0.03 mmol), MeOH (1 mL) and NEt_3 (0.1 mL). The reaction was stirred at room temperature for 24 h and concentrated. The diol was purified by flash chromatography on silica gel (2:1 (v/v) hexane/EtOAc) to yield the pure diol **14e**(*R*,*R*) (21 mg, 83.1% yield) without methanesulfonamide. For the characterization of **14e**(*R*,*R*), please refer to the previous dihydroxylation reaction of dienoate **13e**.

2.1.35. Protection of diol (*ent*)-17e(*S*,*S*) to diacetate (5*S*,6*S*)-5,6-diacetate-6-phenyl-3-en-2-hexanone ((*ent*)-23(*S*,*S*)). To a solution of (*ent*)-**17e**(*S*,*S*) (142 mg, 0.7 mmol) in CH_2Cl_2 (2 mL) was added excess Ac_2O (0.5 mL, 5.3 mmol), pyridine (0.8 mL) and a catalytic amount of DMAP (4 mg, 5 mol%). The reaction was stirred for an hour, after which 2 mL of 1 N sodium bisulfate was added to remove excess base. The organic layer was washed with saturated sodium bicarbonate and the aqueous layer was further extracted with ether (3×2 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) to yield the diacetate (*ent*)-**23** (104 mg, 59.9% yield) as a white solid. R_f=0.20 (5:1 (v/v) hexane/EtOAc); mp: 79–80 °C; $[\alpha]_D^{25}$ +27.6° (*c* 1.04, EtOH); IR (neat, cm^{-1}) 3076, 1747, 1636, 1373, 1220, 1027; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35 (m, 5H), 6.44 (dd, *J*=16.5, 5.0 Hz, 1H), 6.12 (dd, *J*=16.0, 1.5 Hz, 1H), 5.91 (d, *J*=7.0 Hz, 1H), 5.77 (ddd, *J*=6.5, 5.0, 1.5 Hz, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.4, 169.6, 169.5, 139.6, 135.6, 132.0, 129.0, 128.7, 127.2, 75.4, 73.5, 27.4, 21.0, 20.7; HRMS (CI) Cacld for $[C_{16}H_{18}O_5+NH_4]^+$: 308.1498, Found: 308.1496.

2.1.36. Protection of diol 17e(*R*,*R*) to diacetate (5*R*,6*R*)-5,6-diacetate-6-phenyl-3-en-2-hexanone (23(*R*,*R*)). To a solution of **17e**(*R*,*R*) (103 mg, 0.5 mmol) in CH_2Cl_2 (2 mL)

was added excess Ac_2O (0.4 mL, 4.2 mmol), pyridine (0.8 mL) and a catalytic amount of DMAP (3 mg, 0.025 mmol). The reaction was stirred for an hour, after which 2 mL of 1 N sodium bisulfate was added to remove excess base. The organic layer was washed with saturated sodium bicarbonate and the aqueous layer was further extracted with ether (3×2 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) to yield the diacetate **23** (80.7 mg, 59.6% yield) as a white solid. R_f=0.61 (2:1 (v/v) hexane/EtOAc); mp: 80–81 °C; $[\alpha]_D^{25}$ −28.8° (*c* 1.02, EtOH); IR (neat, cm^{-1}) 3076, 1747, 1636, 1373, 1220, 1027; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (m, 5H), 6.45 (dd, *J*=15.5, 5.0 Hz, 1H), 6.11 (dd, *J*=16.0, 1.5 Hz, 1H), 5.91 (d, *J*=6.5 Hz, 1H), 5.77 (ddd, *J*=6.5, 5.0, 1.5 Hz, 1H), 2.16 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.4, 169.6, 169.5, 139.6, 135.6, 132.0, 129.0, 128.7, 127.2, 75.4, 73.5, 27.4, 21.0, 20.7; HRMS (CI) Cacld for $[C_{16}H_{18}O_5+NH_4]^+$: 308.1498, Found: 308.1496.

2.1.37. Deprotection of diacetate (*ent*)-23(*S*,*S*) to diol (5*S*,6*S*)-5,6-diacetate-6-phenyl-3-en-2-hexanone ((*ent*)-17e(*S*,*S*)). To a 5 mL round-bottom flask was added the diacetate (*ent*)-**23**(*S*,*S*) (9.3 mg, 0.03 mmol), MeOH (0.2 mL) and NEt_3 (0.1 mL). The reaction was stirred at room temperature for 24 h and concentrated. The diol was purified by flash chromatography on silica gel (2:1 (v/v) hexane/EtOAc) to yield the pure diol (*ent*)-**17e**(*S*,*S*) (4.8 mg, 73% yield) without methanesulfonamide. For the characterization of (*ent*)-**17e**(*S*,*S*), please refer to the previous dihydroxylation reaction of dienoate **16e**.

2.1.38. Deprotection of diacetate 23(*R*,*R*) to diol (5*R*,6*R*)-5,6-diacetate-6-phenyl-3-en-2-hexanone (17e(*R*,*R*)). To a 5 mL round-bottom flask was added the diacetate **23**(*R*,*R*) (8.4 mg, 0.03 mmol), MeOH (0.1 mL) and NEt_3 (0.1 mL). The reaction was stirred at room temperature for 24 h and concentrated. The diol was purified by flash chromatography on silica gel (2:1 (v/v) hexane /EtOAc) to yield the pure diol **17e**(*R*,*R*) (6.0 mg, 87% yield) without methanesulfonamide. For the characterization of **17e**(*S*,*S*), please refer to the previous dihydroxylation reaction of dienoate **16e**.

2.1.39. (6*R*,7*R*)-6,7-Dihydroxy-octa-2,4-dienoic acid methyl ester 20a. To 4.2 g (27.6 mmol) of triene **19a** in 130 mL of *t*-BuOH and 130 mL water was added $K_3Fe(CN)_6$ (27.24 g, 82.8 mmol), K_2CO_3 (11.43 g, 82.8 mmol), $(DHQD)_2$-PHAL (537 mg, 0.69 mmol), and $CH_3SO_2NH_2$ (2.62 g, 27.6 mmol). This mixture was cooled to 0 °C, OsO_4 (35 mg, 0.138 mmol) was then added, and the solution was stirred overnight. Ethyl acetate (50 mL) was added to the reaction mixture, and the reaction was quenched with aqueous sodium sulfite (30 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with 2 N KOH (20 mL) and brine (30 mL), and dried over anhydrous sodium sulfate. After removal of the solvent in vacuo, flash chromatography on silica gel afforded diol **20a** as a white solid (4.0 g, 82%): mp 53–55 °C; R_f 0.11 (hexane/EtOAc, 3:2), $[\alpha]_D$ 73.7° (*c* 1.3, EtOH), ^1H NMR ($CDCl_3$, 500 MHz) δ 7.23 (dd, *J*=15, 11 Hz, 1H), 6.41 (dd, *J*=15, 11 Hz, 1H), 6.06 (dd, *J*=15, 6 Hz, 1H), 5.86 (d, *J*=15.5, 1H), 3.93 (dd, *J*=6.5, 6.5 Hz, 1H), 3.71 (s, 3H), 3.62 (dq, *J*=6.5, 6.5 Hz, 1H), 3.33 (br, 2H), 1.14 (d, *J*=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5, 143.9, 141.3, 129.5, 121.4, 76.5, 70.6, 51.7, 19.0.

2.1.40. *t*-Butyl (6*R*,7*R*)-6,7-dihydroxy-octa-2,4-dienoate (20c). To a solution of **19c** (4.15 g, 21.4 mmol) in *t*-BuOH (20 mL) and water (10 mL) was added $K_3Fe(CN)_6$ (21.1 g, 64.1 mmol), K_2CO_3 (8.9 g, 64.1 mmol), $NaHCO_3$ (5.4 g, 64 mmol), $(DHQD)_2PHAL$ (332.6 mg, 2 mmol%), and $CH_3SO_2NH_2$ (2.03 g, 21.4 mmol). This mixture was cooled to 0 °C, OsO_4 (54.3 mg, 1 mmol%) was then added, and the solution was stirred at 0 °C for 24 h. The reaction was quenched with aqueous sodium sulfite (30 mL), and ethyl acetate (50 mL) was added to the reaction mixture. After the layers were separated, the aqueous layer was further extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with 2 N KOH (20 mL) and brine (30 mL), and dried over anhydrous sodium sulfate. After removal of the solvent in vacuo, flash chromatography on silica gel (20:1–5:1−2:1–1:2 (v/v) hexane/EtOAc) afforded **20c** as a light yellow liquid (3.82 g, 78.5% yield): R_f 0.16 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D$ 22.9° (*c* 0.85, $CHCl_3$); IR (neat) 3384, 2975, 2933, 1887, 1699, 1644, 1615, 1478, 1455, 1392, 1367, 1307, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.17 (dd, *J*=15.5, 11 Hz, 1H), 6.44 (dd, *J*=16, 12 Hz, 1H), 6.06 (dd, *J*=15, 6 Hz, 1H), 5.84 (d, *J*=15.0 Hz, 1H), 3.98 (dd, *J*=6.5, 6.5 Hz, 1H), 3.68 (dq, *J*=6.5, 6.5 Hz, 1H), 1.49 (s, 9H), 1.20 (d, *J*=6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 142.5, 140.3, 129.8, 124.0, 80.6, 76.7, 70.7, 28.1, 19.0; HRMS (CI) Calcd for $[C_{12}H_{20}O_4+NH_4]^+$: 246.1705 Found: 246.1721.

2.1.41. (6*S*,7*S*)-6,7-Dihydroxy-octa-2,4-dienoic acid *tert*-butyl ester (*ent*)-20c. To 2.2 g (11.3 mmol) of triene **19** in 30 mL of *t*-BuOH and 30 mL water was added $K_3Fe(CN)_6$ (11.15 g, 33.9 mmol), K_2CO_3 (4.68 g, 33.9 mmol), $(DHQ)_2$-PHAL (176 mg, 0.23 mmol), and $CH_3SO_2NH_2$ (1.07 g, 11.3 mmol). This mixture was cooled to 0 °C, OsO_4 (29 mg, 0.113 mmol) was then added, and the solution was stirred overnight. Ethyl acetate (30 mL) was added to the reaction mixture, and the reaction was quenched with aqueous sodium sulfite (30 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with 2 N KOH (20 mL) and brine (30 mL), and dried over anhydrous sodium sulfate. After removal of the solvent in vacuo, flash chromatography on silica gel afforded diol (*ent*)-**20c** (2.01 g, 78%): $[\alpha]_D$ −23° (*c* 1.0, $CHCl_3$); IR (neat) 3384, 2975, 2933, 1887, 1699, 1644, 1615, 1478, 1455, 1392, 1367, 1307, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.17 (dd, *J*=15.5, 11 Hz, 1H), 6.44 (dd, *J*=16, 12 Hz, 1H), 6.06 (dd, *J*=15, 6 Hz, 1H), 5.84 (d, *J*=15.0 Hz, 1H), 3.98 (dd, *J*=6.5, 6.5 Hz, 1H), 3.68 (dq, *J*=6.5, 6.5 Hz, 1H), 1.49 (s, 9H), 1.20 (d, *J*=6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 142.5, 140.3, 129.8, 124.0, 80.6, 76.7, 70.7, 28.1, 19.0; HRMS (CI) Calcd for $[C_{12}H_{20}O_4+NH_4]^+$: 246.1705 Found: 246.1721.

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References and notes

1. For the review of Sharpless AD reaction, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. (b) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1994**, *59*, 949. (c) Johnson, R. A.; Sharpless, K. B. In *Catalytic asymmetric dihydroxylation in catalytic asymmetric synthesis*; Ojima, I., Ed.; VCH: New York, 1994; pp 227–272.
2. (a) Harris, J. M.; O'Doherty, G. A. *Tetrahedron* **2001**, *57*, 5161–5171. (b) Harris, J. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2002**, *43*, 8195–8199. (c) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771–1774. (d) Harris, J. M.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 2983–2986. (e) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033–4036. (f) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863–866.
3. (a) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959–1962. (b) Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682–2685. (c) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777–2780. (d) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005–1009. (e) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 6407–6411.
4. Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447–4450.
5. Berker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345.
6. (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570–7571. (b) Xu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495–2498. (c) Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485–6488. (d) Vidari, G.; Giori, A.; Dapiaggi, A.; Lanfranchi, G. *Tetrahedron Lett.* **1993**, *34*, 6925–6928.
7. Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049–1052.
8. Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 844–849.
9. Mosher esters, see: Sullivan, G. R.; Dale, J.A; Mosher, H.S *J. Org. Chem.* **1973**, *38*, 2143–2147.

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Tunable phosphinite, phosphite and phosphoramidite ligands for the asymmetric hydrovinylation reactions

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Abstract—Only a limited number of ligands have been successfully employed for the Ni-catalyzed asymmetric hydrovinylation reaction. Diarylphosphinites, carrying β-acylamino groups prepared from readily available carbohydrates, in conjunction with highly dissociated counteranions $\{[(3,5\text{-}(CF_3)_2C_6H_3]_4B^-$ or $SbF_6^-\}$, effect the hydrovinylation of vinylarenes under ambient pressure of ethylene with high enantioselectivity. Nitrogen substituents such as $-COCF_3$ and COPh groups lead to isomerization of the primary products (3-arylbutenes) to *Z*- and *E*-2-aryl-2-butenes. In a prototypical synthesis of a 2-arylproionic acid, (*S*)-3-(4-bromophenyl)-1-butene (89% ee) has be transformed into (*R*)-ibuprofen by Ni-catalyzed cross-coupling with *i*-BuMgBr, followed by oxidation of the double bond with $NaIO_4$ and $KMnO_4$. Asymmetric codimerization of norbonene and ethylene using binaphthol-derived phosphoramidites as ligands gives 1:1, 2:1 or polymeric adducts depending on the relative configurations and nature of the BINAP and amine moieties. With one of the phosphoramidite–Ni complexes, counteranions BAr_4^- [Ar = 3,5-$(CF_3)_2C_6H_3$] and SbF_6^-, which had been used interchangeably in other reactions, give either a 1:1 adduct or a 2:1 adduct, respectively.

1. Introduction

Development of new asymmetric catalytic processes depends on the availability of enantiomerically pure ligand precursors that are amenable to fine-tuning for optimum performance.[1] Once the essential features of the ligand system are identified, substantial modifications in the scaffolding and in the steric and electronic environments around the chelating atoms are often necessary to achieve acceptable levels of catalytic efficiency and enantioselectivity. Nowhere is such a strategy more important than in the discovery of new catalytic processes that involve the use of relatively stable carbon feedstocks such as HCN, CO or olefins for selective C–C bond-forming reactions. At the appropriate stages in the catalytic cycle, the ligand should promote activation of the substrate(s) and induce high *selectivity* in the bond-forming process. Following the pioneering works of Cullen[2] and Selke,[3] we have invested considerable effort in the design and use of readily available carbohydrates as precursors[4] for variety diarylphosphinite and phospholane[5] ligands. Thus electronically tuned glucose- and fructose-derived phosphinites (e.g., Fig. 1) were found to be excellent ligands for Ni(0)-catalyzed asymmetric hydrocyanation of vinylarenes[6] and Rh(I)-catalyzed hydrogenation of dehydroamino acids.[7] These studies also provided some of the first demonstrable examples[8] of electronic tuning of asymmetric catalysts for not only hydrocyanation and hydrogenation but also hydroformylation[9] and Pd-catalyzed asymmetric allylation reactions.[10]

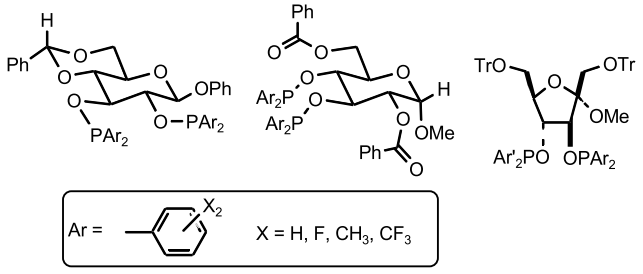
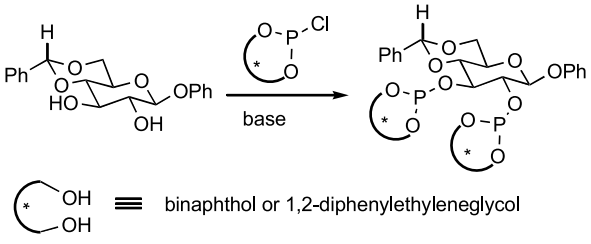


Figure 1. Diarylphosphinite ligands for hydrogenation and hydrocyanation reactions.



(1)

As early as 1991, during the initial studies of asymmetric hydrocyanation we also recognized that the hydroxyl groups

Keywords: Asymmetric catalysis; Hydrovinylation; Phosphinite; Phosphite; Phosphoramidite ligands; Salt effects; Ibuprofen.
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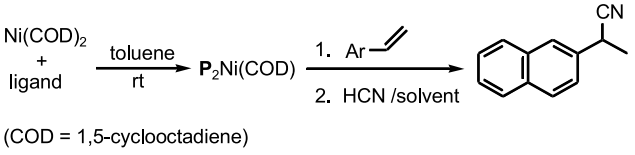
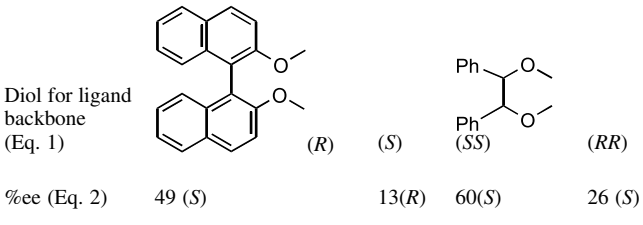
on carbohydrates can be readily converted into phosphite esters (Eq. 1), and depending on the source of the (RO)P(OR′)-Cl,[11] additional elements of chirality can be introduced into the ligand.[12] As can be expected from such modular ligands, which combine two chiral fragments, the sense and extent of asymmetric induction will depend on whether the two elements are matching or mismatching (Eq. 2).[13] Mono- and bis-phosphites of this structural type have since been found to have wide applications in enantioselective Rh-catalyzed hydrogenation reactions.[14]



(2)



In related developments, Feringa et al. have reported the synthesis and applications of highly versatile phosphoramidite ligands derived from binaphthol and various chiral amines.[15] Mono- and bi-dentate analogs of Feringa's ligands have been used in a number of reactions including hydrogenations,[16] conjugate addition reactions,[17] and Ir-catalyzed allylation reactions.[18]

In a study that is especially relevant to this report, Leitner et al. found that the Feringa's phosphoramidites are excellent ligands for the asymmetric hydrovinylation of vinylarenes.[19] Ni-catalyzed asymmetric hydrovinylation is a very demanding reaction with only a limited number of ligands giving acceptable selectivity for the desired 3-arylbutenes.[20] In this paper, we disclose the full details of our own studies on the application of carbohydrate-derived phosphinite and phosphite ligands for the asymmetric hydrovinylation reaction.[21] Phosphoramidite ligands are suitable also for hydrovinylation of norbornene.[21b] In this instance, dramatic changes on the course of the reaction with minor changes in the structure of the ligand and nature of the counteranion were noticed. The details of this study are also reported here.[22]

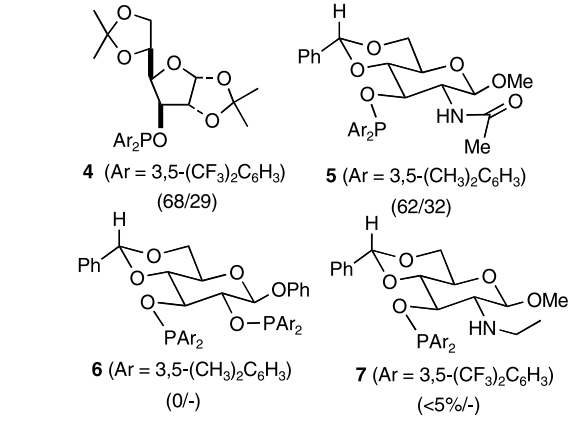
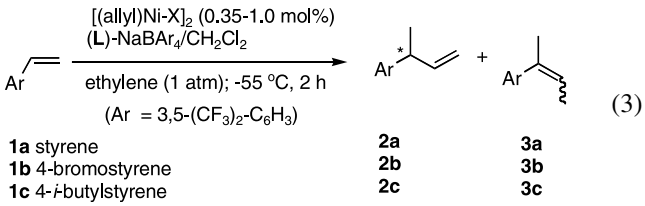


Figure 2. Diarylphosphinite ligands for hydrovinylation (yield of product/ee for hydrovinylation of styrene (Eq. 3) are shown in brackets).



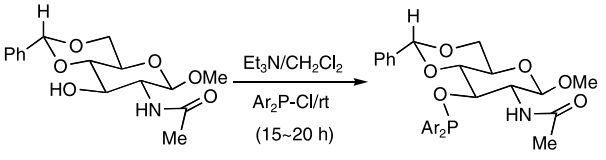
(3)

2. Results

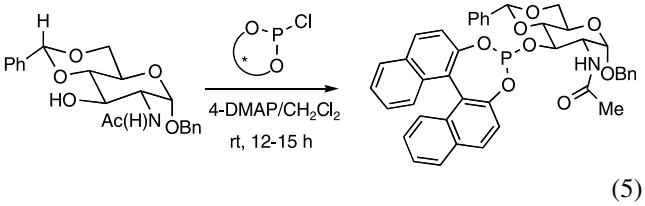
2.1. Hydrovinylation of vinylarenes

2.1.1. Ligands from monosaccharides. In our initial survey of ligands prepared from several monosaccharide derivatives it became apparent that simple monodentate diarylphosphinites like **4** and **5** (Fig. 2) were viable ligands for the hydrovinylation of styrene under our standard conditions (Eq. 3), where as bidentate bisphosphinites[23] like **6**, or β-amino-phosphinites like **7** were not.[24]

Among the various ligands we examined, the β-acetamido-diarylphosphinites (e.g., **5**) showed the most promise, and thus were chosen for further development. The syntheses of this type of ligands were carried out as follows: inside a drybox, to a solution of 1 equiv each of the alcohol and triethylamine in CH_2Cl_2 is added 1 equiv of the chlorodiarylphosphine[6a] in CH_2Cl_2 (Eq. 4). The resulting mixture is stirred overnight at rt and is subsequently concentrated in vacuo. The residue is then dissolved in a small amount of toluene, filtered through a pad of celite to remove the amine hydrochloride. Further concentration and recrystallization from cyclohexane or hexane gives the pure ligand.



(4)



(5)

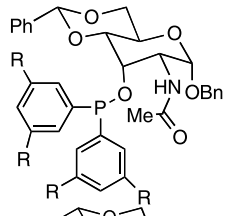
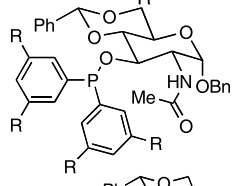
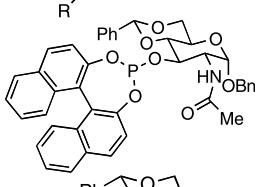
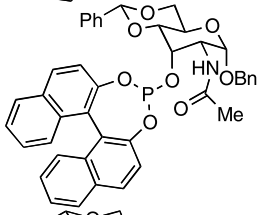
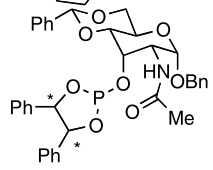
Syntheses of the phosphite ligands were accomplished by adding a solution of the chlorodioxophospholane[11a] (from (*R*/*S*) binaphthol or (*RR*/*SS*)-hydrobenzoin) in CH_2Cl_2 to an equimolar mixture of the sugar and 4-dimethylaminopyridine (Eq. 5). The mixture is stirred overnight and subsequently worked up as described before. The pure

phosphite ligands were obtained by column chromatography inside the drybox.

Typically, the catalyst precursor is prepared by mixing stoichiometric amounts of allyl nickel bromide dimer and the ligand (1:1 Ni/**L**) in CH_2Cl_2, followed by exchanging the bromide ion by addition of Na^+ Ar_4B^- (Ar=3,5-$(CF_3)_2$-C_6H_3) or another appropriate Ag salt (Eq. 3). The precipitated salts are removed by filtration through celite. Oxygen-free ethylene is then introduced into the flask after cooling the Ni-complex to the appropriate temperature (−70 to −55 °C), followed by the substrate dissolved in CH_2Cl_2. After ~2 h, the reaction is quenched with ammonium chloride, the product is isolated by evaporation of the solvent. Selectivity factors are determined by NMR spectroscopy, GC and HPLC.

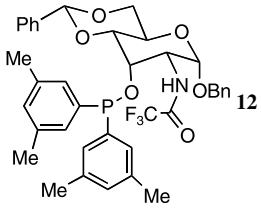
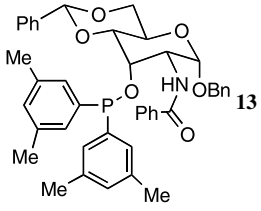
2.1.2. Asymmetric hydrovinylation of prototypical vinylarenes. Table 1 shows the yields and ee's obtained when various β-acetamidophosphinites are used as ligands for the Ni(II)-catalyzed asymmetric hydrovinylation of various vinylarenes (Eq. 3). In this study, two series of sugars were examined, the *allo*-series (entries 1, 4 and 5) and *gluco*-series (entries 2 and 3). In general, outstanding selectivity for the primary product, 3-aryl-1-butene (**2**) is observed with the diarylphosphinite ligands as long as the *N*-substituent is an acetyl group (vide infra for other acyl groups). In overall yield and selectivity, in the phosphinite series, the *allo*-derivatives (entry 1) are better than the *gluco*-derivatives (entry 2). Whether a 3,5-bis-CH_3-C_6H_3-substituent or a 3,5-bis-CF_3-C_6H_3-substituent on phosphorus is better depends on the configuration of the carbon to which is attached the diarylphosphinite moiety. In the *gluco*-series (entry 2), for both styrene and 4-bromostyrene, the CF_3-aromatic substituent is better, whereas in the *allo*-series (entry 1) the CH_3-aromatic substituent is clearly superior. In the hybrid ligands carrying the sugar and the BINAPO moieties, the combination of the (*R*)-BINAP and D-gluco appear to give the best yield and selectivity for styrene hydrovinylation (entries 3 and 4). The hydrobenzoin-derived phosphite generally gave poor selectivity, the best result coming from a combination of (*SS*)-hydrobenzoin and the D-allopyranoside (entry 5, ligand **11D**).

Table 1. Asymmetric hydrovinylation of vinylarenes using phosphinite and phosphite ligands[a]

Entry	Ligand		Styrene		4-Br-styrene		4-*i*-Bu-styrene	
			Yield[b]	%ee	Yield	%ee	Yield	%ee
1.		**8A** R=CH_3 **8B** R=CF_3	89[c] 95	81 (*S*) 62 (*S*)	94 19	89 (*S*) 43 (*S*)	99 99	74(*S*) 59 (*S*)
2.		**9A** R=CH_3 **9B** R=CF_3	93 93	9 (*S*) 45(*S*)	88	13 (*S*) 47(*S*)	— 36	— 61(*S*)
3.		**10A** =(*R*)-$BINAPO_2$ **10B** =(*S*)-$BINAPO_2$	95 26	62(*S*) 2 (*R*)	— —	— —	— —	— —
4.		**11A** =(*R*)-$BINAPO_2$ **11B** =(*S*)-$BINAPO_2$	84 83[d]	44 (*S*) 19 (*S*)	— —	— —	99 —	38 (*S*) —
5.		**11C**=(*RR*) **11D**=(*SS*)	53 83	5 (*R*) 30 (*S*)	— —	— —	— —	— —

[a] For typical reaction conditions see Eq. 3. Yield of 3-arylbutene (**2**). Selectivity for **2** >99% unless otherwise mentioned.
[b] Some of the variable yields of 3-phenylbutene reflect the volatility of the product.
[c] Selectivity 89%; rest **3a**.
[d] Selectivity 83%; rest **3a**.

Table 2. Asymmetric hydrovinylation of vinylarenes. Effect of *N*-substituent

Entry	Ligand, **L**	Conver. (%)	Selectivity		
			% **2a**	% c/t-**3a**	% ee (**2a**)
1.	 **12**	>99[a]	~40	~60	87 (*S*)
2.	 **13**	>99[b] >99[c]	~66 ~23	34 77	80 (*S*) 82 (*S*)

[a] Conditions: see Eq. 3. 2 mol% [(η^3-allyl)Ni**L**]BARF/2 h.
[b] 3 mol% [(η^3-allyl)Ni**L**/BARF]/0.5 h.
[c] 3 mol% [(η^3-allyl)Ni**L**/BARF]/2.0 h.

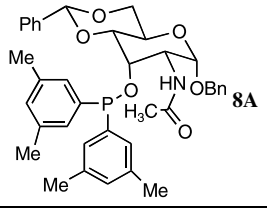
2.1.3. Effect of *N*-acyl substituent: isomerization of the primary product. Having identified **8A** (entry1, Table 2) as the best ligand for hydrovinylation of styrene, 4-bromostyrene and 4-isobutylstyrene, we decided to examine the effect of nitrogen substituents on the course of the reaction. We find that a seemingly minor change in the *N*-substituent has a profound effect on the overall utility of the reaction. The results obtained upon substituting the $-COCH_3$ group with $-COCF_3$ and –COPh groups are shown in Table 2. Even though the *N*-C(O)CF_3 ligand **12** gave 3-phenyl-1-butene (**2a**) with one of the highest enantioselectivities we have observed (87%, entry 1), isomerization of this product to 2-phenyl-2-butene (**3a**) significantly erodes the overall selectivity for the reaction. Ligand **13** with an *N*-C(O)Ph group also behaves in a similar fashion. Quenching the reaction at various times (30 or 120 min) seems to indicate that both enantiomers of 3-phenylbutenes undergo the isomerization with nearly equal facility (entry 2).

2.1.4. Effect of counteranion. We have previously shown that counteranions play a very significant role in the efficiency and selectivity of the hydrovinylation reaction and there is a synergistic relation between the nature of the ligand and the counteranion.[23,24] The effect of the counteranion was examined in the context of hydrovinylation of 4-bromostyrene using the best ligand, **8A**.

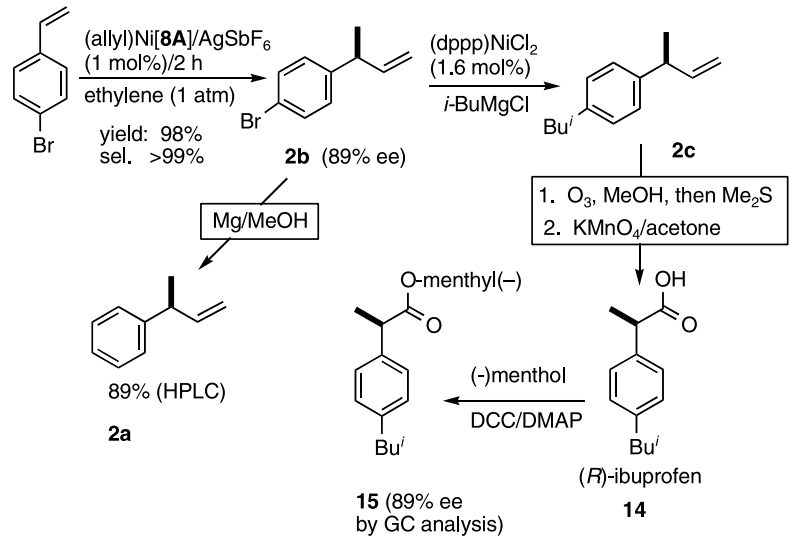
The results are shown in Table 3. These results confirm the marginally superior effect of SbF_6 as a counteranion in the hydrovinylation of 4-bromostyrene. Thus the use of Ar_4B resulted in up to 6% formation of the isomerized product **3b**, while SbF_6 gave an exquisite reaction with >99% selectivity for the desired 3-(4-bromophenyl)butene in 89% ee (entry 2). Both BF_4 and OTf gave lower conversions and selectivities under identical conditions (entries 3 and 4).

2.1.5. Asymmetric hydrovinylation of 4-bromostyrene and identification of the major product. The enantiomeric excess of 3-(4-bromophenyl)-but-1-ene (**2b**), a key compound {($[\alpha]_D^{25}$ +9.9±1 (*c* 7.02, $CHCl_3$)}, from which several 2-arylpropionic acids could be prepared by cross-coupling chemistry (vide infra), was determined by three independent methods, all agreeing within experimental error. The ee's for compound **2b** and the corresponding debrominated derivative, 3-phenyl-1-butene (**2a** prepared by treatment of **2b** with Mg in MeOH, >99% yield) were determined by HPLC on chiralcel OJ column. Kumada coupling of **2b** and *i*-BuMgBr in the presence of 1.6 mol% of (dppe)$NiCl_2$ gave **2c**[25] (89%ee, HPLC). Subsequent ozonolysis and oxidation of the resulting aldehyde[26] gave ibuprofen (Scheme 1), whose configuration and enantiomeric excess were established by conversion to the known (−)-menthyl esters.[27] Gas chromatographic analysis of

Table 3. Asymmetric hydrovinylation of vinylarenes. Effect of counteranions[a]

Entry	Ligand	Counteranion X	4-Bromostyrene		
			Conversion (%)	Selectivity (% **3a**)	% ee
1	 **8A**	BARF	>99	94	89 (*S*)
2		SbF_6	98	>99	89 (*S*)
3		BF_4	24	>99	86 (*S*)
4		OTf	70	>99	74 (*S*)

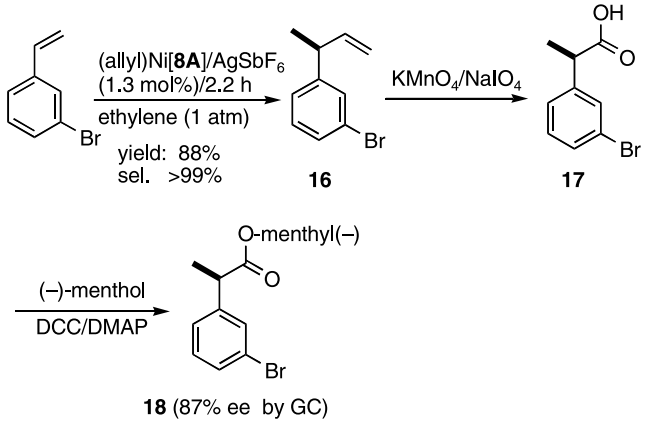
[a] Conditions: see Scheme 1, step 1. 1 mol% [(η^3-allyl)Ni**L**X]$_2$/CH_2Cl_2, −55 °C/2 h.



Scheme 1. Asymmetric hydrovinylation of 4-bromostyrene.

(−)-menthyl esters of ibuprofen using chiralsil-*L*-val column revealed baseline separation, with a diastereomeric excess of 89% for the (*R*)-ibuprofen ester. This confirms the overall selectivity and the absolute configuration of the primary product of hydrovinylation.

Hydrovinylation of 3-bromostyrene under these conditions gave 88% yield of 3-(3-bromophenyl)-but-1-ene (**16**) with >99% selectivity for the 3-arylbut-1-ene. The enantioselectivity of the product (87% ee, *S*) was ascertained by first converting this into (−)-menthyl esters of the 2-(3-bromophenyl)-propionic acid. The diastereomeric (−)-menthyl esters were analyzed by gas chromatography (Scheme 2).[28] For comparison, authentic samples of racemic **17** and the corresponding (−)-methyl esters were prepared from racemic **16**.

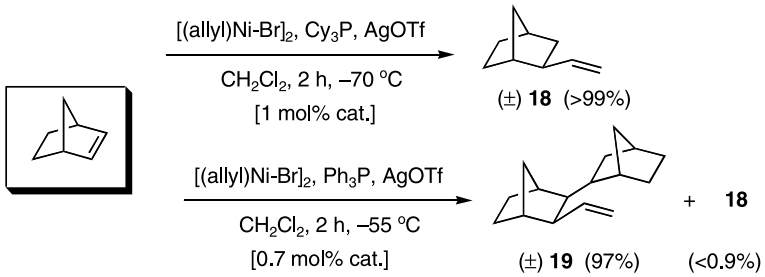


Scheme 2. Asymmetric hydrovinylation of 3-bromostyrene.

2.1.6. Hydrovinylation of norbornene. In 2003 we reported that hydrovinylation of norborne is an excellent reaction giving either a 1:1 (norbornene/ethylene) adduct or a 2:1 adduct depending on the size of the phosphine that is employed (Scheme 3).[22,29,30] As shown in Scheme 3, a bulky phosphine, Cy_3P (cone angle 180°), gives a 1:1 adduct whereas a smaller phosphine, Ph_3P (cone angle 145°), gave 2:1 adduct. We also reported that 2-benzyloxy-2′-diphenylphosphino-1,1′-binaphthyl gave ∼50% ee for the hydrovinylation product (−)**18**[31,32](Table 4, entry 1).

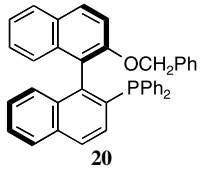
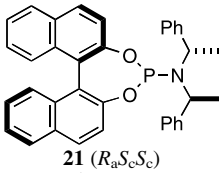
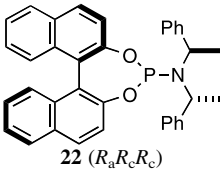
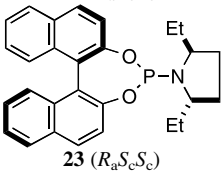
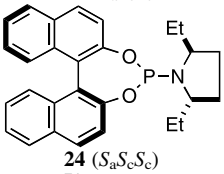
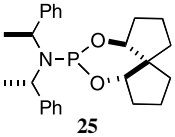
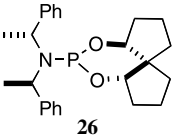
In view of the excellent results obtained by Leitner[19] on the use of binaphthol-derived phosphoramidites for the asymmetric hydrovinylation of styrene derivatives, we decided to examine these and related ligands for the hydrovinylation of norbornene under our reaction conditions (Scheme 4). The results are shown in Table 4.

The selectivities of these reactions under catalysis by phosphoramidite–Ni complexes (entries 2–7, Table 4) show remarkable dependence on the counteranion and the nature of the P–N appendages. Whereas the phosphoramidite **21**

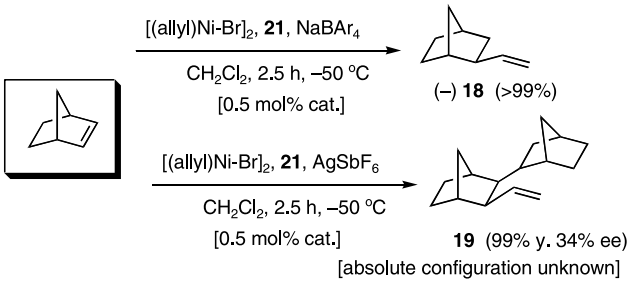


Scheme 3. Ligand dependence of hydrovinylation of norbornene.

Table 4. Asymmetric hydrovinylation of norbornene[a]

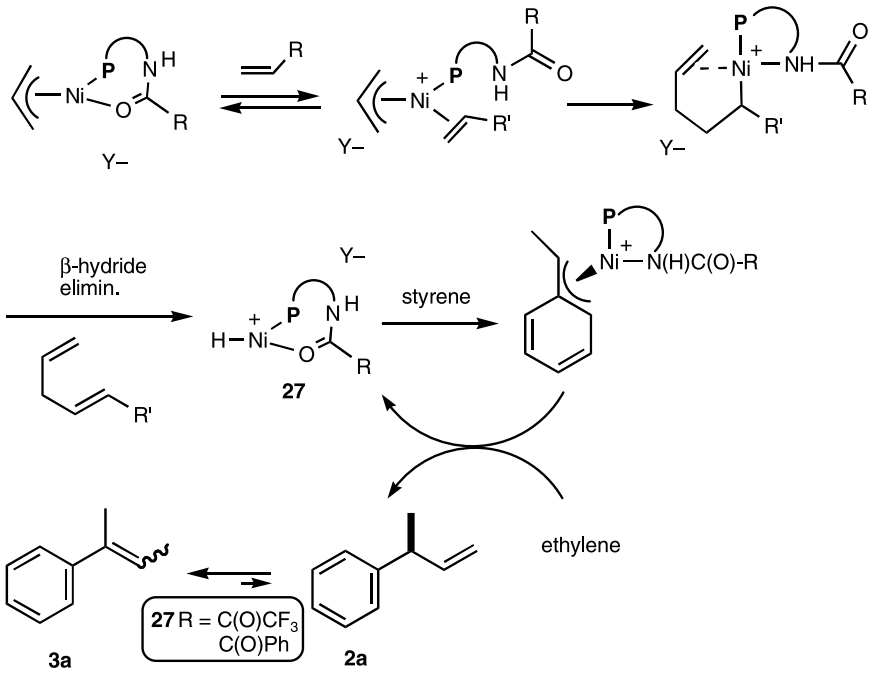
Entry	Ligand, **L**	Additive	*T* °C/t (h)	**18** (%)[b]	**19** (%)[b]	% ee[c]	Comments
1(a)	 **20**	NaBARF	−50/2.5	69[d]	0	44	
1(b)		$AgSbF_6$	−50/2.0	>99	0	50	Ref. 22
1(c)		$AgNTf_2$	−50/2.0	>99	0	50	
2(a)	 **21** ($R_aS_cS_c$)	NaBARF	−50/2.5	>99	0	80	—
2(b)		AgOTf	−50/2.5	20[d]	0	—	—
2(c)		$AgSbF_6$	−50/2.5	0	>99	34	—
3.	 **22** ($R_aR_cR_c$)	NaBARF	−50/2.5	<2%	0	—	—
4(a)	 **23** ($R_aS_cS_c$)	$AgSbF_6$ or	−50/3	0	0	—	Polymer (100%)
4(b)		NaBARF	−50/3	0	0	—	Polymer (100%)
5	 **24** ($S_aS_cS_c$)	$AgSbF_6$	−50/3	0	0	—	Polymer (100%)
6(a)	 **25**	$AgSbF_6$ or	−50/2.5	30	35	—	
6(b)		NaBARF	−50/2.5	1	—	—	—
7(a)	 **26**	$AgSbF_6$ or	−50/2.5	3	28	—	—
7(b)		NaBARF	−50/2.5	2	—	—	

[a] See Scheme 4 for typical procedure. Results of at least two experiments in each case.
[b] GC and NMR, isolated yield vary because of volatility of **18**.
[c] By NMR (see text).
[d] Rest starting material.



Scheme 4. Counteranion dependence of hydrovinylation of norbornene.

($R_aS_cS_c$) is a good ligand (entry 2a and 2c), the corresponding ($R_aR_cR_c$)-diastereomer **22** gives less than 2% of the product (entry 3). For the ligand **21**, the counteranion determines whether 1:1 or 1:2 adduct is produced (Scheme 3). With NaBARF as the additive, only 1:1 adduct **18** is produced (entry 2a), whereas with $AgSbF_6$, which we have successfully used in place of NaBARF in some of the early hydrovinylation experiments (Table 3, entries 1 and 2), the only product is the 2:1 adduct **19**, formed in nearly quantitative yield (entry 2c). Perhaps the most striking result is the effect of the amine component of the phosphoramidites (entries 4 and 5). Thus phosphoramidites derived from (2*S*,4*S*)-diethylpyrrolidine and either (*R*)-binaphthol or (*S*)-binaphthol (**23** and **24**) give none of the simple adducts **18** or **19**. Nearly quantitative yield of polymeric



Scheme 5. Abbreviated mechanism of asymmetric hydrovinylation and olefin isomerization.

materials were formed under the standard conditions (entries 6 and 7).[33]

Phosphoramidites **25** and **26** are poor ligands and showed no selectivity in the formation of either the 1:1 or the 2:1 adduct (entry 4). Clearly, $AgSbF_6$ appears to give better yields.

3. Discussion

While it is premature to propose models[23,34] for the asymmetric induction in any of the studies reported in this paper, some observations are worthy of note. The diarylphosphinite ligands derived from β-acylaminoalcohols are useful ligands for hydrovinylation of vinylarenes. The two asymmetric centers in the backbone, likely variations of the acyl group and the *P*-aryl-substituents provide myriad possibilities for further tuning of these ligands. We have not conclusively shown that the *N*-acyl group is the hemilabile group involved in the reaction. Yet, the complete lack of reactivity of a ligand with a β-amino group vis-à-vis a β-amido (e.g., **7** vs **5**, Fig. 2) group and the effect of the *N*-acyl groups (Table 2) are highly suggestive of a crucial role for this functionality.[35] It is conceivable that the $[\mathbf{L}Ni–H]^+$ species, **27** (Scheme 4), which is the presumed catalyst is more reactive with olefins when an *N*-C(O)CF_3 or *N*-C(O)Ph group is present at the β-position of the ligand, leading to indiscriminate addition–elimination reactions which results in isomerization of the primary product **2a** (Scheme 5).

Another notable observation is the counteranion effect seen in the hydrovinylation of norbornene using ligand **21** (Table 4, entry 2). At present we have no explanation for the fact that BARF anion gives a 1:1 adduct, **18**, and SbF_6 a 2:1 adduct, **19** (Scheme 3). However, one can speculate that the synergistic relationship between a possible hemilabile coordination of one of the Ph groups to Ni and each of the anions could be quite different. In the absence of such a phenyl group (for example, in ligands, **23** and **24**) a more active catalyst, not unlike the naked nickel catalyst popularized by Goodall et al. for polymerization of norbornene, is generated, and polymerization ensues (Table 4, entries 4, 5).[33b] Traditionally, these cationic Ni-complexes have only olefinic ligands and/or Ni–C σ-bonds, and the reaction is done in the presence of highly dissociated counter anions. Cationic Ni-complexes containing bulky phosphine ligands have recently been reported to be effective for non-living polymerization of styrene.[36] Without additional work, including a full characterization of the phosphoramide-derived catalyst precursor(s) and the norbornene polymers they produce, a discussion of the unusual ligand-dependent selectivity of the Ni(II)-complexes will be highly speculative. Further studies along these lines will be forthcoming.

4. Conclusions

Diarylphosphinites, carrying a β-acylamino groups prepared from readily available carbohydrates, in conjunction with highly dissociated counterions $\{[(3,5\text{-}(CF_3)_2C_6H_3]_4B^-$ or $SbF_6^-\}$, effect the hydrovinylation of vinylarenes under ambient pressure of ethylene with the high enantioselectivity. Nitrogen substituents such as $–COCF_3$ and COPh groups lead to isomerization of the primary products (3-arylbutenes) to *Z*- and *E*-2-aryl-2-butenes. The intermediate 3-arylbutenes are useful for the synthesis of anti-inflammatory 2-arylpropionic acids. Asymmetric codimerization of norbonene and ethylene using binaphthol-derived phosphoramidites as ligands gives 1:1, 2:1 or polymeric adducts depending on the relative configurations and nature of the BINAP and amine moieties. With one of

the phosphoramidite–Ni complexes, counteranions BAr_4^- [Ar=3,5-$(CF_3)_2C_6H_3$] and SbF_6^-, which had been used interchangeably in other reactions, give either a 1:1 adduct or a 2:1 adduct, respectively.

5. Experimental

5.1. General procedures

Reactions requiring air-sensitive manipulations were conducted under an inert atmosphere of nitrogen in a Vacuum Atmospheres drybox or by using Schlenk techniques. Methylene chloride and toluene were distilled from calcium hydride under nitrogen and stored over molecular sieves. Tetrahydrofuran, diethyl ether, and hexane were distilled under nitrogen from sodium/benzophenone ketyl. Ethylene (99.5%) was purchased from Matheson Inc., and passed through Drierite before use. Styrene was purchased from Aldrich, vacuum-transferred, and stored at −30 °C. For ozonolysis, ozone gas was delivered using a Welsbach ozone generator. Analytical TLC was performed on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. Flash column chromatography was carried out on silica gel 40 (Scientific Adsorbents Incorporated, Microns Flash). Gas chromatographic analyses were performed on a Hewlett-Packard 5890 equipped with an HP-ultra-1 crosslinked methyl silicone capillary column (25 m length×0.2 mm i.d.) and a FID detector connected to a HP 3396 integrator. Helium was used as the carrier gas. Chiral gas chromatographic separations of the (−)-menthol esters 2-arylpropionic acids were accomplished using Chirasil-L-Val on WCOT fused silica (25 m×0.25 mm, 0.12 μm film thickness) capillary GC column purchased from Chrompack (1130 Route 202 South Raritan, New Jersey 08869). The absolute configuration of 3-phenyl-1-butene was determined by GC analysis using a 50 m Lipodex C capillary column (conditions: 1.5 mL helium/min, 35 °C (50 min), 0.1 °C/min (60 min), 41 °C (30 min); retention times: *R*-isomer 95.8 min, *S*-isomer 97.2 min). Determination of the configuration of other compounds is described under the appropriate experiments. Enantiomeric excesses of 3-aryl-1-butenes were determined by HPLC using a Daicel Chiralcel OJ column using hexane as the solvent where base-line separation was obtained. Optical rotations were recorded on a Perkin–Elmer Model 241 polarimeter at the sodium D line in chloroform treated with 4 Å molecular sieves. Compounds for which an exact mass is reported exhibited no significant peaks at *m/z* greater than that of the parent. Elemental analyses were done by Atlantic Microlab, Inc., Norcross, GA.

Starting materials diphenylchlorophosphine, 2-acetamido-2-deoxy-α-D-glucopyranose, 1,2:5,6-*O*-diisopropylidene-D-glucofuranose, (*S*,*S*)-(−)-hydrobenzoin and (*R*,*R*)-(+)-hydrobenzoin, 4-bromostyrene, 3-bromostyrene, 2-vinylnaphthalene, norbornene and (−)-menthol and various silver salts were purchased from commercial sources. The following compounds were prepared by the procedures from the references cited: chloro-bis-[3,5-*di*-(trifluoromethyl)-phenyl]phosphine,[4a] chloro-bis-(3,5-dimethylphenyl)phosphine,[4a] chloro-dioxophospholanes[11a] from binaphthol and hydroxybenzoin, (*R*)- and (*S*)-binaphthols,[37] sugar precursors benzyl 2-acetamido-2-deoxy-4,6-*O*-phenylmethyl-α-D-glucopyranoside,[38] 2-amino-2-deoxy-4,6-*O*-phenylmethyl-α-D-glucopyranoside,[38] benzyl 2-acetamido-2-deoxy-4,6-*O*-phenylmethyl-α-D-allopyranoside,[39] diarylphosphinite ligand **6**,[6a] phosphoramidites ligands[40] **21** and **22**, 4-*i*-butylstyrene,[41] $NaBAr_4$ (Ar=3,5-$(CF)_3$–C_6H_3).[42]

5.2. Synthesis of phosphinite and phosphite ligands

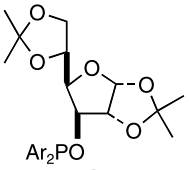
The preparations of all air-sensitive trivalent phosphorus compounds were carried out under an inert atmosphere of nitrogen in a Vacuum Atmospheres drybox. Since air-sensitive phosphorus compounds result in poor C, H-analysis, the purities of the ligands were confirmed by ^1H and ^{31}P NMR, and in most instances the ligands are >95% pure. The phosphinite ligands were synthesized according to one of the following procedures unless stated otherwise.[6a]

Procedure A. To a solution of 1.0 equiv of a chlorodiarylphosphine and 1.0 equiv of 4-dimethylaminopyridine (DMAP) in toluene (5 mL) was added dropwise 1.0 equiv of the alcohol in toluene (2 mL). The mixture was stirred for 6–10 h at rt and filtered through a short pad of Celite to remove the precipitated DMAP·HCl. The filtrate was concentrated to dryness in vacuo, and the crude product was recrystallized from cyclohexane and/or hexane inside the drybox to afford the corresponding phosphinite as a white crystalline solid.

Procedure B. To a solution of 1 equiv of an alcohol and 1 equiv of triethylamine (TEA) or DMAP in dichloromethane (5 mL) was added dropwise 1 equiv of a chlorodiarylphosphine in dichloromethane (2 mL). The resulting mixture was stirred overnight at rt and was concentrated in vacuo. The residue was suspended in a small amount of toluene, filtered through a short pad of Celite to remove TEA hydrochloride or DMAP hydrochloride, and then was concentrated to dryness in vacuo. The crude product was purified by recrystallization inside the drybox from cyclohexane and/or hexane to afford the corresponding phosphinite as a white crystalline solid.

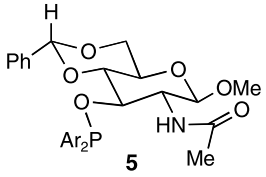
Procedure C. To a solution of 1 equiv of an alcohol and 1 equiv of DMAP in dichloromethane (5 mL) was added, dropwise, 1 equiv of chlorodiarylphosphonite in dichloromethane (2 mL). The resulting mixture was stirred overnight at rt and concentrated in vacuo. The residue was suspended in a small amount of toluene, filtered through a short pad of Celite to remove DMAP hydrochloride, and then concentrated to dryness in vacuo. The crude product was chromatographed (inside drybox) to afford the corresponding phosphite as a white crystalline solid.

5.2.1. 3-*O*-[bis-(α,α,α,α′,α′,α′-Hexafluoro-3,5-xylyl)phosphino]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose [4, Ar=3,5-$(CF_3)_2C_6H_3$)]. *Procedure B*. 73% Yield; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00–7.90 (m, 6H, aromatic), 5.92 (d, *J*=3.6 Hz, 1H), 4.63 (dd, *J*=3.6, 1.8 Hz, 1H), 4.54 (dd, *J*=9.1, 2.7 Hz, 1H), 4.25–4.20 (m, 1H), 4.14–4.02 (m, 3H), 1.51 (s, 3H, Me), 1.40 (s, 3H, Me), 1.30 (s, 3H, Me) 1.17 (s, 3H, Me); ^{31}P NMR (101 MHz, $CDCl_3$) δ 105.8 (s, 1P).



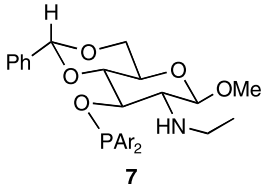
4

5.2.2. Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(di-3,5-xylylphosphino)-β-D-glucopyranoside [5, Ar = 3,5-$(CH_3)_2C_6H_3$)]. *Procedure B*. 92% Yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–6.82 (m, 11H, aromatic), 5.46 (s, 1H, benzylic), 5.24 (br d, J = 8.0 Hz, 1H, NH), 4.91 (d, J = 8.3 Hz, 1H, H-1), 4.66 (td, J = 9.4, 9.1 Hz, 1H, H-3), 4.36 (dd, J = 10.4, 4.9 Hz, 1H, H-6eq), 3.77 (t, J = 10.2 Hz, 1H, H-6ax), 3.75 (t, J = 9.2 Hz, 1H, H-4), 3.59–3.44 (m, 2H, H-2, H-5), 3.49 (s, 3H, OMe), 2.29 (s, 6H, 2Me), 2.06 (s, 6H, 2Me), 1.59 (s, 3H, CH_3CO); ^{31}P NMR (101 MHz, $CDCl_3$) δ 120.9 (s, 1P).



5

5.2.3. Methyl 4,6-*O*-benzylidene-3-*O*-[bis(α,α,α,α′,α′,α′-hexafluoro-3,5-xylyl)phosphino]-2-deoxy-2-(ethylamino)-β-D-glucopyranoside (7, Ar = 3,5-$(CF_3)_2C_6H_3$). *Procedure B*. 90% Yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.05 (m, 11H, aromatic), 5.30 (s, 1H, benzylic), 5.10 (d, 8 Hz), 4.38–4.31 (m, 2H), 4.13 (m, 1H), 3.81–3.71 (m, 2H), 3.56 (s, 3H, OMe), 3.43 (m, 1H), 2.87–2.78 (m, 2H), 2.45 (m, 1H), 0.82 (t, 3H, CH_3); ^{31}P NMR (101 MHz, $CDCl_3$) δ 106.2 (s, 1P).



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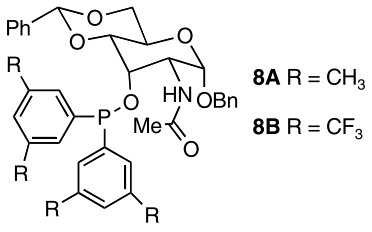
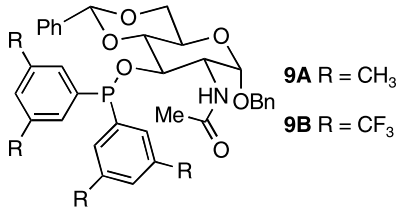
5.2.4. Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(di-3,5-xylylphosphino)-α-D-allopyranoside (8A). *Procedure B*. 90% Yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–6.97 (m, 16H, aromatic), 5.59 (d, J = 8.5 Hz, 1H, NH), 5.56 (s, 1H, benzylic), 4.85 and 4.53 (AB, J = 12.0 Hz, 2H, OCH_2Ph), 4.84 (d, J = 3.9 Hz, 1H, H-1), 4.60–4.42 (m, 2H, H-2, H-3), 4.39–4.23 (m, 2H, H-5, H-6eq), 3.77–3.69 (m, 2H, H-4, H-6ax), 2.18 (s, 6H, 2Me), 2.16 (s, 6H, 2Me), 1.34 (s, 3H, CH_3CO); ^{31}P NMR (101 MHz, $CDCl_3$) δ 123.6 (s, 1P).



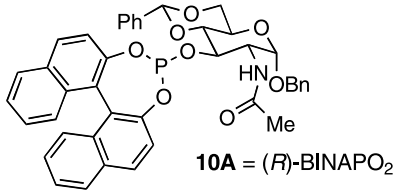
5.2.5. Benzyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-[bis(α,α,α,α′,α′,α′-hexafluoro-3,5-xylyl)phosphino]-2-deoxy-α-D-allopyranoside (8B). *Procedure B*. 75% Yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45–6.94 (m, 16H, aromatic), 5.62 (d, J = 8.5 Hz, 1H, NH), 5.46 (s, 1H, benzylic), 4.89 (d, J = 4.8 Hz, 1H, H-1), 4.88 and 4.70 (AB, J = 12.0 Hz, 2H, OCH_2Ph), 4.75 (m, 1H, H-3), 4.39–4.17 (m, 3H, H-2, H-5, H-6eq), 3.75 (dd, J = 9.5, 2.6 Hz, 1H, H-4), 3.67 (t, J = 10.2 Hz, 1H, H-6ax), 1.56 (s, 3H, CH_3CO); ^{31}P NMR (101 MHz, $CDCl_3$) δ 106.9 (s, 1P).

5.2.6. Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(di-3,5-xylylphosphino)-α-D-glucopyranoside (9A). *Procedure B*. 92% Yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–6.82 (m, 16H, aromatic), 5.53 (br d, J = 9.2 Hz, 1H, NH), 5.44 (s, 1H, benzylic), 4.95 (d, J = 3.6 Hz, 1H, H-1), 4.71 and 4.45 (AB, J = 11.8 Hz, 2H, OCH_2Ph), 4.48 (td, J = 10.1, 3.6 Hz, 1H, H-2), 4.35 (td, J = 9.5, 9.2 Hz, 1H, H-3), 4.23 (dd, J = 10.1, 4.6 Hz, 1H, H-6eq), 3.93 (td, J = 9.8, 4.6 Hz, 1H, H-5), 3.78 (t, J = 9.1 Hz, 1H, H-4), 3.76 (t, J = 10.1 Hz, 1H, H-6ax), 2.30 (s, 6H, 2Me), 2.07 (s, 6H, 2Me), 1.50 (s, 3H, CH_3CO); ^{31}P NMR (101 MHz, $CDCl_3$) δ 120.8 (s, 1P)



5.2.7. Benzyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-[bis(α,α,α,α′,α′,α′-hexafluoro-3,5-xylyl)phosphino)-2-deoxy-α-D-glucopyranoside (9B). *Procedure B*. 89% Yield; ^{1}H NMR (300 MHz, C_6D_6) δ 8.40–6.84 (m, 16H, aromatic), 5.10 (s, 1H, benzylic), 5.00 (br d, J = 10.0 Hz, 1H, NH), 4.71 (td, J = 10.2, 3.8 Hz, 1H, H-2), 4.61 (d, J = 3.8 Hz, 1H, H-1), 4.31 and 3.98 (AB, J = 11.6 Hz, 2H, OCH_2Ph), 4.26 (m, 1H, H-3), 4.00 (m, 1H, H-6eq), 3.86 (td, J = 9.8, 4.9 Hz, 1H, H-5), 3.40 (t, J = 10.2 Hz, 1H, H-4), 3.34 (t, J = 9.3 Hz, 1H, H-6ax), 1.13 (s, 3H, CH_3CO); ^{31}P NMR (101 MHz, C_6D_6) δ 105.8 (s, 1P).

5.2.8. Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyrano-side cyclic (*R*)-[1,1′-binaphthalene]-2,2′-diyl Phosphite (10A). *Procedure C*. 70% Yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.20 (m, 22H, aromatic), 5.80 (d, J = 9.4 Hz, 1H, NH), 5.56 (s, 1H, benzylic), 4.98 (d, J = 3.5 Hz, 1H, H-1), 4.72 and 4.48 (AB, J = 11.7 Hz, 2H, OCH_2Ph), 4.61–4.44 (m, 2H, H-2, H-3), 4.27 (dd, J = 10.1, 4.7 Hz, 1H, H-6eq), 3.91 (td, J = 9.9, 4.7 Hz, 1H, H-5), 3.74 (t, J = 10.2, 1H, H-6ax), 3.71 (t, J = 9.2 Hz, 1H, H-4), 2.09 (s, 3H, CH_3CO); ^{31}P NMR (101 MHz, $CDCl_3$) δ 148.2 (s, 1P).

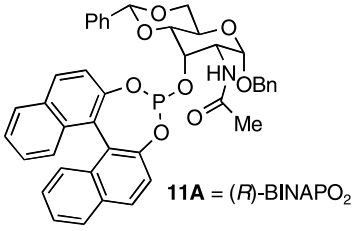


10A = (*R*)-BINAPO$_2$

10B = (*S*)-BINAPO$_2$

5.2.9. Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside cyclic (*S*)-[1,1′-binaphthalene]-2,2′-diyl phosphite (10B). *Procedure C*. Quantitative yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94–7.14 (m, 22H, aromatic), 5.67 (s, 1H, benzylic), 5.55 (d, J=9.1 Hz, 1H, NH), 4.97 (d, J=3.7 Hz, 1H, H-1), 4.73 and 4.48 (AB, J=11.7 Hz, 2H, OCH_2Ph), 4.52 (q, J=9.7 Hz, 1H, H-3), 4.38–4.25 (m, 2H, H-2, H-6eq), 3.99 (td, J=9.9, 4.7 Hz, 1H, H-5), 3.85 (t, J=10.2 Hz, 1H, H-6ax), 3.77 (t, J=9.3 Hz, 1H, H-4), 1.78 (s, 3H, CH_3CO); ^{31}P NMR (101 MHz, $CDCl_3$) δ 150.9 (s, 1P).

5.2.10. Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside cyclic (*R*)-[1,1′-binaphthalene]-2,2′-diyl phosphite (11A). *Procedure C*. 80% Yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–6.86 (m, 22H, aromatic), 5.78 (d, J=9.5 Hz, 1H, NH), 5.71 (s, 1H, benzylic), 4.86 (dt, J=9.5, 3.0 Hz, 1H, H-2), 4.78 (d, J=4.5 Hz, 1H, H-1), 4.58 and 4.30 (AB, J=12.2 Hz, 2H, OCH_2Ph), 4.45–4.27 (m, 3H, H-3, H-5, H-6eq), 3.84–3.75 (m, 2H, H-4, H-6ax), 1.67 (s, 3H, CH_3CO); ^{31}P NMR (101 MHz, $CDCl_3$) δ 156.0 (s, 1P).

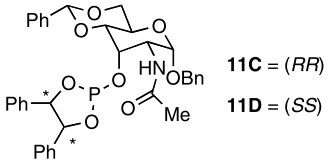


11A = (*R*)-BINAPO$_2$

11B = (*S*)-BINAPO$_2$

5.2.11. Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside cyclic (*S*)-[1,1′-binaphthalene]-2,2′-diyl phosphite (11B). *Procedure C*. 88% Yield; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.82–6.88 (m, 22H, aromatic), 6.09 (d, J=9.4 Hz, 1H, NH), 5.54 (s, 1H, benzylic), 4.79 (dt, J=8.7, 2.9 Hz, 1H, H-2), 4.72 (d, J=4.4 Hz, 1H, H-1), 4.43 and 4.24 (AB, J=12.5 Hz, 2H, OCH_2Ph), 4.34 (m, 1H, H-3), 4.08–3.98 (m, 2H, H-5, H-6eq), 3.64–3.57 (m, 2H, H-4, H-6ax), 1.97 (s, 3H, CH_3CO); ^{13}C NMR (71.6 MHz, $CDCl_3$) δ 169.3, 148.1, 147.4, 137.4, 137.3, 132.8, 131.5, 130.9, 130.3, 129.3, 129.2, 128.4, 128.3, 128.3, 128.2, 127.5, 127.2, 127.1, 127.0, 126.6, 126.3, 126.2, 126.0, 125.0, 124.9, 121.9, 121.9, 121.5, 101.6, 96.4, 77.2, 71.6, 71.4, 69.8, 68.9, 57.7, 48.9, 48.9; ^{31}P NMR (101 MHz, $CDCl_3$) δ 150.6 (s, 1P).

5.2.12. Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside cyclic (*R*,*R*)-1,2-diphenylethylene phosphite (11C). *Procedure C*. 84% Yield; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36–7.03 (m, 20H, aromatic), 5.99 (d, J=9.45 Hz, 1H, NH), 5.47 (s, 1H, benzylic), 5.19 (d, J=9.6 Hz, 1H), 4.82 (d, J=4.5 Hz, 1H), 4.76 and 4.54 (AB, J=12.2 Hz, 2H, OCH_2Ph), 4.68–4.63 (m, 2H), 4.35 (m, 1H), 4.19–4.09 (m, 2H), 3.66–3.36 (m, 2H), 1.71 (s, 3H, CH_3CO); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 137.6, 137.5, 137.3, 136.7, 136.7, 129.5, 129.1, 129.0, 128.8, 128.8, 128.6, 128.3, 127.0, 102.5, 96.8, 87.4, 82.8, 77.6, 70.8, 70.0, 69.8, 69.5, 58.5, 49.5; ^{31}P NMR (101 MHz, $CDCl_3$) δ 144.0 (s, 1P).

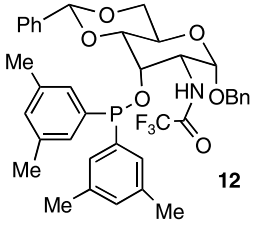


11C = (*RR*)

11D = (*SS*)

5.2.13. Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside cyclic (*S*,*S*)-1,2-diphenylethylene phosphite (11D). *Procedure C*. 83% Yield; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45–6.83 (m, 20H, aromatic), 6.06 (d, J=9.5 Hz, 1H, NH), 5.54 (s, 1H, benzylic), 4.93 (d, J=9.2 Hz, 1H), 4.80–4.68 (m, 3H), 4.52 and 4.27 (AB, J=11.7 Hz, 2H, OCH_2Ph), 4.37–4.15 (m, 3H), 3.72–3.64 (m, 2H), 1.82 (s, 3H, CH_3CO); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 138.1, 137.6, 137.5, 137.0, 136.9, 129.6, 129.0, 128.9, 128.9, 128.7, 128.6, 128.5, 128.3, 127.4, 127.3, 126.9, 102.7, 97.7, 87.3, 83.7, 71.5, 71.1, 70.9, 69.7, 66.3, 58.8, 49.7; ^{31}P NMR (101 MHz, $CDCl_3$) δ 144.9 (s, 1P).

5.2.14. Benzyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(di-3,5-xylylphosphino)-2-(2,2,2-trifluoroacetamido)-α-D-allopyranoside (12). *Procedure B*. 81% Yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–6.90 (m, 16H, aromatic), 6.46 (d, J=9.4 Hz, 1H, NH), 5.47 (s, 1H, benzylic), 4.82 (d, J=4.3 Hz, 1H, H-1), 4.80 and 4.51 (AB, J=12.0 Hz, 2H, OCH_2Ph), 4.53 (m, 1H, H-3), 4.41 (td, J=10.2, 5.1 Hz, 1H, H-5), 4.26 (dt, J=9.5, 3.9 Hz, 1H, H-2), 4.19 (dd, J=10.3, 5.2 Hz, 1H, H-6eq), 3.68–3.64 (m, 2H, H-4, H-6ax), 2.12 (s, 6H, 2Me), 2.08 (s, 6H, 2Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1, 144.6, 141.0, 140.1, 139.8, 139.6, 134.4, 133.3, 131.5, 131.3, 130.9, 130.8, 130.7, 130.6, 130.4, 130.1, 129.9, 129.0, 104.7, 98.2, 80.8, 72.9, 71.8, 68.5, 61.0, 52.3, 23.9, 23.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 126.1 (s, 1P).



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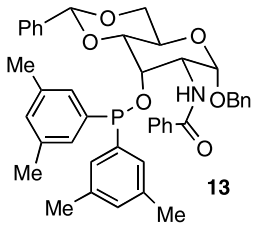
5.2.15. Benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(di-3,5-xylylphosphino)-α-D-allopyranoside (13). *Procedure B*. 77% Yield; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34–6.82 (m, 21H, aromatic), 6.35 (d, J=9.2 Hz, 1H, NH), 5.45 (s, 1H, benzylic), 4.89 (d, J=4.2 Hz, 1H, H-1), 4.70 and 4.48 (AB, J=12.0 Hz, 2H, OCH_2Ph), 4.61–4.41 (m, 3H, H-2, H-3, H-5), 4.17 (dd, J=10.2, 5.2 Hz, 1H, H-6eq), 3.72–3.61 (m, 2H, H-4, H-6ax), 2.07 (s, 6H, 2Me), 1.99 (s, 6H, 2Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 144.0, 142.9, 138.8, 138.1, 138.9, 137.6, 133.7, 131.9, 131.8, 130.9, 129.1, 128.9, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.5, 127.2, 126.8, 102.5, 97.3, 78.8, 70.7, 70.7, 66.3, 58.9, 50.3, 21.7, 21.6; ^{31}P NMR (101 MHz,

$CDCl_3$) δ 123.6 (s, 1P).



5.3. Hydrovinylation reactions

The preparations of all hydrovinylation catalysts were carried out under a nitrogen atmosphere in a Vacuum Atmospheres drybox. The hydrovinylation reactions were conducted under an inert atmosphere of nitrogen using Schlenk techniques.

Procedure A. Use of triphenylphosphine and AgOTf[23]. The following is a typical procedure for the Ni(II)-catalyzed hydrovinylation reactions. To a red solution of 0.0035 equiv of $[Ni(allyl)Br]_2$ in dichloromethane (1.5 mL) was added a solution of 0.0070 equiv of triphenylphosphine in dichloromethane (1.5 mL). Then, the resulting yellow solution was added to a suspension of 0.0080 equiv of silver triflate in dichloromethane (2 mL). After 1.5 h of stirring at rt, the brown suspension was filtered through a short pad of Celite into a Schlenk flask, removed from the drybox, and cooled to −55 °C. Oxygen-free ethylene (≈1 atm) was then introduced into the yellow catalyst solution, and 1.0 mmol of a hydrovinylation substrate was added dropwise through a rubber septum with a syringe. The resulting reaction mixture was stirred for 2 h at −55 °C under an ethylene atmosphere (≈1 atm), quenched with half-saturated aqueous ammonium chloride solution (5 mL), and product was extracted with diethyl ether or dichloromethane (50 mL). The organic phase was dried over magnesium sulfate, analyzed by GC to determine the conversion of the substrate, and concentrated under reduced pressure to afford the corresponding hydrovinylation product.

Procedure B. Typical for asymmetric hydrovinylation reactions. The following is a typical procedure for the Ni(II)-catalyzed asymmetric hydrovinylation reactions of norbornene and 4-bromostyrene using NaBARF as the additive. To a red solution of 0.01 equiv of $[Ni(allyl)Br]_2$ in dichloromethane (1.5 mL) was added a solution of 0.021 equiv of a chiral phosphorus ligand (**L**) in dichloromethane (1.5 mL). Then, the resulting orange solution was added to a suspension of 0.029 equiv of the additive in dichloromethane (2 mL). The mixture was stirred for 1.5 h at rt, filtered through a short pad of celite into a Schlenk flask, and taken out of the drybox. Oxygen-free ethylene (≈1 atm) was then introduced to the orange catalyst solution at the appropriate temperatures shown in Tables 3 and 4. The hydrovinylation substrate (1 mmol) was added dropwise via a syringe. The resulting reaction mixture was stirred for the indicated times at low temperature under an ethylene atmosphere (≈1 atm). The reaction was quenched with half-saturated aqueous ammonium chloride (5 mL), and the product was extracted with diethyl ether or dichloromethane (50 mL). The organic layer was dried over magnesium sulfate, analyzed by GC to determine the conversion of the substrate. ^{1}H NMR spectra was also used to determine the isomeric rations. The organic extract was concentrated under reduced pressure to afford the corresponding hydrovinylation product. Enantiomeric excesses were determined by HPLC using a Daicel Chiralcel OJ column eluting with hexane (0.3–0.6 mL/min) for styrene derivatives.

Procedure C. Use of $AgSbF_6$ and $AgBF_4$ in Ni-catalyzed hydrovinylations of 4-bromostyrene (Table 3). A solution of 0.0050 equiv of $[Ni(allyl)Br]_2$ and 0.010 equiv of ligand **8A** in dichloromethane (3 mL) was stirred for 30 min at rt and then added to a suspension of 0.011 equiv of a silver salt in dichloromethane (2 mL). The resulting brown suspension was stirred for 5 min, filtered through a short pad of celite into a Schlenk flask, and then taken out of the drybox. Oxygen-free ethylene (≈1 atm) was introduced into the yellow-brown catalyst solution at −55 °C, and 1.0 mmol of 4-bromostyrene was added dropwise via a syringe. The resulting reaction mixture was stirred for 2 h at −55 °C under an ethylene atmosphere (≈1 atm), quenched with half-saturated aqueous ammonium chloride (5 mL), and extracted with dichloromethane (50 mL). The concentrated solution was analyzed as described before.

5.3.1. [(*S*)-1-Methylallyl]benzene. *Procedure B* (**L**=**8A**). 0.030 equiv of catalyst used; reaction temperature: −70 °C; quantitative yield (89% of 3-phenylbut-1-ene), ee=81% (*S*); ^{1}H NMR (300 MHz, $CDCl_3$) of 3-phenylbut-1-ene: δ 7.37–7.21 (m, 5H, aromatic), 6.06 (ddd, J_{trans}=17.0 Hz, J_{cis}=10.3 Hz, J=6.5 Hz, 1H), 5.10 (dt, J_{trans}=17.1 Hz, J=1.6 Hz, 1H), 5.07 (dt, J_{cis}=10.3 Hz, J=1.5 Hz, 1H), 3.51 (m, 1H), 1.41 (d, J=7.0 Hz, 3H); NMR spectra of minor impurities useful for determining selectivity: (*E*)-2-phenylbut-2-ene: δ 7.41–7.20 (m, 5H, aromatic), 5.89 (qq, J=6.9, 1.4 Hz, 1H), 2.07 (m, 3H), 1.82 (dq, J=6.8, 1.2 Hz, 3H); (*Z*)-2-phenylbut-2-ene: δ 7.41–7.20 (m, 5H, aromatic), 5.58 (qq, J=6.9, 1.4 Hz, 1H), 2.07 (m, 3H), 1.62 (dq, J=6.8, 1.5 Hz, 3H).

The absolute configuration of 3-phenyl-1-butene was determined by GC analysis using a 50 m Lipodex C capillary column[25] [conditions: 1.5 mL helium/min, 35 °C (50 min), 0.1 °C/min (60 min), 41 °C (30 min); retention times: *R*-isomer 95.8 min, *S*-isomer 97.2 min].

5.4. Reactions using ligands 12 and 13 with β-NHC(O)CF_3 and β-NHC(O)Ph groups (Table 2)

Procedure B (**L**=**12**). 0.020 equiv of catalyst used; >99% yield (40% of (*S*)-3-phenylbut-1-ene, 60% of (*E*)- and (*Z*)-2-phenylbut-2-ene); ee=87% (*S*).

Procedure B (**L**=**13**, 30 min.): 0.030 equiv of catalyst used; >99% yield (66% of (*S*)-3-phenylbut-1-ene, 34% of (*E*)- and (*Z*)-2-phenylbut-2-ene); ee=80% (*S*).

Procedure B (**L**=**13**, 120 min): 0.030 equiv of catalyst used; >99% yield (23% of (*S*)-3-phenylbut-1-ene, 77% of (*E*)- and (*Z*)-2-phenylbut-2-ene); ee=82% (*S*).

5.4.1. 1-Bromo-4-[(*S*)-1-methylallyl]benzene (2b).

Procedure B (**L**=**8A**, SbF_6 counteranion). 0.010 equiv of catalyst used; quantitative yield (~98% yield of 3-(4-bromophenyl)but-1-ene, ee=89% (*S*)); ^{1}H NMR (300 MHz, $CDCl_3$) of 3-(4-bromophenyl)but-1-ene δ 7.48–7.40 (m, 2H, aromatic), 7.12–7.06 (m, 2H, aromatic), 5.97 (ddd, J_{trans}=17.7 Hz, J_{cis}=9.8 Hz, J=6.4 Hz, 1H), 5.05 (dt, J_{trans}=17.6 Hz, J=1.5 Hz, 1H), 5.05 (dt, J_{cis}=9.9 Hz, J=1.5 Hz, 1H), 3.44 (quin, J=6.9 Hz, 1H), 1.35 (d, J=7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 150.3, 139.1, 136.7, 127.5, 121.3, 50.3, 28.3; Purity by GC and NMR >98%; Anal. Found (calcd) C 57.00 (56.90), H 5.30 (5.25), Br 37.72 (37.85); $[\alpha]_D^{18}$ +9.9±0.1 (*c* 7.02, $CHCl_3$).

5.4.2. 1-Isobutyl-4-[(*S*)-1-methylallyl]benzene (2c). *Procedure B* (**L**=**8A**). 0.020 equiv of catalyst used; quantitative yield; ee=74% (*S*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–7.05 (m, 4H, aromatic), 6.01 (ddd, J_{trans}=17.0 Hz, J_{cis}=10.3 Hz, J=6.5 Hz, 1H), 5.05 (dt, J_{trans}=17.2 Hz, J=1.6 Hz, 1H), 5.02 (dt, J_{cis}=10.3 Hz, J=1.5 Hz, 1H), 3.45 (m, 1H), 2.44 (d, J=7.2 Hz, 2H), 1.85 (sept, J=6.8 Hz, 1H), 1.35 (d, J=7.0 Hz, 3H), 0.91 (d, J=6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 143.2, 139.8, 129.5, 127.3, 113.2, 45.5, 43.2, 30.6, 22.8, 21.2); Purity by GC and NMR: >99%; $[\alpha]_D^{18}$ +6.8±0.1(*c* 2.1, $CHCl_3$).

5.4.3. Conversion to 2b to 2a [(*S*)-1-methylallyl]benzene. In a Schlenk flask was charged compound **2b** (45 mg, 0.21 mmol) in methanol (6 mL) and attached a vigreux column with a balloon of nitrogen. Mg turnings (350 mg) were added in small portion, and stirring was continued for 1 d at rt. The reaction mixture was diluted with diethyl ether (30 mL) and water (5 mL). The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure to afford 25 mg (89%) of 3-phenyl-1-butene as a colorless oil. The product was analyzed by GC (>99% yield) and HPLC (ee=89% (*S*).

5.4.4. Conversion of 2b to 2c (*S*)-(1-isobutyl-4-[1-methylallyl]benzene). A solution of isobutyl bromide (400 mg, 2.92 mmol) in diethyl ether (5 mL) was added to Mg turnings (100 mg, 4.11 mmol) in diethyl ether (5 mL). The mixture was stirred overnight at rt and added dropwise to a mixture of compound **2b** (360 mg, 1.7 mmol) and (dppp) $NiCl_2$ (15 mg, 0.028 mmol) in diethyl ether (10 mL). The resulting reaction mixture was heated at reflux overnight, quenched with half-saturated aqueous ammonium chloride, and extracted with diethyl ether (50 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The crude product and chromatographed on silica with hexane as solvent to afford 300 mg (95% yield) of (*S*)-**2c** as a colorless oil, ascertained by HPLC of having ee of 89% (*S*).

5.4.5. (*R*)-2-(4-Isobutylphenyl)propionic acid (14).[21] A solution of compound **2c** (170 mg, 1.06 mmol) in dichloromethane–methanol (2:1, 30 mL) was cooled to −78 °C, and ozone was passed through the solution until the blue color persisted. It was stirred for 30 min at −78 °C, nitrogen was purged for few minutes to remove excess ozone, and dimethylsulfide (0.5 mL) was added to the mixture. The resulting mixture was permitted to warm to 0 °C, and stirring was continued for 1 h at 0 °C and for another hour at rt. It was concentrated under reduced pressure, diluted with water, and extracted with petroleum ether (bp 40–60 °C). The organic extract was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated to dryness in vacuo to afford 153 mg (96%) of the intermediate aldehyde as a colorless oil. The crude product was used for the next step without further purification.

To a suspension of aldehyde from the above step (100 mg, 0.67 mmol) and magnesium sulfate (123 mg, 0.5 mmol) in acetone (15 mL) was added dropwise a solution of potassium permanganate (116 mg, 0.734 mmol) in acetone (10 mL) for 30 min. The resulting mixture was stirred for 2 h at rt, and the solvent was removed under reduced pressure. The residue was extracted with hot water (3× 20 mL) and filtered. The filtrate was washed with chloroform (10 mL), acidified with 1 N aqueous hydrochloric acid to pH 2, and then extracted with chloroform (3×30 mL). The combined organic extracts were dried over magnesium sulfate and concentrated to dryness in vacuo to afford 70 mg (66%) of **14** as an off white solid. To ascertain the absolute configuration and the enantioselectivity, the crude product **14** (0.5 mg in 100 μL of dichloromethane) was converted to the corresponding ibuprofen (−)-menthyl esters by mixing with 100 μL of an esterification solution, prepared as described below, and then stirring the resulting mixture for 30 min. The esterification solution was prepared by dissolving 3.5 g of (−)-menthol, 0.12 g of dicyclohexylcarbodiimide, 6 mg of 4-dimethylaminopyridine, and 25 μL of 1 M HCl in 1 mL of dichloromethane. The diastereomeric menthyl esters were analyzed by GC on a Chirasil-L-Val column (conditions: 150 °C; retention times: *R*-acid ester 29.9 min, *S*-acid ester 30.9 min). The major acid isomer was identified as *R*-ibuprofen (89% ee) by comparison of retention times with that of authentic samples. Correspondingly, the olefin product, **2c** (3-(4-isobutylphenyl)-but-1-ene), was established as having the *S* configuration.

5.4.6. 2-(3-Bromophenyl)-1-butene (16, racemic). To a solution of allylnickel bromide (2.2 mg, 0.0061 mmol) in CH_2Cl_2 (1.0 mL), was added a solution of triphenylphosphine (3.2 mg, 0.0122 mmol) in CH_2Cl_2 (2.0 mL). The resulting orange solution was added to a suspension of silver triflate (3.8 mg, 0.015 mmol) in CH_2Cl_2 (1.0 mL), and the resulting mixture was stirred at rt for 1.5 h. The mixture was filtered through celite to get a clear yellow solution which was subsequently cooled to −52 °C. Ethylene was introduced to the reaction followed by addition of 3-bromostyrene (**1**, 148 mg, 0.86 mmol) in 0.5 mL of CH_2Cl_2. The reaction was stirred at −52 °C for 3 h and was quenched by adding saturated aqueous NH_4Cl solution (5 mL). The mixture was extracted twice with ether. GC showed >99% conversion and >99% selectivity. The dried organic layer was evaporated to afford crude product (**16**, 170 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): 1.35 (d, J=7.0, 3H); 3.45 (q, J=6.8, 1H); 5.03–5.13 (m, 2H); 7.10–7.21 (m, 2H); 7.31–7.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.80; 43.10; 114.03; 112.72; 126.18; 129.44; 130.18; 130.60; 142.57; 148.15.

5.4.7. 2-(3-Bromophenyl)-propionic acid (17, racemic). To a solution of 2-(3-bromophenyl)-1-butene (racemic **16**, 47 mg, 0.22 mmol) in 1:2 *t*-butanol/H_2O (18 mL), was added $KMnO_4$ (108 mg, 0.68 mmol), $NaIO_4$ (880 mg, 4.1 mmol) and K_2CO_3 (223 mg, 1.6 mmol). The pH of the reaction solution was adjusted to 8 with 3 M NaOH aqueous solution. The reaction was stirred for 3 h at rt. Concentrated HCl was added to adjust the pH of the solution to 1, and $NaHSO_3$ was added to reduce $KMnO_4$ until the reaction mixture turned yellow greenish. The mixture was extracted with ether and the ether layer was extracted with 3 M NaOH aqueous solution. The aqueous layer was acidified with concentrated HCl and then extracted with ether. The dried organic layer was evaporated and the product was subjected to chromatography (10:1 CH_2Cl_2/MeOH) to get 2-(3-bromophenyl)-propionic acid (36 mg, 72%). ^1H NMR (400 MHz, $CDCl_3$): 1.40 (d, 3H); 3.58 (q, 1H); 7.03–7.21 (m, 2H); 7.23–7.44 (m, 2H).

5.4.8. (−)-Menthyl (*R*+*S*) 2-(3-bromophenyl)-propionate (18). To a mixture of 2-(3-bromophenyl)-propionic acid from the previous step (36 mg, 0.16 mmol), (−)-menthol (62 mg, 0.40 mmol), DCC (1,3-dicyclohexylcarbodiimide, 49 mg, 0.24 mmol) and a few crystals of DMAP, was added anhydrous CH_2Cl_2 (2.0 mL). The resulting mixture was stirred for 15 h at rt. The reaction mixture was filtered to remove the urea. The filtrate was evaporated and the residue was dissolved in ether. After filtration to remove the insoluble materials, the filtrate was washed with 0.5 M HCl twice and then with saturated $NaHCO_3$. The dried organic layer was evaporated and chromatography (10:1 hexanes/ether) of the residue afforded the desired product as a 1:1 mixture of diastereomers (55 mg, 95%). The two isomers were cleanly separated on chirasil-*S*-val- column (R_T ester from (*R*)-acid 20.41 min.; ester from (*S*)-acid 21.86 min). ^1H NMR (250 MHz, $CDCl_3$): 0.57 (d, 3H); 0.71–2.16 (m, 16H), 3.68 (quint, 1H), 4.66 (dq, 1H), 7.12–7.28 (m, 2H); 7.37–7.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 16.04; 16.40; 18.23; 18.59; 20.85; 20.94; 22.17; 22.21; 23.38; 23.58; 25.99; 26.43; 31.54; 31.60; 34.42; 34.44; 40.65; 41.62; 45.73; 45.79; 47.15; 47.34; 74.96; 75.04; 122.70; 126.39; 130.20; 130.31; 130.86; 131.90; 143.21; 143.32; 173.58; 173.67.

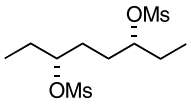
5.4.9. (*S*)-2-(3-Bromophenyl)-1-butene (16). To a solution of allylnickel bromide (1.8 mg, 0.0050 mmol) in CH_2Cl_2 (1.0 mL), was added a solution of **8A** ligand in CH_2Cl_2 (1.5 mL) at rt. The resulting solution was stirred for 30 min. before it was added to a suspension of $AgSbF_6$ (3.8 mg, 0.011 mmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred for 5 min before it was filtered through celite into a Schlenk tube. The celite pad was washed with CH_2Cl_2 (1.5 mL). The solution was cooled down to −52 °C and ethylene was introduced. 3-Bromostyene (138 mg, 0.75 mmol) in CH_2Cl_2 (0.5 mL) was added slowly. The reaction was stirred for 2.2 h before it was quenched with saturated NH_4Cl (5 mL) and extracted twice with ether. The dried ether layer was evaporated to get crude product (157 mg, 99%), GC of which showed 88% conversion with >99% selectivity. ^1H and ^{13}C NMR are consistent with the structure. ^1H NMR (400 MHz, $CDCl_3$): 1.36 (d, 3H); 3.45 (quint, 1H), 5.02–5.12 (m, 2H), 5.93–6.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.80; 43.10; 114.03; 122.72; 126.18; 129.44; 130.18; 130.60; 142.57; 148.15.

5.4.10. (−)-Menthyl (*R*)-2-(3-bromophenyl)-propionate (18). The optically enriched (*S*)-2-(3-bromophenyl)-1-butene (**16**) was also oxidized and esterified with (−)-menthol to the (−)-menthyl ester as described for the racemic counterpart. Gas chromatography on chirasil *S*-Val column showed this material to be of 87% ee.

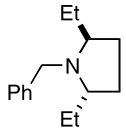
5.5. Synthesis of phosphoramidite ligands

5.5.1. Synthesis of 2,5-diethylpyrrolidine·HCl. (−)-(2*S*, 5*S*)-2,5-Diethylpyrrolidine·HCl was synthesized from (3*R*, 6*R*)-octane-3,6-diol by following the literature procedure[43] described for (+)-(2*R*, 5*R*)-2, 5-dimethylpyrrolidine. HCl, via mesylation of the diol, reaction of the dimesylate with benzyl amine to get *N*-benzyl-(2*S*, 5*S*)-2, 5-diethylpyrrolidine followed by debenzylation and salt formation.

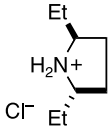
5.5.2. Dimesylate of (*RR*)-octane-3,6-diol. The crude product was found to be pure by NMR. Yield ~100%. ^1H NMR (400 MHz, $CDCl_3$) δ 4.72–4.69 (m, 2H), 3.01 (s, 6H), 1.75 (dd, J=3, 2.7 Hz, 4H), 1.72–1.65 (m, 4H), 0.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.2, 39, 29.5, 27.8, 9.7.



5.5.3. (+)-*N*-Benzyl-(2*S*, 5*S*)-2,5-diethylpyrrolidine. The product was isolated in 72% yield as an oil by flash column chromatography (SiO_2, 3% EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J=7.2 Hz, 2H), 7.19 (t, J=7.2 Hz, 2H), 7.1 (t, J=7.2 Hz, 1H), 3.73 (d, J=14 Hz, 1H), 3.58 (d, J=14 Hz, 1H), 2.71 (br s, 2H), 1.83–1.72 (m, 2H), 1.56–1.47 (m, 2H), 1.42–1.36 (m, 2H), 1.13–1.02 (m, 2H), 0.7 (t, J=7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 128.7, 128.4, 126.7, 62.2, 51.6, 28, 23.5, 10.8. $[\alpha]_D^{22}$ +111.9 (*c* 3, CH_2Cl_2).



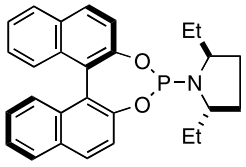
5.5.4. (−)-(2*S*, 5*S*)-2,5-Diethylpyrrolidine·HCl. The product was obtained as a pale yellowish solid in 82% yield after crystallization from a 4:1 solvent mixture of CH_2Cl_2, hexanes. ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (br s, 2H), 3.55 (br s, 2H), 2.15–2 (m, 4H), 1.72–1.6 (m, 4H), 0.99 (t, J=7 Hz, 6H); ^{13}C NMR (100, $CDCl_3$) δ 61.4, 30.3, 26.1, 11.4. $[\alpha]_D^{22}$ −2.87 (*c* 3, CH_2Cl_2); mp 222–226 °C.



5.6. Preparation of binaphthyl-*O*, *O*′-dioxo-*N*-[(2*S*, 5*S*)-diethylpyrrolidino]phospholidines

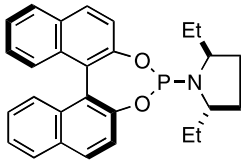
In a flame dried two necked flask equipped with a stirring bar, long reflux condenser attached to a guard tube filled with NaOH pellets, were placed binaphthol (286 mg, 1 mmol) and 5 mL of freshly purified PCl_3. The mixture was refluxed at 82 °C for 4 h. After cooling to rt, the reaction flask was tightly closed and taken inside a glove box. Removal of PCl_3 under high vacuum afforded 355 mg of colorless solid (^{31}P NMR: δ 176, s) which was redissolved in dry toluene (6 mL) and cooled to approximately −20 °C in the freezer. To this cold solution 164 mg (1 mmol) of (2*S*, 5*S*)-2, 5-diethylpyrrolidine. HCl and triethylamine (3 mL) were added successively, and stirred at rt for 20 h. Toluene was removed under reduced pressure. To the residue 3× 3 mL portions of a mixture of hexanes, ether (3:1) was added to dissolve the product leaving most of the $Et_3N\cdot HCl$. Filtration, concentration of the filtrate followed by flash column chromatographic purification (SiO_2, 100% hexanes) afforded phosphoramidite **23** [from (*R*)-binaphthol] or **24** [from (*S*)-binaphthol] as a colorless solid in 40–45% yield.

5.6.1. (*R*)-2,2′-*O*, *O*-(1, 1′-Binaphthyl)-*O*, *O*′-dioxo-*N*-[(2*S*, 5*S*)-2,5-diethylpyrrolidino]phospholidine (23). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.94–7.84 (m, 4H), 7.47–7.2 (m, 8H), 3.52–3.45 (m, 2H), 1.9–1.72 (m, 2H), 1.55–1.41 (m, 4H), 1.3–1.18 (m, 2H), 0.65 (t, J=7.5 Hz, 6H); ^{31}P NMR (101 MHz, $CDCl_3$) δ 149.9.



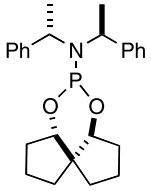
23 ($R_aS_cS_c$)

5.6.2. (*S*)-2,2′-*O*, *O*-(1, 1′-Binaphthyl)-*O*, *O*′-dioxo-*N*-[(2*S*, 5*S*)-2,5-diethylpyrrolidino]-phospholidine (24). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87–7.76 (m, 4H), 7.32–7.09 (m, 8H), 3.16 (br s, 2H), 1.71–1.64 (m, 4H), 1.5–1.22 (m, 4H), 0.55 (t, J=7.5 Hz, 6H); ^{31}P NMR (101 MHz, $CDCl_3$) δ 155.9.



24($S_aS_cS_c$)

5.6.3. 1,6-*O*, *O*-(1*S*, 5*S*, 6*S*)-*cis*,*cis*-spiro[4.4]nonyl-*O*, *O*′-Dioxo-*N*, *N*-bis[(1*S*)-phenylethyl]-aminophospholidine (25). In a Schlenk flask equipped with a stirring bar and a rubber septum was placed PCl_3 (0.39 mmol, 34 μL) in toluene (2 mL) at −60 °C under N_2. Triethylamine (0.77 mmol, 107 μL) in neat was introduced through a syringe followed by a toluene (2 mL) solution of (1*S*, 5*S*, 6*S*)-spiro[4.4]nonane-1,6-diol (0.35 mmol, 55 mg).[44] The resultant mixture was stirred at −60 °C for 2 h. The rubber septum was quickly replaced by a glass stopper while flushing N_2 and the reaction flask was taken inside a glove box. Toluene was removed under vacuum and the residue was added 3×3 mL of 3:1 hexanes, ether and filtered through cotton. The filtrate was concentrated to dryness. The residue was dissolved in 3 mL of toluene and cooled to approximately −20 °C. Triethylamine (0.3 mL) and (*R*)-bis(α-methylbenzyl) amine (0.7 mmol, 158 mg) in 2 mL of toluene were added successively and the resultant mixture was stirred at rt overnight. Toluene was removed under reduced pressure and to the residue was added 3× 3 mL of 3:1 hexanes, ether mixture. Filtration through cotton and concentration of the filtrate gave a crude product which was purified by flash column chromatography (SiO_2, 100% hexanes) to afford 82 mg (57%) of pure **25** as a colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.1 (s, 10H), 4.62–4.45 (m, 3H), 4.15–4.13 (m, 1H), 2.04–1.6 (m, 10H), 1.72 (d, J=7.25 Hz, 6H), 1.43–1.36 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 144.3, 128.2, 128, 126.5, 81.9 and 81.8, 53.6 and 53.4, 37.6 and 36.8, 34.9 and 34.8, 33.4 and 33.3, 23.9 and 22.9, 22.7 and 22.5; ^{31}P NMR (101 MHz, $CDCl_3$) δ 130.



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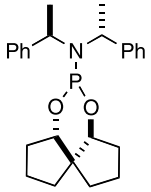
5.6.4. 1,6-*O*, *O*-(1*S*, 5*S*, 6*S*)-*cis*, *cis*-spiro[4.4]nonyl-*O*, *O*′-dioxo-*N*, *N*-bis[(1*R*)-phenylethyl]aminophospholidine (26). Following the above procedure **26** (172 mg, 61%) was obtained as a colorless solid starting from PCl_3 (0.76 mmol, 66 μL), triethylamine (1.52 mmol, 0.21 mL), (1*S*, 5*S*, 6*S*)-spiro[4.4]nonane-1,6-diol (0.69 mmol, 108 mg) and then triethylamine (0.5 mL), (*S*)-bis(α-methylbenzyl) amine (1.4 mmol, 315 mg).[1]H NMR (250 MHz $CDCl_3$) δ 7.19–7.05 (m, 10H), 4.75–4.62 (m, 2H), 4.35 (dd, J=4.75, 2.75 Hz, 1H), 4.12 (dd, J=3.5, 1.75 Hz, 1H), 2.06–1.88 (m, 6H), 1.9–1.62 (m, 4H), 1.72 (d, J=7.25 Hz, 6H), 1.5–1.35 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 142, 128.3, 128, 126.6, 82.3 and 81.2, 57, 52.4 and 52.3, 37.8 and 37, 34.7 and 33.8, 24.1 and 23.1, 22.5 and 22.3; ^{31}P NMR (101 MHz, $CDCl_3$) δ 126.1.



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Acknowledgements

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References and notes

1. Recent monographs dealing with asymmetric catalysis: (a) Ojima, I.; Catalytic Asymmetric Synthesis; Wiley-VCH: New York, 2000. (b) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Comprehensive Asymmetric Catalysis; Springer: Berlin, 1999; Vol. 1–3. For a recent thematic issue on enantioselective catalysis, see: *Chem. Rev.* **2003**, *103*, 2761–3400.
2. Cullen, W. R.; Sugi, Y. *Tetrahedron Lett.* **1978**, 1635–1636.
3. Selke, R. *React. Kinetic. Catal. Lett.* **1979**, *10*, 135–138.
4. (a) RajanBabu, T. V.; Casalnuovo, A. L.; Ayers, T. A.; Nomura, N.; Jin, J.; Park, H.; Nandi, M. *Curr. Org. Chem.* **2003**, *7*, 301–316. For a recent comprehensive review on the use of carbohydrates as ligand precursors in asymmetric catalysis, see: (b) Diéguez, M.; Pamies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189–3215.
5. Yan, Y.; RajanBabu, T. V. *J. Org. Chem.* **2000**, *65*, 900–906.
6. (a) Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869–9882. (b) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 6325–6326.
7. (a) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101–4102. (b) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012–6028.
8. For other early examples see; Achiwa, Jacobsen, Nishiyama (a) Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett* **1992**, 169–178. (b) Jacobsen, E. N.; Zhang, W.; Guler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703–6704. (c) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306–4309. (d) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089–1122.
9. RajanBabu, T. V.; Ayers, T. A. *Tetrahedron Lett.* **1994**, *35*, 4295–4298.
10. (a) Nomura, N.; Mermet-Bouvier, Y. C.; RajanBabu, T. V. *Synlett* **1996**, 745–746. (b) Clyne, D. S.; Mermet-Bouvier, Y. C.; Nomura, N.; RajanBabu, T. V. *J. Org. Chem.* **1999**, *64*, 7601–7611.
11. (a) Wink, D. J.; Kwok, T. J.; Yee, A. *Inorg. Chem.* **1990**, *29*, 5006–5008. For the first report of related carbohydrate-derived phosphites see: (b) Brunner, H.; Pieronczyk, W. *J. Chem. Res. (S)* **1980**, 76.
12. For the use of phosphite ligands for other asymmetric hydrocyanation reactions: (a) Baker, M. J.; Pringle, P. G. *J. Chem. Soc., Chem. Commun.* **1991**, 1292–1293. (b) Yan, M.; Xu, Q.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2000**, *11*, 845–849. (c) Horiuchi, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron: Asymmetry* **1997**, *8*, 57–63. (d) Goertz, W.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Chem. Eur. J.* **2001**, *7*, 1614–1618.
13. (a) Enantioselective hydrocyanation of aromatic vinyl compounds, RajanBabu, T. V.; Casalnuovo, A. L. US Patent 5,175,335, 1992, The DuPont Company.(b) RajanBabu, T. V.; Casalnuovo, A. L.; Ayers, T. A. In *Ligand Tuning in Asymmetric Catalysis: Hydrocyanation and Hydrogenation Reactions*; Doyle, M. P., Ed.; Advances in Catalytic Processes; JAI: Greenwich, 1997; Vol. 2, pp 1–41.
14. For typical examples see: (a) Reetz, M. T.; Mehler, G. *Angew. Chem. Int., Ed.* **2000**, *39*, 3889–3890. (b) Diéguez, M.; Ruiz, A.; Claver, C. *Chem. Commun.* **2001**, 2702–2703. (c) Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *Org. Lett.* **2003**, *5*, 4137–4139. (d) Hua, Z.; Vassar, V. C.; Ojima, I. *Org. Lett.* **2003**, *5*, 3831–3834.
15. Feringa, B. L. *Acc. Chem. Res.* **2000**, 346–353 and references cited therein.
16. Pena, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553.
17. (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Ombos, R.; de Vries, A. H. M. *Angew. Chem. Int., Ed.* **2001**, *36*, 2620–2623. (b) Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681–684. (c) Boiteau, J.-G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2003**, *68*, 9481–9484. (d) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701.
18. (a) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426–3427. (b) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529–3532.
19. (a) Franció, G.; Faraone, F.; Leitner, W. *J. Am. Chem. Soc.* **2002**, *124*, 736–737. (b) Hölscher, M.; Franció, G.; Leitner, W. *Organometallics* **2004**, *23*, 5606.
20. (a) RajanBabu, T. V. *Chem. Rev.* **2003**, *103*, 2845–2860. (b) Jolly, P. W.; Wilke, G. In *Hydrovinylation*; Cornils, B., Herrmann, W. A., Eds.; Applied Homogeneous Catalysis with Organometallic Compounds; VCH: New York, 1996; Vol. 2, pp 1024–1048.
21. For a preliminary report, see: (a) Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2002**, *124*, 734–735. (b) Phosphoramidites derived from binaphthols were among the ligands we originally screened for the hydrovinylation of vinylarenes. However, phosphoramidites from dimethylamine and BINAPO$_2$P-Cl gave low yield and selectivity (17%, 5% ee). Park H.; Ph.D. Thesis, 2000, The Ohio State University. See also: Ref. 21(a), Supporting Information.
22. For an initial report see, Kumareswaran, R.; Nandi, N.; RajanBabu, T. V. *Org. Lett.* **2003**, *5*, 4345–4348.
23. RajanBabu, T. V.; Nomura, N.; Jin, J.; Nandi, M.; Park, H.; Sun, X. *J. Org. Chem.* **2003**, *68*, 8431–8446.
24. For the effect of various ancillary hemilabile groups see, Nandi, M.; Jin, J.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1999**, *121*, 9899–9900.
25. We obtained a value of $+6.80\pm0.1$ (*c* 2.1, $CHCl_3$) for (*S*)-**2c** of 74% ee. Hayashi reported a value of $+5.66$ (neat) for material estimated to be 80% ee. See: (a) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. J. *Org. Chem.* **1983**, *48*, 2195–2202. (b) Wilke reported $+6.18$ for a sample ($\sim$85% ee) obtained by hydrovinylation of 4-isobutylstyrene. Wilke, G.; Monkiewicz, J.; Kuhn, H. US Patent 4,912,274, 1990. *Chem. Abstr.* **1991**, *114*, 43172. In light of our results, which were all corroborated by HPLC measurements, the previously reported values of $[\alpha]^D$ values may have to be revised.
26. Parrinello, G.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7122–7127.
27. Nomura, N.; Jin, J.; Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459–460.
28. We thank Dr. Xiufeng Sun for this experiment.
29. Hydrovinylation of norbornene is one of the first asymmetric, metal-catalyzed C–C bond-forming reactions reported. See:

Bogdanovíc, B.; Henc, B.; Löser, A.; Meister, B.; Pauling, H.; Wilke, G. *Angew. Chem. Int., Ed. Engl.* **1973**, *12*, 954–964. For more recent results from the Wilke group, see Ref. 20b.
30. For other reports of hydrovinylation of norbornene, see: (a) Müller, G.; Ordinas, J. I. *J. Mol. Catal.* **1997**, *125*, 97–108. (b) Yi, C. S.; He, Z.; Lee, D. W. *Organometallics* **2001**, *20*, 802–804. For hydrovinylation of norbornadiene, see, Ref. 29 and, Pillai, S. M.; Tembe, G. L.; Ravindranathan, M. *J. Mol. Catal.* **1993**, *84*, 77–86.
31. For identification of the relative and absolute configuration of (−)-**18** and relative configuration **19**, see Ref. 22. The absolute configuration of **19** has not been determined.
32. For other asymmetric catalyzed reactions of norbornene see: Hydrocyanation: Hodgson, M.; Parker, D.; Taylor, R. J.; Ferguson, G. *Organometallics* **1988**, *7*, 1761–1766. Baker, M. J.; Pringle, P. G. *J. Chem. Soc., Chem. Commun.* **1991**, 1292–1293. Horiuchi, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron: Asymmetry* **1997**, *8*, 57–63. Yan, M.; Xu, Q.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2000**, *11*, 845–849. Hydrosilylation: Hayashi, T. *Acta Chem. Scand.* **1996**, *50*, 259–266. Hydroalkenylation: Ozawa, F.; Kabatake, Y.; Kubo, A.; Hayashi, T. *J. Chem. Soc., Chem. Commun.* **1994**, 1323–1324.
33. (a) Polymerization of norbornene by Ni(II)-complexes has been extensively studied by Goodall et al. For a leading Ref. see, (a) Addition Polymers Derived from Norbornene-Functional Monomers and Process Therefor, Goodall, B. L.; Benedikt, G. M.; McIntosh, I. L. H.; Barnes, D. A.; Rhodes, L.F., US Patent 5,571,881, 1996, The B.F. Goodrich Company. (b) Goodall, B. L. Cycloaliphatic polymers via late transition metal catalysis. In *Late Transition Metal Polymerization Catalysis*; Rieger, B., Baugh, L. S., Kacker, S., Striegler, S., Eds.; Wiley-VCH: Weinheim, 2003; pp 101–154.
34. Zhang, A.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 1515–1517.
35. For other examples, see Ref. 24.
36. (a) Jimémez-Tenorio, M.; Puerta, M. C.; Salcedo, I.; Valerga, P.; Costa, S. I.; Silva, L. C.; Gomes, P. T. *Organometallics* **2004**, 3139–3146 and references cited therein. See also, (b) Bonnet, M. C.; Dahan, F.; Ecke, A.; Keim, W.; Schulz, R. P.; Tkatchenko, I. *Chem. Commun.* **1994**, 615–616.
37. Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991–7994.
38. Gross, P. H.; Jeanloz, R. W. *J. Org. Chem.* **1967**, *32*, 2759–2763.
39. Reckendorf, W. M. *Chem. Ber.* **1969**, *102*, 4207.
40. (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem. Int., Ed.* **1997**, *36*, 2620–2623. (b) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865–2878.
41. Nugent, W. A.; McKinney, R. J. *J. Org. Chem.* **1985**, *50*, 5370–5372.
42. Brookhart, M.; Grant, B.; Volpe, A. *Organometallics* **1992**, *11*, 3920–3922.
43. Short, R. P.; Kennedy, R.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755–1756.
44. Nieman, J. A.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1973–1976.

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The effect of pre-existing stereocenters in the intramolecular asymmetric Stetter reaction

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Abstract—A series of disubstituted cyclopentanones have been synthesized by the intramolecular Stetter reaction. Racemic substrates containing one chiral center were used, allowing us the opportunity to observe a parallel kinetic resolution in the synthesis of 2,3- and 2,4-disubstituted cyclopentanones. The Stetter reaction of 2,5-disubstituted cyclopentanones proved to be substrate controlled, resulting in the selective formation of the *cis*-diasteromers with low ee.

1. Introduction

The asymmetric synthesis of disubstituted cyclopentanones remains a challenge for organic chemists. The most common route to disubstituted cyclopentanones relies on conjugate addition to an appropriately substituted cyclopentenone. This strategy has been used for the enantiopure synthesis of 2,3- and 2,4-disubstituted cylcopentanones, the latter via kinetic resolution.[1] We have recently developed a family of catalysts for the asymmetric intramolecular Stetter reaction, which are capable of forming substituted cyclopentanones in high ee and yield (Fig. 1).[2–5] During the course of these investigations, we became interested in the effect of pre-existing stereocenters in the backbone. Although we were naturally intrigued by the possibility of inducing a kinetic resolution, we were also cognizant of the need to understand how these catalysts would behave with chiral substrates, since one might envision using this reaction at a late stage in a complex molecule synthesis. Herein, we describe our results.

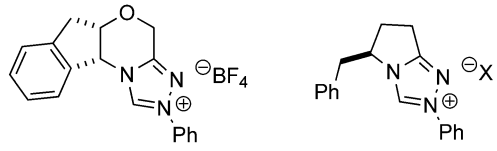
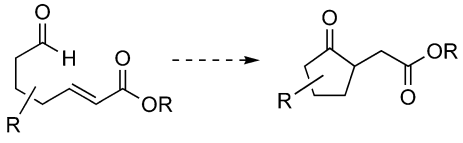


Figure 1. Catalysts for the intramolecular asymmetric Stetter reaction.

The application of chiral catalysts to racemic substrates offers the opportunity for kinetic resolution.[6] Kinetic resolutions by non-enzymatic systems have become increasingly valuable. Traditional kinetic resolution occurs when one enantiomer of substrate reacts at a faster rate than the other allowing for the synthesis of enantiopure product with a maximum yield of 50%. Dynamic kinetic resolution occurs when the pre-existing stereocenter is racemized faster than the desired enantioselective process offering the potential to synthesize single enantiomer products in high yields from racemic material. Parallel kinetic resolution occurs when different products are formed from each substrate enantiomer.[7] In this context, we became interested in assessing the impact of substitution at every position between the aldehyde and the Michael acceptor on rate and enantioselectivity in the intramolecular asymmetric Stetter reaction (Eq. 1).


(1)

2. 2,4-Disubstituted cyclopentanones

2.1. Substrate synthesis

Substrate synthesis commenced with the appropriate 3-substituted glutaric anhydride. Reduction with sodium borohydride provides the 3-substituted lactone. Further reduction with Dibal-H affords the lactol that may be treated with (carboethoxymethylene) triphenyl-phosphorane.

Keywords: Stetter reaction; Cyclopentanones; Stereoselective.
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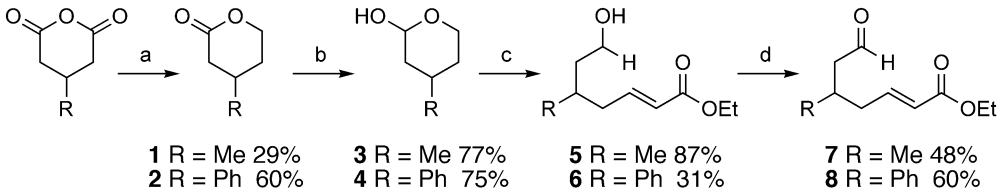


Reagents: a) $NaBH_4$; TFA, b) Dibal-H, c) (carboethoxymethylene)triphenyl-phosphorane, d) Swern.

Scheme 1. Synthesis of **7** and **8**.

Swern oxidation of the resultant primary alcohol completes a four step unoptimized synthesis of **7** and **8** (Scheme 1).

2.2. Intramolecular Stetter results

The results for the cyclization of **7** and **8** are shown in Scheme 2. Substrate **7** cyclizes to provide *trans*-**9** in 98% ee and *cis*-**9** in 94% ee, as an equimolar mixture of inseparable diastereomers. Substrate **8** cyclizes to provide *trans*-**10** in 98% ee and *cis*-**10** in 96% ee, as an equimolar mixture. The outcome appears to be independent of steric bulk suggesting that the pre-existing stereocenters at the 5-position have no effect on the intramolecular Stetter reaction.

3. Synthesis of 2,3-disubstituted cyclopentanones

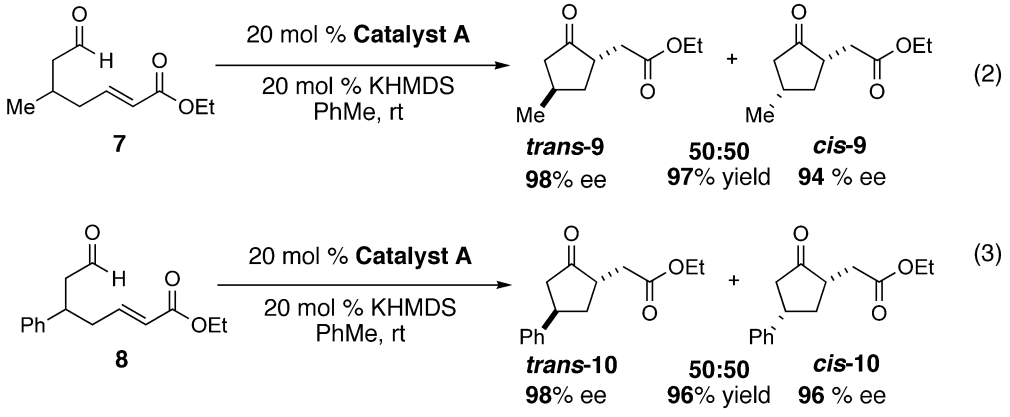
3.1. Substrate synthesis

Two different routes were used for the synthesis of substrates **12** and **14**. The synthesis of **12** began with the differentially protected dialdehyde from the Schreiber ozonolysis of cyclopentene.[8] The hydrazone is formed by treatment with *N*,*N*-dimethyl hydrazine. Alkylation of this intermediate with iodomethane, followed by removal of the hydrazone afforded the intermediate aldehyde.[9] The aldehyde was treated with (carboethoxymethylene) triphenyl-phosphorane, followed by triflouroacetic acid to afford **12** (Scheme 3).

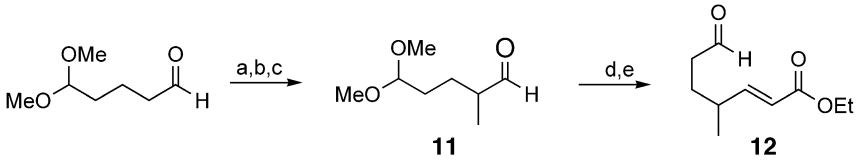
The synthesis of **14** began with the addition of allyl magnesium chloride to isopropylacrolein. The secondary alcohol then underwent an anionic oxy-cope rearrarangement by treatment with KH in hot dioxane. Treatment of the resulting aldehyde with (carboethoxymethylene) triphenyl-phosphorane, followed by Lemieux oxidation affords **14** (Scheme 4).[10]

3.2. Intramolecular Stetter results

The results for the cyclization of **12** and **14** are shown in Scheme 5. Upon treatment with catalyst A, **12** cyclizes smoothly to afford *trans*-**15** in 90% ee and *cis*-**15** in 95% ee, again as an inseparable mixture of diastereomers. Subjection of **14** to catalyst A revealed a different picture affording *cis*-**16** in 96% ee, and *trans*-**16** in 84% ee. The lower

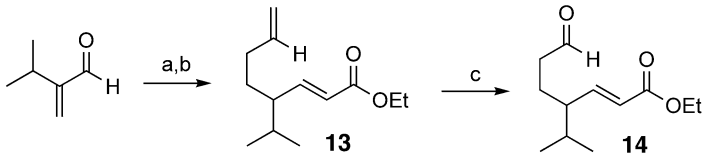


Scheme 2. Synthesis of 2,4-disubstituted cyclopentanones.



Reagents: a) *N*,*N*-dimethylhydrazine, b) LDA, iodomethane (85%), c) $NaIO_4$ (34%), d) (carboethoxymetylene)tri-phenyl-phosphorane (81%), e) trifloroacetic acid (72%).

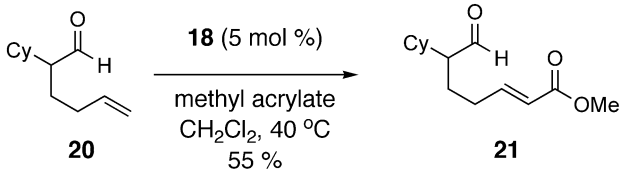
Scheme 3. Synthesis of **12**.



Reagents: a) allyl-MgCl (84%), b) KH, reflux; (carboethoxymethylene)triphenylphosphorane (41%), c) osmium tetroxid; lead tetraacetate (34%)

Scheme 4. Synthesis of **14**.

enantioselectivity for the latter was reflected in a slightly skewed diastereomeric mixture of these two, favoring *trans*-**16** by 53:47. These results could be improved by the use of catalyst B.



(6)

4. Synthesis of 2,5-disubstituted cylopentanones

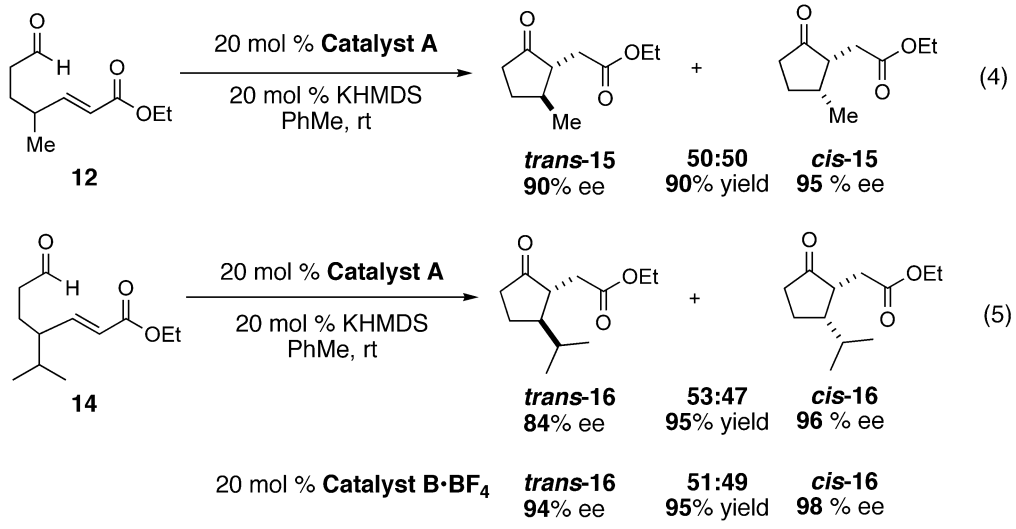
4.1. Substrate synthesis

The synthesis of substrate **19** began with alkylation of hydrocinnamaldehyde *N*,*N*-dimethyl hydrazone with 4-bromobutene.[11] After hydrazone cleavage, the aldehyde was subjected to cross metathesis with methyl acrylate,[12] providing **19** (Scheme 6).

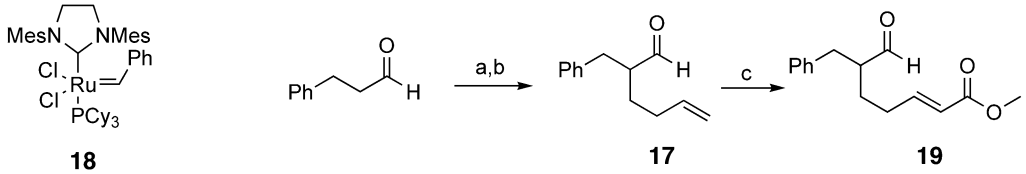
Substrate **21** was made by cross metathesis of 5-cyclohexyl-hex-5-enal (**20**) with methyl acrylate (Eq. 6). The enal **20** was prepared in direct analogy to the precursor to **13** (see Scheme 4).

4.2. Synthesis of 2,5-disubstituted cyclopentanones

The results for the cyclization of **19** and **21** are shown in Scheme 7. Under the conditions used for the previous substrates (20 mol% catalyst), **19** failed to give reproducible results, a situation that was rectified upon increasing the catalyst loading to 50 mol%. Cyclization of **19** affords a 95% yield of product, with 85:15 selectivity favoring the *cis* diastereomer, formed as a racemate. Cyclization of **21** affords *cis*-**23** in low ee but excellent selectivity over its *trans* isomer, validating the fact that the alpha stereocenters overrides catalyst preference and determines selectivity in

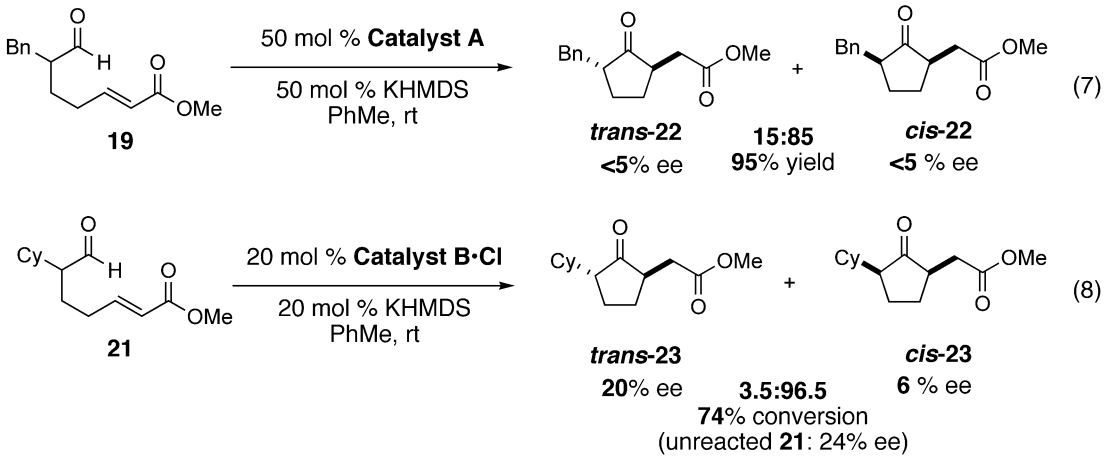


Scheme 5. Synthesis of 2,3-disubstituted cyclopentanones.



Reagents: a) *N*,*N*-dimethyhydrazine, b) LDA, 4-bromobutene; Ambelyst-15, (19 %) c) **18** (5 mol %), methyl acrylate (67 %)

Scheme 6. Synthesis of **19**.



Scheme 7. Synthesis of 2,5-disubstituted cyclopentanones.

these cyclizations. In an incomplete reaction with this substrate (Eq. 8), we noted that the unreacted starting material was modestly enantioenriched which corresponds to an *s* value of 1.4.

5. Kinetic and thermodynamic ratios

In light of the above results we set out to determine the kinetic and thermodynamic ratios for the disubstituted cyclopentanones **10**, **16**, and **22**. The kinetic ratios were determined by cyclization with 1 equiv of achiral triazolium salt and the thermodynamic ratios were determined by heating the substrates in toluene in the presence of excess triethylamine (Scheme 8). It is intriguing to note that the achiral catalyst provides low selectivity in the formation of **22**. This is in sharp contrast to the ability of our chiral triazolium salts to form the *cis* product in high diastereoselectivity, a situation that we ascribe to the large steric differences between the achiral and chiral azolium salts.

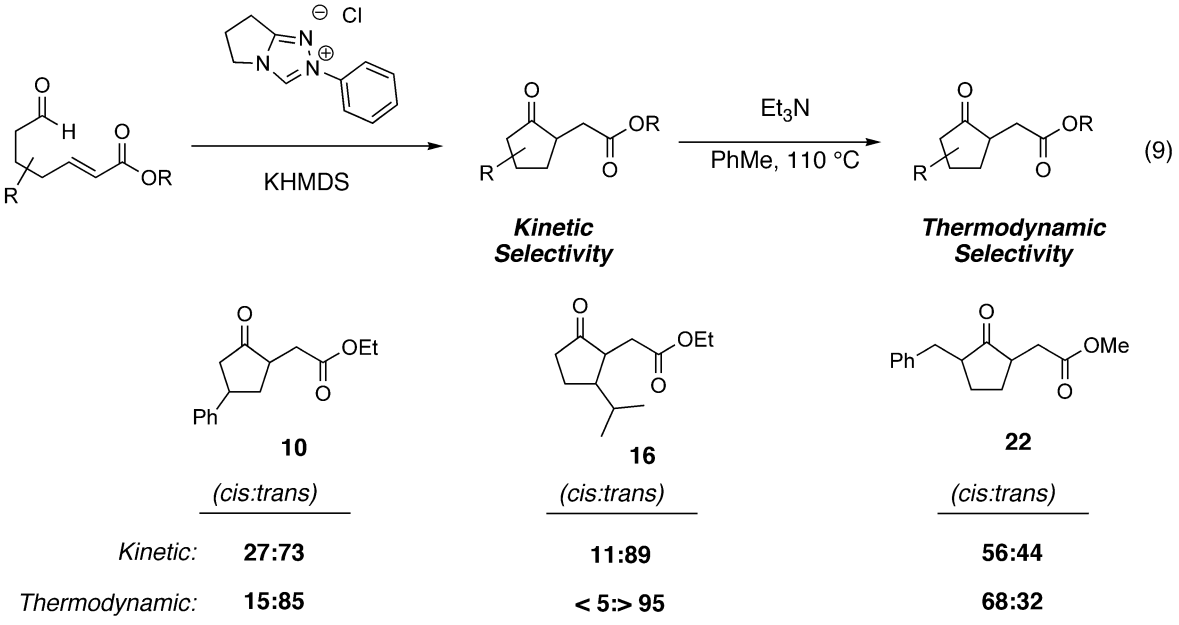
6. Conclusion

We have shown that the Stetter reaction is a viable option for the synthesis of disubstituted cyclopentanones. 2,3- and 2,4-disubstituted cyclopentanones are synthesized via a parallel kinetic resolution providing both *trans* and *cis* diastereomers in high ee. There appears to be little effect of steric bulk at the 4- and 5- positions of the substrates indicating that there is very little interaction with the catalyst. Substituents next to the aldehyde seem to override catalyst control and dictate the course of the reaction to selectively form the 2,5-*cis* disubstituted cyclopentanones in good yield.

7. Experimental

7.1. General

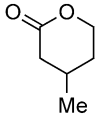
General procedure for the intramolecular asymmetric Stetter reaction. To a flame dried round bottom flask was



Scheme 8. Kinetic and thermodynamic ratios of disubstituted cyclopentanones.

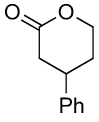
added 0.2 equiv of catalyst. Toluene (5 mL) was then added followed by KHMDS (0.5 M in tetrahydrofuran). The solution was stirred for 10 min followed by the addition of substrate. After 24 h the reaction mixture was filtered through a short plug of silica gel eluting with diethyl ether. Column chromatography (9:1, hexane/ethyl acetate) afforded analytically pure material.

7.1.1. 4-Methyl-tetrahydro-pyran-2-one (1).[15]



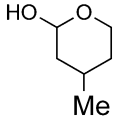
To a stirred solution of 3-methylglutaric anhydride (1.0 g, 7.8 mmol) in 30 mL tetrahydrofuran was added sodium borohydride (0.59 g, 15.6 mmol). After stirring overnight, 10 mL of 10% v/v HCl was slowly added. The solution was then placed in a separatory funnel and extracted with diethyl ether (3×). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The yellow oil was then dissolved in 5 mL methylene chloride and 0.3 mL trifluoroacetic acid was added followed by stirring overnight. To the mixture was then added 50 mL diethyl ether and the solution placed in a separatory funnel, followed by washing with sat. aq. $NaHCO_3$ (3×), and brine (1×). The organic layer was then dried over $MgSO_4$ and concentrated in vacuo. The resulting oil was then purified by column chromatography eluting with (9:1, hexane/diethyl ether) to afford 0.260 g product (2.28 mmol, 29%). R_f=0.18 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (m, 1H), 4.23 (ddd, 1H, J=11.2, 10.6, 3.7 Hz), 2.65 (m, 1H), 2.03–2.13 (m, 2H), 1.89 (m, 1H), 1.49 (m, 1H), 1.04 (d, 3H, J=6.23 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 68.5, 38.2, 30.7, 26.6, 21.5; IR (NaCl, neat) 1732, 1458, 1444, 1257, 1229 cm^{-1}.

7.1.2. 4-Phenyl-tetrahydro-pyran-2-one (2).[15]



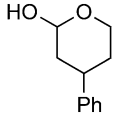
A flame-dried flask was charged with 3-phenylglutaric acid (2.00 g, 9.6 mmol) and 30 mL methylene chloride. The solution was cooled to 0 °C and triflouroacetic anhydride (4.0 mL, 28.8 mmol) was added. The mixture was stirred for 2 h at this temperature, then concentrated in vacuo. The solution was placed under vacuum (1 mmHg) overnight. The white solid was then dissolved in 50 mL tetrahydrofuran and sodium borohydride was added (0.73 g, 19.2 mmol), followed by stirring for 24 h. 20 mL 10% v/v HCl was then slowly added, followed by 20 mL diethyl ether; the layers were separated and the aq. layer was extracted with 20 mL diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo affording an oil. The oil was dissolved in 50 mL methylene chloride and 1 mL triflouroacetic acid was added, followed by stirring for 16 h. 50 mL saturated. aq. sodium bicarbonate was slowly added and the layers separated. The organic layer was extracted with 20 mL methylene chloride (2×). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The clear oil was purified by column chromatography (3:1, hexane/ethyl acetate) affording 1.01 g product as a colorless oil (5.7 mmol, 60%). R_f=0.13 (3:1, hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 5H), 4.42 (m, 1H), 4.30 (ddd, 1H, J=11.2, 10.7, 3.6 Hz), 3.15 (m, 1H), 2.82 (m, 1H), 2.54 (m, 1H), 2.08 (m, 1H), 1.94 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.5, 142.7, 128.8, 127.0, 126.3, 68.5, 37.4, 37.2, 30.1.

7.1.3. 4-Methyl-tetrahydro-pyran-2-ol (3).



To a stirred solution of 1 (0.260 g, 2.28 mmol) in 10 mL toluene at −78 °C was added Dibal-H (3.0 mL, 3.00 mmol, 1 M in hexane). The mixture was stirred for 2 h at which time 10 mL of a saturated aq. solution of Rochelle's Salt was added. The solution was allowed to warm to room temperature and stirred overnight. 10 mL of a saturated aq. solution of sodium bicarbonate was added and the organic layer was separated. The aq. layer was then extracted 3× with 10 mL diethyl ether. The organic layers were dried over $MgSO_4$, and concentrated in vacuo. This afforded 0.203 g of pure product as a mixture of diastereomers (1.75 mmol, 77%). R_f=0.17 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (s, 1H), 4.65 (d, 1H, J=9.2 Hz), 3.99 (m, 2H), 3.62 (m, 1H), 3.48 (ddd, 1H, J=12.1, 11.9, 2.2 Hz), 3.41 (s, 1H), 2.83 (s, 1H), 2.00 (m, 1H), 1.89 (m, 1H), 1.46–1.77 (m, 4H), 1.15–1.34 (m, 3H), 1.04 (m, 1H), 0.97 (d, 3H, J=6.6 Hz), 0.91 (d, 3H, J=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.1, 91.5, 65.6, 59.7, 41.6, 38.7, 34.1, 33.5, 29.4, 23.6, 22.1, 21.9; IR (NaCl, neat) 3386, 2952, 2928, 1068, 1026, 988 cm^{-1}.

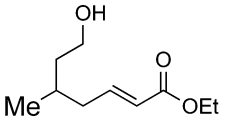
7.1.4. 4-Phenyl-tetrahydro-pyran-2-ol (4).



2 (0.50 g, 2.8 mmol) was dissolved in 20 mL toluene and chilled to −78 °C. Dibal-H (0.54 mL, 3.0 mmol) was then added and the reaction stirred for 2 h at −78 °C. Methanol (1 mL) was then added and the solution warmed to room temperature. Diethyl ether 20 mL and Rochelle's salt (saturated. aq. 20 mL) were then added. The solution was stirred until the layers separated. The layers were separated and the aq. layer was extracted with diethyl ether (50 mL). The combined organics were dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (3:1, hexane/diethyl ether) afforded 0.370 g product as a white solid (mixture of diastereomers) (2.1 mmol, 75%). R_f=0.15 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.30 (m, 10H), 5.41 (s, 1H), 4.80 (s, 1H), 4.11–4.19 (m, 2H), 3.74 (m, 1H), 3.64 (m, 1H), 3.16–3.24 (m, 2H), 2.82 (m, 1H), 2.67 (s, 1H), 2.12 (m, 1H), 1.97 (m, 1H), 1.69–1.84 (m, 5H), 1.56 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 145.5, 144.5, 128.6, 128.5, 127.4, 126.8, 126.7, 126.6,

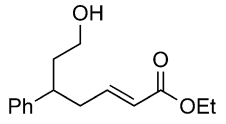
126.3, 96.3, 91.7, 65.8, 59.8, 40.6, 40.3, 37.5, 34.5, 33.0, 32.8.

7.1.5. 7-Hydroxy-5-methyl-hept-2-enoic acid ethyl ester (5).



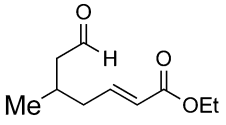
To a stirred solution of 3 (0.083 g, 0.714 mmol) in 5 mL tetrahydrofuran was added (carboethoxymethylene) triphenyl-phosphorane (0.497 g, 1.4 mmol). The solution was heated to 40 °C and stirred overnight. The solution was concentrated in vacuo and subjected to column chromotagraphy (3:1, hexane/ethyl acetate) affording 0.107 g product as a clear oil (0.62 mmol, 87%). R_f=0.06 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (m, 1H), 5.82 (d, 1H, J=15.7 Hz), 4.18 (q, 2H, J=7.1 Hz), 3.69 (m, 2H), 2.23 (m, 1H), 2.08 (m, 1H), 1.81 (m, 1H), 1.63 (m, 1H), 1.43 (m, 1H), 1.28 (t, 3H, J=7.1 Hz), 0.94 (d, 3H, J=6.6 Hz).

7.1.6. 7-Hydroxy-5-phenyl-hept-2-enoic acid ethyl ester (6).



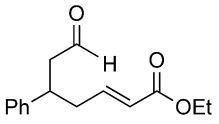
To a flame dried flask was added (carboethoxymethylene) triphenyl-phosphorane (4.5 g, 12.9 mmol) and 20 mL tetrahydrofuran, followed by addition of 4 (1.25 g, 10.8 mmol). The mixture was stirred overnight and subjected directly to column chromatography (4:1, hexane/ethyl acetate), affording 0.82 g of product (3.3 mmol, 31%). R_f=0.20 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 5H), 6.81 (m, 1H), 6.75 (d, 1H, J=15.6 Hz), 4.12 (q, 2H, J=7.0 Hz), 3.48 (m, 1H), 2.90 (m, 1H), 2.51 (ddd, 2H, J=7.4, 7.4, 1.2 Hz), 1.97 (m, 1H), 1.81 (m, 1H), 1.23 (t, 3H, J=7.2 Hz), 1.13 (s, 1H, –OH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.4, 146.8, 143.5, 128.7, 128.5, 147.5, 126.7, 122.9, 60.7, 60.2, 41.6, 39.6, 38.6, 14.2.

7.1.7. 5-Methyl-7-oxo-hept-2-enoic acid ethyl ester (7).



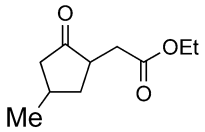
Oxalyl chloride (0.628 g, 4.95 mmol) and 10 mL methylene chloride was added to a flask and chilled to −78 °C. DMSO (0.773 g, 9.90 mmol) was added and the solution stirred for 5 min, then 5 (0.84 g, 4.50 mmol) in 10 mL methylene chloride was added. After 15 min triethylamine (2.29 g, 22.50 mmol) was added, the mixture was stirred for 5 min at −78 °C, then allowed to warm to room temperature and stirred overnight. 20 mL water was added and the organic layer separated. The aqeous layer was extracted 2× with 10 mL methylene chloride. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The oil was subjected to column chromatography (4:1, hexane/ethyl acetate), affording 0.400 g (2.17 mmol, 48%) of product as a clear oil. R_f=0.13 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, 1H, J=1.5 Hz), 6.89 (m, 1H), 5.83 (d, 1H, J=15.6 Hz), 4.18 (q, 2H, J=7.2 Hz), 2.43 (m, 1H), 2.13–2.33 (m, 4H), 1.28 (t, 3H, J=7.3 Hz), 1.00 (d, 3H, J=6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 166.3, 146.2, 123.5, 60.3, 50.2, 39.1, 27.5, 19.9, 14.2; IR (NaCl, neat) 1721, 1654, 1270, 1167 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}O_3$, 184.1099. Found 184.1099.

7.1.8. 7-Oxo-5-phenyl-hept-2-enoic acid ethyl ester (8).



To a flamed dried flask was added 10 mL methylene chloride and oxalyl chloride (0.29 mL, 3.34 mmol). The solution was cooled to −78 °C and DMSO (0.47 mL, 6.60 mmol) was added. After 5 min 6 (0.75 g, 3.0 mmol) was added. The solution was stirred for 15 min, followed by addition of triethylamine (1.52 g, 15 mmol). After 5 min the solution was warmed to room temperature and stirred overnight. Water (50 mL) was added and the layers separated, followed by extraction with methylene chloride. The combined organics were dried over $MgSO_4$ and concentrated in vacuo. The oil was subjected to column chromatography (4:1, hexane/ethyl acetate) affording 0.45 g of product as a yellow oil (1.8 mmol, 60%). R_f=0.17 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, 1H, J=1.5 Hz), 7.28 (m, 5H), 6.79 (m, 1H), 5.79 (dd, 1H, J=37.1, 1.1 Hz), 4.15 (q, 2H, J=7.0 Hz), 3.39 (m, 1H), 2.78 (d, 2H, J=7.3 Hz), 2.55 (t, 2H, J=7.0 Hz) 1.26 (t, 3H, J=7.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.8, 166.1, 145.5, 142.4, 128.8, 127.3, 127.0, 123.6, 60.3, 49.4, 39.0, 14.2; IR (NaCl, neat) 1721, 1660, 1276, 1204 1045 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{18}O_3$, 247.1334. Found 247.1335.

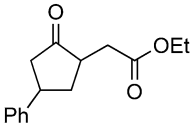
7.1.9. (4-Methyl-2-oxo-cyclopentyl)-acetic acid ethyl ester (9).



According to the general procedure, 7 (0.035 g, 0.19 mmol), catalyst A (0.014 g, 0.038 mmol), and KHMDS (0.076 mL, 0.038 mmol, 0.5 M in tetrahydrofuran), produced the product as a 1:1, mixture of inseparable diastereomers. Purification by column chromatography (95:5, hexane/diethyl ether) afforded 9 (34.0 mg, 97%). R_f=0.44 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, 4H, J=7.3 Hz), 2.64–2.74 (m, 3H), 2.33–2.54 (m, 7H), 2.19 (m, 1H), 1.78–2.03 (m, 4H), 1.25 (t, 6H, J=7.2 Hz), 1.14 (d, 3H, J=6.4 Hz), 1.09 (d, 3H, J=6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.7, 218.7, 172.1, 172.0, 60.6, 47.2,

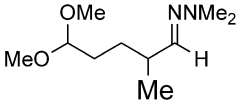
46.0, 45.9, 42.7, 38.0, 36.1, 34.6, 34.0, 29.6, 27.8, 20.9, 20.2, 14.2; IR (NaCl, neat) 1721, 1654, 1270, 1167 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}O_3$, 184.1099. Found 184.1092. GC analysis (G-TA, 100 °C, 3.0 mL/min; *trans* (tr (minor)=32.4 min, tr (major)=28.7 min), *cis* (tr (minor)=29.7 min, tr (major)=33.8 min)) gave the enantiomeric composition of the *trans* product: 98% ee, and the *cis* product: 94% ee.

7.1.10. (2-Oxo-4-phenyl-cyclopentyl)-acetic acid ethyl ester (10).

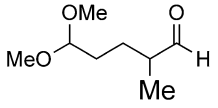


According to the general procedure, 8 (25.0 mg, 0.10 mmol), catalyst A (7.5 mg, 0.02 mmol), and KHMDS (0.040 mL, 0.02 mmol, 0.5 M in tetrahydrofuran), produced the product as a 50:50 mixture of inseparable diastereomers. Purification by column chromatography (95:5, hexane/diethyl Ether) afforded 9 (24.0 mg, 96%). R_f=0.25 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.34 (m, 10H), 4.09–4.15 (m, 4H), 3.59 (m, 1H, *trans*), 3.35 (m, 1H, *cis*), 2.30–2.80 (m, 12H), 2.22 (m, 1H), 1.81 (m, 1H), 1.23 (ddd, 6H, J=7.1, 7.1, 2.6 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 218.7, 217.2, 171.9, 171.8, 143.8, 142.8, 128.7, 126.8, 126.7, 126.6, 60.7, 46.9, 45.2, 44.7, 42.9, 40.1, 38.3, 37.2, 36.4, 34.6, 33.8, 14.2; IR (NaCl, neat) 1734, 1180 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{18}O_3$, 247.1334. Found 247.1322. GC analysis (G-TA, 140 °C, 3.0 mL/min; *trans* (tr (minor)=78.9 min, tr (major)=76.2 min), *cis* (tr (minor)=84.5 min, tr (major)=90.6 min)) gave the enantiomeric composition of the *trans* product: 98% ee, and the *cis* product: 96% ee.

7.1.11. 5,5-Dimethoxy-2-methyl-pentanal (11).

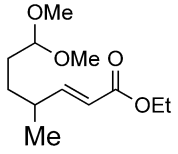


To 5,5-dimethoxy-pentanal (21.05 g, 144.0 mmol) stirred at 0 °C was added *N*,*N*-dimethyl hydrazine (13.12 mL, 172.0 mmol) with continued stirring for 30 min. 50 mL water and 50 mL diethyl ether were added followed by removal of the aq. layer. The organic layer was dried over $MgSO_4$, and concentrated in vacuo affording 23.36 g of product that was used without purification. To a solution of diisopropyl amine (4.78 g, 47.2 mmol) in 50 mL tetrahydrofuran at −78 °C was added 1.5 M *n*-butyllithium (31.9 mL, 47.2 mmol). The mixture was warmed to 0 °C over 5 min and then cooled to −78 °C. *N*′-(5,5-Dimethoxy-pentylidene)-*N*-*N*-dimethyl-hydrazone (5.08 g, 27.0 mmol) in 50 mL tetrahydrofuran was then added and the mixture was stirred at 0 °C for 2 h, then cooled to −78 °C. Methyl iodide (5.75 g, 40.5 mmol) was then added and the solution stirred for 1 h at this temperature. The solution was then warmed to room temperature and stirred for 1 h. The solution was poured into 200 mL of a 2:1 solution of H_2O/methylene chloride. 50 mL saturated sodium bicarbonate solution was added and the layers separated. The aq. layer was washed with 50 mL (2×) methylene chloride. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to afford 4.65 g of product (27.0 mmol, 85%). R_f=0.10 (3:1, hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (d, 1H, J=6.4 Hz), 4.30 (t, 1H, J=5.5, 5.8 Hz), 3.24 (d, 6H, J=1 Hz), 2.64 (s, 6H), 2.31 (m, 1H), 1.40 (m, 2H), 1.56 (m, 2H), 1.00 (d, 3H, J=6.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 143.3, 104.4, 52.6, 52.5, 43.2, 36.8, 30.1, 30.0, 19.0.

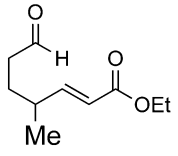


N′-(5,5-Dimethoxy-2-methyl-pentylidene)-*N*,*N*-dimethyl-hydrazine (1.50 g, 7.4 mmol) was dissolved in 100 mL tetrahydrofuran and 100 mL 0.1 M pH=7 phosphate buffer (95 mL H_2O, 2.85 mL 1 M Na_2HPO_4, 2.12 mL 1 M NaH_2PO_4). Sodium periodate (8.5 g, 40.0 mmol) was added and the mixture stirred overnight. The solution was then diluted with 100 mL diethyl ether and the layers separated. The aq. layer was then extracted with 100 mL diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Column chromatography (4:1, hexane/diethyl Ether) afforded 0.4 g of product as a clear oil (2.5 mmol, 34%). R_f=0.38 (3:1, hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 4.29 (t, 1H, J=5.5 Hz), 3.25 (s, 6H), 2.29 (m, 1H), 1.72 (m, 1H), 1.56 (m, 1H), 1.33 (m, 1H), 1.04 (d, 3H, J=7.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 204.5, 104.1, 52.7, 45.8, 29.7, 25.2, 13.3.

7.1.12. 4-Methyl-7-oxo-hept-2-enoic acid ethyl ester (12).



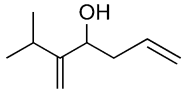
(Carboethoxymethylene) triphenyl-phosphorane (0.98 g, 2.8 mmol) was dissolved in 20 mL tetrahydrofuran and 11 (0.37 g, 2.3 mmol) was added. The reaction was stirred overnight. The reaction was concentrated and subjected directly to column chromatography (4:1, hexane/ethyl acetate) to afford 0.43 g of product as a clear oil (1.9 mmol, 81%). R_f=0.59 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (m, 1H), 5.76 (d, 1H, J=15.8 Hz), 4.31 (t, 1H, J=5.3 Hz), 4.16 (q, 2H, J=7.1 Hz), 3.28 (s, 6H), 2.29 (m, 1H), 1.56 (m, 2H), 1.41 (m, 2H), 1.26 (t, 3H, J=7.1 Hz), 1.04 (d, 3H, J=6.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.7, 153.8, 120.0, 104.4, 60.1, 52.8, 52.7, 36.3, 30.7, 30.2, 19.4, 14.2.



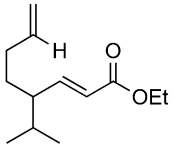
7,7-Dimethoxy-4-methyl-hept-2-enoic acid ethyl ester

(0.53 g, 2.3 mmol) was dissolved in 10 mL dichloromethane. H_2O (1 mL), triflouroacetic acid (0.5 mL) were added and the solution stirred overnight. Aq. sodium bicarbonate (20 mL) was added and the layers separated. The aq. layer was extracted with 10 mL diethyl ether. The combined organics were dried over $MgSO_4$, concentrated in vacuo, and subjected to column chromatography (95:5, hexane/ethyl acetate) affording 0.31 g of product as a clear oil (1.7 mmol, 72%). R_f=0.36 (9:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 6.76 (dd, 1H, J=15.8, 8.1 Hz), 5.76 (d, 1H, J=15.8 Hz), 4.15 (q, 2H, J=7.0 Hz), 2.41 (t, 2H, J=8.1 Hz), 2.33 (m, 1H), 1.68 (m, 2H), 1.25 (t, 3H, J=7.2 Hz), 1.05 (d, 3H, J=6.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.6, 166.5, 152.7, 120.7, 60.2, 41.4, 35.8, 27.7, 19.3, 14.1; IR (NaCl, neat) 1719, 1270, 1179 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}O_3$, 185.1177. Found 185.1179.

7.1.13. 4-Isopropyl-octa-2,7-dienoic acid ethyl ester (13).

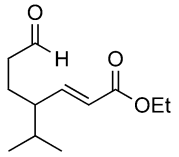


Isopropylacrolein (4.00 g, 40.8 mmol) was dissolved in 100 mL tetrahydrofuran and chilled to −78 °C. Allyl magnesium chloride (20.3 mL, 40.8 mmol, 2.0 M solution in tetrahydrofuran) was then added and the solution stirred for 1 h at −78 °C. 10 mL of 10% v/v HCl was then added and the solution warmed to room temperature. The layers were separated and the aq. layer was extracted with 20 mL Et_2O, dried with $MgSO_4$ and concentrated in vacuo. Column chromatography afforded 4.80 g of product as a colorless oil (34.2 mmol, 84%). R_f=0.54 (3:1, hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (m, 1H), 5.12 (m, 2H), 5.05 (dd, 1H, J=1.1, 1.1 Hz), 4.91 (s, 1H), 4.12 (m, 1H), 2.40 (m, 1H), 2.25 (m, 2H), 1.64 (d, 1H, J=4.0 Hz), 1.06 (d, 3H, J=6.8 Hz), 1.04 (d, 3H, J=7.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.1, 134.8, 118.1, 107.1, 72.9, 40.9, 30.4, 23.1, 22.5.



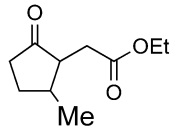
Potassium hydride (1.16 g, 29 mmol) was dissolved in 50 mL dioxane and 6-methyl-5-methylene-hept-1-en-5-ol (2.0 g, 14.0 mmol) in 50 mL dioxane was added. The solution was heated at 100 °C overnight. 50 mL of 10% v/v HCl and 100 mL Et_2O were then added. The layers were separated, the organics dried over $MgSO_4$, and concentrated to approx. 100 mL. (carboethoxymethylene) triphenylphosphorane (5.0 g, 14.4 mmol) was added and the solution stirred overnight. Silica gel (15 g) was added and the mixture concentrated and subjected to column chromatography affording 1.20 g of the desired product (5.7 mmol, 41%). R_f=0.56 (9:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (dd, 1H, J=9.9, 15.8 Hz), 5.76 (m, 2H), 4.97 (m, 2H), 4.81 (q, 2H, J=7.3 Hz), 1.83–2.10 (m, 3H), 1.67 (m, 1H), 1.56 (m, 1H), 1.40 (m, 1H), 1.29 (t, 3H, J=7.0 Hz), 0.89 (d, 3H, J=7.0 Hz), 0.85 (d, 3H, J=7.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.4, 151.2, 138.3, 122.3, 114.6, 60.2, 48.6, 31.7, 31.7, 30.7, 20.7, 19.2, 14.4.

7.1.14. 4-Isopropyl-7-oxo-hept-2-enoic acid ethyl ester (14).



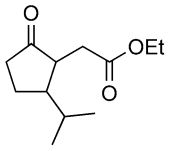
13 (0.50 g, 2.4 mmol), was dissolved in 8 mL *t*-BuOH and 2 mL H_2O followed by the addition of trimethylamine *N*-oxide dihydrate (0.20 g, 2.6 mmol), pyridine (0.19 g, 2.4 mmol), OsO_4 (1.45 mL, 0.24 mmol, 4 wt % solution in H_2O) and stirred at 80 °C overnight. Et_2O (50 mL) was added and the layers separated. The organics were dried over $MgSO_4$, concentrated in vacuo and dissolved in 50 mL toluene. Lead tetraacetate (1.37 g, 3.1 mmol) was then added followed by stirring for two h. Silica gel (2.0 g) was then added followed by concentrating in vacuo. Column chromatography afforded 0.17 g of the desired product (0.80 mmol, 34%). R_f=0.20 (3:1, hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 6.67 (dd, 1H, J=15.7, 9.9 Hz), 6.74 (d, 1H, J=15.7 Hz), 4.16 (q, 2H, J=7.0 Hz), 2.36 (m, 2H), 1.89 (m, 2H), 1.62 (m, 2H), 1.26 (t, 3H, J=7.0 Hz), 0.89 (d, 3H, J=6.6 Hz), 0.85 (d, 3H, J=7.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.5, 166.0, 150.0, 123.0, 60.3, 48.6, 42.0, 31.8, 23.7, 20.5, 19.2, 14.3; IR (NaCl, neat) 1719, 1254, 1164 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{20}O_3$, 213.1491. Found 213.1498.

7.1.15. (2-Methyl-5-oxo-cyclopentyl)-acetic acid ethyl ester (15).



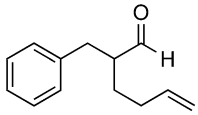
According to the general procedure, 12 (0.020 g, 0.11 mmol), catalyst A (0.008 g, 0.022 mmol), and KHMDS (0.044 mL, 0.022 mmol, 0.5 M in tetrahydrofuran), produced the product as a 50:50 mixture of inseparable diastereomers. Purification by column chromatography (95:5, hexane/diethyl ether) afforded 15 (18.0 mg, 90%). R_f=0.43 (3:1, hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11–4.20 (m, 4H), 2.50–2.77 (m, 4H), 2.36 (m, 1H), 1.90–2.30 (m, 8H), 1.73 (m, 1H), 1.42 (m, 2H), 1.21–1.26 (m, 6H), 1.12 (d, 3H, J=6.0 Hz), 0.84 (d, 3H, J=7.2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 218.9, 218.5, 172.6, 172.1, 60.6, 53.1, 50.6, 37.6, 37.0, 34.1, 32.7, 32.2, 30.3, 29.7, 27.9, 19.1, 14.8, 14.1; IR (NaCl, neat) 1736, 1186 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}O_3$, 185.1177. Found 185.1183. GC analysis (G-TA, 90 °C, 2.5 mL/min; *trans* (tr (minor)=44.8 min, tr (major)=43.3 min), *cis* (tr (minor)=48.9 min, tr (major)=49.6 min)) gave the enantiomeric composition of the *trans* product: (90% ee), and the *cis* product: (95% ee).

7.1.16. (2-Isopropyl-5-oxo-cyclopentyl)-acetic acid ethyl ester (16).



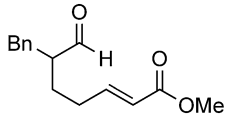
According to the general procedure, 14 (0.020 g, 0.094 mmol), catalyst A (0.007 g, 0.019 mmol), and KHMDS (0.036 mL, 0.018 mmol, 0.5 M in tetrahydrofuran), produced the product as a 53:47 mixture of inseparable diastereomers. Purification by column chromatography (95:5, hexane/diethyl ether) afforded 16 (19.0 mg, 95%). R_f=0.49 (3:1, hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06–4.15 (m, 4H), 2.78 (q, 1H, J=7.2 Hz), 2.59 (m, 2H), 2.53 (m, 1H), 2.35 (m, 2H), 2.15–2.24 (m, 5H), 1.99 (m, 2H), 1.86 (m, 1H), 1.76 (m, 2H), 1.64 (m, 1H), 1.49 (m, 1H), 1.22 (q, 6H, J=7.0 Hz), 0.96 (d, 3H, J=6.8 Hz), 0.92 (d, 3H, J=6.6 Hz), 0.87 (d, 3H, J=6.8 Hz), 0.73 (d, 3H, J=6.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 219.4, 219.3, 172.3, 172.0, 60.7, 60.6, 48.8, 48.4, 47.5, 44.9, 37.2, 36.6, 33.4, 30.5, 29.5, 27.8, 22.4, 22.3, 21.9, 21.2, 18.9, 17.5, 14.1; IR (NaCl, neat) 1736, 1372, 1252, 1183 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{20}O_3$, 213.1494. Found 213.1491. GC analysis (G-TA, 90 °C, 2.0 mL/min; *trans* (tr (minor)=123.1 min, tr (major)=116.0 min), *cis* (tr (minor)=151.8 min, tr (major)=141.8 min)) gave the enantiomeric composition of the *trans* product: (84% ee), and the *cis* product: (96% ee).

7.1.17. 2-Benzyl-hex-5-enal (17).



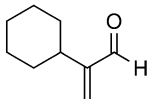
To hydrocinnamaldehyde (8.80 g, 65.6 mmol) stirred at 0 °C was added *N*,*N*-dimethyl hydrazine (4.73 mL, 78.7 mmol) with continued stirring for 30 min. 50 mL water and 50 mL diethyl ether were added followed by removal of the aq. layer. The organic layer was dried over $MgSO_4$, and concentrated in vacuo affording 10.00 g of product that was used without purification. To a solution of LDA (12.5 mmol) in 30 mL of tetrahydrofuran at 0 °C was added hydrocinnamaldehyde *N*,*N*-dimethylhydrazone (2.00 g, 11.3 mmol) in 10 mL of tetrahydrofuran. The resulting suspension was allowed to stir for 2 h at 0 °C, at which time 4-bromo-1-butene (1.69 g, 12.5 mmol) was added. After warming to room temperature the reaction mixture was stirred for an additional 12 h. Aq. workup afforded the crude alkylated hydrazone. The hydrazone was dissolved in 50 mL acetone and 10 mL water, and 12 g of amberlyst-15 was added. The mixture was stirred overnight. Solution was then filtered and subject to column chromatography (95:5, hexane/ethyl acetate) To afford 0.41 g of pure product (2.2 mmol, 19%). R_f=0.42 (9:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (d, 1H, J=2.2 Hz), 7.24 (m, 5H), 5.73 (m, 1H), 5.01 (m, 2H), 2.97 (m, 1H), 2.71 (m, 2H), 2.09 (m, 2H), 1.78 (m, 1H), 1.57 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 204.4, 138.6, 137.5, 128.9, 128.5, 126.4, 115.5, 52.6, 35.0, 30.1, 27.6; IR (NaCl, neat) 3064, 3028, 3977, 2926, 2855, 2715, 1728, 1641, 1603, 1497, 1454.

7.1.18. 6-Benzyl-7-oxo-hept-2-enoic acid methyl ester (19).

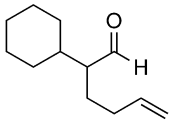


To [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloro(phenylmethylene)-(tricyclohexyl phosphine) ruthenium] (0.045 g, 0.053 mmol) in 10 mL methylene chloride was added methyl acrylate (0.915 g, 10.6 mmol) and 17 (0.200 g, 1.06 mmol). The solution was heated to 40 °C and stirred overnight. Silica gel (1 g) was then added and the solvent removed in vacuo. Column chromatography (9:1, hexane/ethyl acetate) yielded 0.176 g product (0.72 mmol, 67%). R_f=0.40 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, 1H, J=1.8 Hz), 7.23 (m, 5H), 6.88 (m, 1H), 5.79 (d, 1H, J=15.4 Hz), 3.72 (s, 3H), 3.03 (m, 1H), 2.70 (m, 2H), 2.22 (m, 2H), 1.83 (m, 1H), 1.61 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 203.7, 166.8, 147.8, 138.1, 128.9, 128.7, 126.6, 121.7, 52.5, 51.5, 35.1, 29.5, 26.6; IR (NaCl, neat) 1724, 1657, 1436, 1274, 1208 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{18}O_3$, 247.1334. Found 247.1327.

7.1.19. 2-Cyclohexyl-hex-5-enal (20).



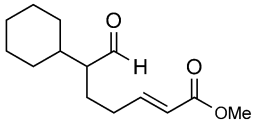
2-Cyclohexyl-ethanal (5.50 g, 43.6 mmol), formaldehyde (4.40 mL, 47.9 mmol, 30% in H_2O), piperidine (0.22 mL, 2.2 mmol), and concentrated HCl (0.087 mL, 1.1 mmol) were added to a flask equipped with a reflux condenser. The solution was heated overnight at 80 °C. Steam distillation followed by extraction with diethyl ether and standard aq. workup afforded 4.0 g of product (29.0 mmol, 66%).[13] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H), 6.17 (s, 1H), 5.90 (s, 1H), 2.42 (m, 1H), 1.65–1.74 (m, 5H), 1.25–1.39 (m, 2H), 1.03–1.19 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.3, 155.3, 132.5, 35.8, 32.0, 26.4, 26.2.



A flame dried flask was charged with cyclohexylacrolein (0.77 g, 5.6 mmol) and 10 mL by tetrahydrofuran followed by cooling to −78 °C. Allyl magnesium chloride (3.1 mL, 6.1 mmol, 2 M in tetrahydrofuran) was added and the reaction stirred for 1 h. The reaction was quenched 10% HCl and extracted with ether. The organics were dried over $MgSO_4$, and concentrated in vacuo. The crude alcohol in 5 mL dioxane was then added to potassium hydride (0.45 g, 11.1 mmol) in 50 mL dioxane and heated overnight at

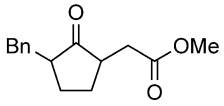
110 °C. Standard aq. workup and column chromatography (95:5, hexane/diethyl ether) afforded the 0.55 g product as a clear oil (3.1 mmol, 55%). R_f=0.63 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (d, 1H, J= 3.3 Hz), 5.72 (m, 1H), 4.97 (m, 2H), 1.86–2.13 (m, 3H), 1.53–1.76 (m, 8H), 1.00–1.28 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.4, 137.7, 115.1, 57.0, 38.3, 31.7, 30.8, 30.1, 26.5, 26.3, 25.1.

7.1.20. 6-Cyclohexyl-7-oxo-hept-2-enoic acid methyl ester (21).



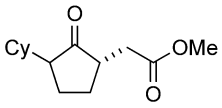
A flame dried flask was charged with [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloro(phenylmethylene)-(tricyclohexyl phosphine) ruthenium] (0.049 g, 0.055 mmol) and 5 mL dichloromethane. 20 (0.20 g, 1.1 mmol) and methyl acrylate (1.0 mL, 11.1 mmol) were added and the solution was heated to 40 °C for 72 h. Silica gel (1 g) was then added and the solvent removed in vacuo. Column chromatography (9:1, hexane/ethyl acetate) yielded 0.225 g product (0.95 mmol, 85%). R_f=0.36 (3:1, hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, 1H, J=3.3 Hz), 6.89 (m, 1H), 5.80 (d, 1H, J=15.4 Hz), 3.70 (s, 1H), 2.03–2.60 (m, 3H), 1.54–1.84 (m, 8H), 1.02–1.30 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 204.7, 166.7, 148.1, 121.4, 56.9, 51.4, 38.3, 30.8, 30.2, 30.1, 26.4, 26.3, 24.1; IR (NaCl, neat) 1724, 1658, 1448; HRMS (FAB+) calcd for $C_{14}H_{23}O_3$, 239.1647. Found 239.1646.

7.1.21. (3-Benzyl-2-oxo-cyclopentyl)-acetic acid methyl ester (22).



According to the general procedure, 19 (0.010 g, 0.043 mmol), catalyst A (0.008 g, 0.022 mmol), and KHMDS (0.043 mL, 0.022 mmol, 0.5 M in tetrahydrofuran), produced the product as a 95:5 mixture of inseparable diastereomers. Purification by column chromatography (95:5, hexane/diethyl ether) afforded 22 (9.5 mg, 95%). R_f=0.40 (3:1, hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.28 (m, 10H), 3.66 (s, 3H), 3.65 (s, 3H), 3.15 (dd, 1H, J=13.8, 4.0 Hz, *trans*), 3.04 (q, 1H, J=9.2 Hz, *cis*), 2.42–2.76 (m, 8H), 2.27–2.35 (m, 2H), 2.03–2.18 (m, 3H), 1.93 (m, 1H), 1.74 (m, 1H), 1.40–1.55 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 219.5, 219.2, 172.5, 172.5, 139.7, 129.0, 128.9, 128.4, 126.3, 126.2, 51.8, 51.8, 50.7, 49.0, 46.0, 45.0, 36.0, 35.9, 34.1, 34.0, 27.2, 26.5, 25.6; IR (NaCl, neat) 1735, 1437, 1261, 1196, 1175 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{18}O_3$, 247.1334. Found 247.1332. HPLC analysis (AS, 99:1, Hex/*i*PrOH, 0.2 mL/min; *trans* (tr (minor)=130.8 min, tr (major)=82.2 min.), *cis* (tr (minor)=104.4 min, tr (major)=111.7 min.)) gave the enantiomeric composition of the *trans* product: <5% ee, and the *cis* product: <5% ee.

7.1.22. (3-cyclohexyl-2-oxo-cyclopentyl)-acetic acid methyl ester (23).[14]



According to the general procedure, 21 (0.020 g, 0.084 mmol), catalyst A (0.005 g, 0.017 mmol), and KHMDS (0.034 mL, 0.017 mmol, 0.5 M in tetrahydrofuran), produced the product as a 3.5:96.5 mixture of inseparable diastereomers. GC analysis (BDM, 3.0 mL/min; *trans* (tr (minor)=53.8 min, tr (major)=51.5 min), *cis* (tr (minor)=49.7 min, tr (major)=47.8 min)) gave the enantiomeric composition of the *trans* product: 20% ee, and the *cis* product: 6% ee.

References and notes

1. (a) Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129–1131. (b) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892–2893.
2. The Stetter reaction: (a) Stetter, H.; Kuhlmann, H. In Paquette, L. A., Ed.; Organic Reactions; Wiley: New York, 1991; Vol. 40, pp 407–496. (b) Stetter, H.; Kuhlmann, H. *Chem. Ber.* **1976**, *109*, 2890–2896.
3. Intramolecular Stetter: Ciganek, E. *Synthesis* **1995**, 1311–1314.
4. Enantioselective Intramolecular Stetter: (a) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899–1920. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res* **2004**, *37*, 534–541.
5. (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299. (b) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934–1936. (c) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877.
6. Kinetic Resolution Reviews: (a) Kagan, H. B.; Fiaud, J. C. In Eliel, E. L., Fiaud, J. C., Eds.; Top. Stereochem.; Wiley: New York, 1988; Vol. 18, pp 249–330. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26. (c) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446.
7. Vedejs has coined and defined the term parallel kinetic resolution. Included in this definition is the following statement: 'Another PKR application is inherent in reactions where two enantiomers of a racemic substrate are selectively converted into separable, chiral products (regioisomers, diastereoisomers, etc.) by a single chiral reagent or catalyst.' See: Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584–2585. Also see: (a) Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885–888. (b) Dehli, J. R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 265–370.
8. Claus, R. E.; Schreiber, S. L.; Organic Syntheses Collective Volume VII; 1990, 168.
9. Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8274–8277.
10. Brown, H. C.; Weissman, S. A.; Perumal, P. T.; Dhokte, U. P. *J. Org. Chem.* **1990**, *55*, 1217–1223.
11. Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872–882.

12. Toste, F. D.; Chatterjee, A. K.; Grubbs, R. H. *Pure Appl. Chem.* **2002**, *74*, 7–10.
13. Riehs, G.; Urban, E. *Tetrahedron* **1996**, *52*, 1221–1230.
14. Ryu, I.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2002**, *124*, 3812–3813.
15. Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849–7854.

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Synthesis of 2-methyl-4-methoxydiphenylamine by palladium catalyzed C–N coupling—high synthetic versatility by use of a flexible catalytic system

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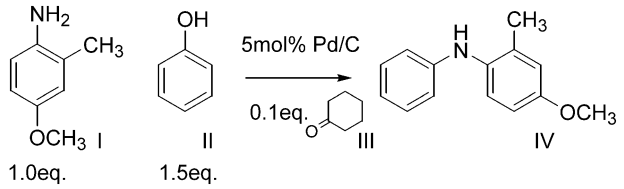
Abstract—The synthetic versatility of the Buchwald–Hartwig Amination is demonstrated by the synthesis of the industrially important intermediate 2-methyl-4-methoxydiphenylamine. Using four routes differing in the choice of the starting materials, the diarylamine could be synthesized in excellent yields, however, each reaction required a different combination of ligand, base and solvent. This new approach is compared to established industrial routes.

1. Introduction

Requests for the manufacture of highly substituted anilines occur with increasing frequency and intensity in fine chemical business these days. Especially, in the exciting fields of functional dyes, xerographic or electronically conducting materials, we frequently observe the structural motif of the diphenylamines.

While the past 150 years of organic synthesis have brought forth a considerable amount of techniques to set up this structure,[1] still continuously uncommon synthetic approaches are revealed. For example, the title compound 2-methyl-4-methoxydiphenylamine **IV** (MMDPA) can be produced by a transfer hydrogenation as demonstrated by the Mitsui company[2] (Scheme 1).



Scheme 1. Mitsui process to generate MMDPA **IV**.

MMDPA **IV** itself is a common intermediate in fine chemical industry and has lately been cited frequently in the context of the aminofluoran dye family, a dye class useful for thermographic and pressure sensitive recording.[3]

Although not being active in this field of application ourselves, we became aware of this product MMDPA **IV**, since it in principle could be made by application of the Buchwald–Hartwig Amination,[4] a technology that the fine chemical department of Lanxess, formerly Bayer Chemicals, has identified to be one of the contemporary key chemical technologies in organic synthesis.[5,17]

We therefore were eager to show that MMDPA **IV** could be made by use of this technology (Scheme 2), but also, since this technology involves the use of expensive transition metals and complex phosphine ligands, whether it can be made economically.

2. Results and discussion

Scheme 2 shows four possible approaches to MMDPA **IV** both from bromo- and chloroarenes **VIII** and **VII** as starting materials, but also by coupling of the corresponding functionalized aniline **I**. The possibility to use different combinations of starting materials represents a charming feature of this new technology, since the starting materials could in principle be picked depending on their availability and price on the market. For the rest of this paper, the four approaches will be abbreviated as ways A to D.

Keywords: Buchwald–Hartwig Amination; Palladium; Homogeneous catalysis; Diarylamines.
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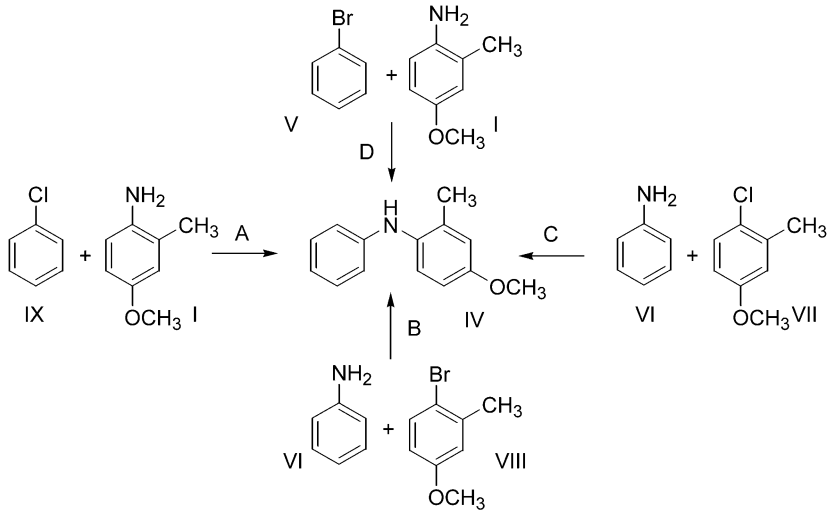


Scheme 2. Four possible ways to MMDPA **IV** by C–N coupling.

To check the validity of our approach, we set up a reaction screening to make MMDPA **IV**. The reactions were run in a block with either 48 or 12 parallel reactions[6] under argon. Generally, we run these screenings using an internal standard, therefore allowing the determination of GC yields. However, in our experience the results of a screening in the early phase, that is, with no prior experience in the reaction observed, can be misleading by judgement of the GC yield. We often observed that the conversion of the starting material gives a better first overview of a new reaction. Since we always repeat the selected results on scale and isolate the products, we can ensure the correlation of conversion and yield in the cases we discuss here.

The palladium source we used was industrial grade palladium–dibenzylideneacetone ($Pd_2(dba)_3$). To our experience, this quality of $Pd^{[0]}$-complex guarantees best results concerning reproducibility in the screening.

In addition to palladium, a phosphine ligand is necessary to catalyze the reaction. The current literature reveals numerous structurally different phosphines that lead to completely different catalysts with different activity. We therefore screened up to eight ligands for this transformation as illustrated in Scheme 3.

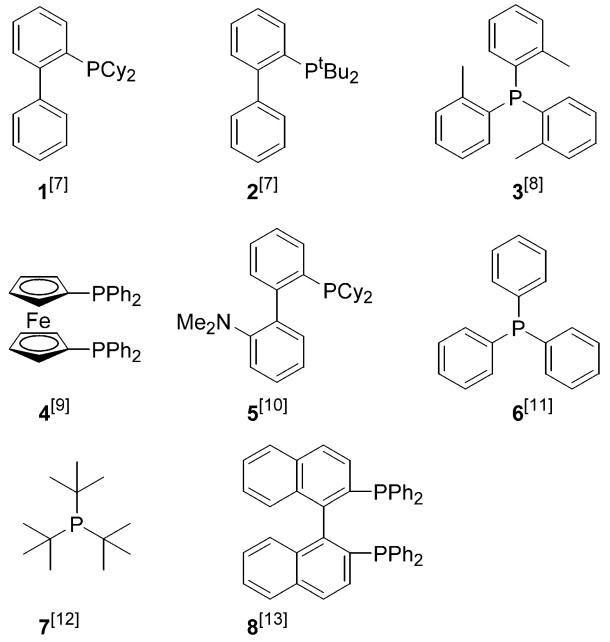
Another important factor is the stoichiometric use of a base that is necessary to run this reaction. We chose from a set of up to six bases, most of them have previously been reported as being rather effective. The bases used were cesium carbonate,[7,14] potassium carbonate,[11] sodium carbonate, cesium fluoride, potassium phosphate[7,15] and sodium *tert*-butylate.[8]

The solvent may play an important role in Buchwald–Hartwig Aminations, examples in the current literature mostly focus on either toluene or dioxane. However, several examples were reported in which DMF, NMP, alcohols or even aqueous media were successful.[4a] In this work, we restricted ourselves to either toluene, xylenes or aniline.

The first reaction to be examined was system B, the condensation of aniline **VI** and 4-methoxy-2-methylbromobenzene **VIII** in a toluene solution at 110 °C (Fig. 1).

One quickly notes that ligand **5** shows very high conversion of the starting material with several inorganic bases. Also ligand **8** gives high conversions with the very common C–N coupling bases Cs_2CO_3 and NaO^tBu.

We then tested the same reaction under different conditions (i.e., in refluxing aniline instead of a toluene solution). Here, aniline serves as a solvent as well as a reagent for this transformation. Its excess and the elevated temperature are likely to have a positive influence on the conversion. We restricted ourselves to an array of four ligands and three bases (Fig. 2).



Scheme 3. Typical phosphine ligands[7–13] for Buchwald–Hartwig Aminations used in the screening.

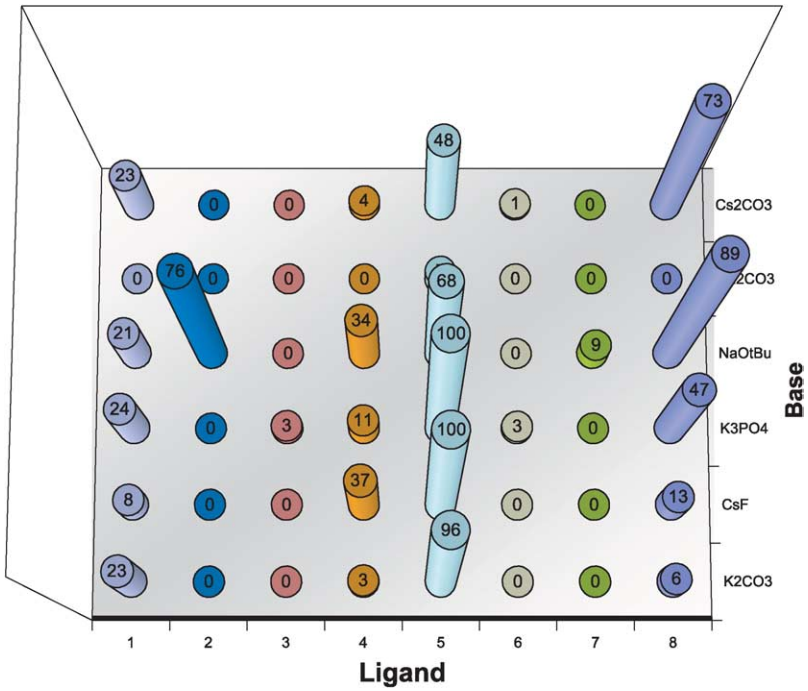


Figure 1. Screening of system B in toluene at 110 °C. Reported is the conversion of starting material. Reactions were run with 1 equiv aniline, 1 equiv methoxy-2-methylbromobenzene, 1.4 equiv base, 0.5 mol% of $Pd_2(dba)_3$ and 2 mol% of phosphine (1 mol% of phosphine for **4** and **8**).

Under these conditions one can observe full conversion of starting material with simple PPh_3 **6** using Cs_2CO_3 as base. In fact, Cs_2CO_3 also gives full conversion using Buchwald's ligand **5** and BINAP **8**.

Since especially the results with ligand **6** seemed interesting from a scale up perspective, we repeated the reaction on the level of 1 mol of starting material and were able to isolate a yield of 93% of MMDPA **IV** after distillation.

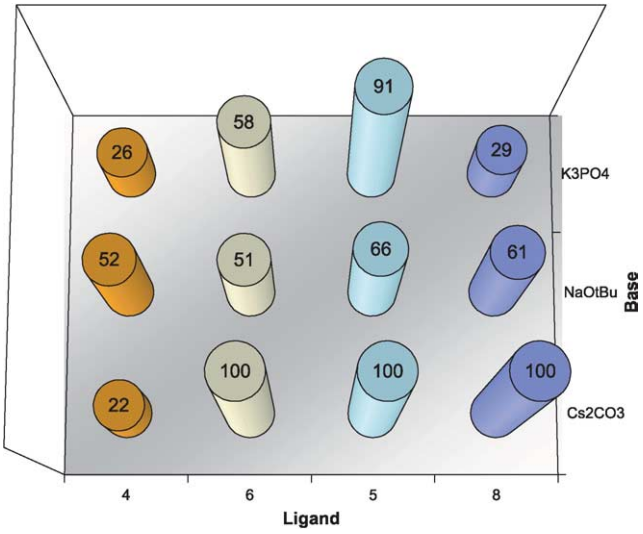


Figure 2. Screening of system B in aniline at 184 °C. Reported is the conversion of starting material. Reactions were run using 1 equiv aniline, 1 equiv methoxy-2-methylbromobenzene, 1.4 equiv base, 0.5 mol% of $Pd_2(dba)_3$ and 2 mol% of phosphine **5**, 1 mol% of phosphine **4** and **8**, 4 mol% of phosphine **6**.

When we looked at system C, in which aniline **VI** is reacted with 4-methoxy-2-methyl-chlorobenzene **VII**, the current literature suggests to expect worse results compared to the corresponding arylbromide coupling.[4] This could be confirmed when running the screening under standard conditions in toluene solution at 110 °C (Fig. 3).

However, still two results of the screening may be considered as good enough for further elaboration. Again the known combination of Buchwald ligand **5** with the strong base sodium *tert*-butylate creates an efficient system, but even better conversion was observed using $P(^tBu)_3$ **7**[17] in combination with potassium phosphate.

Again we used the possibility of aniline of serving both as solvent and amine part for the reaction and ran a smaller screening in refluxing aniline (Fig. 4).

We observed an increase in activity due to the changed media and temperature, with highest conversions using the combination of Buchwald ligand **5** either with potassium phosphate or cesium carbonate as base.

One of the results with ligand **5** and potassium phosphate was confirmed on the level of 1 mol of starting material. Similar to the case of aryl bromide **VIII**, a yield of 96% of the desired MMDPA **IV** could be isolated after distillation.

When regarding system D, in which 4-methoxy-2-methyl-aniline **I** can be used as one of the starting materials, one should expect smooth conversion to MMDPA **IV**. A rather electron rich aniline is coupled with a moderately active aryl bromide, therefore, constituting ideal conditions for a C–N coupling (Fig. 5).

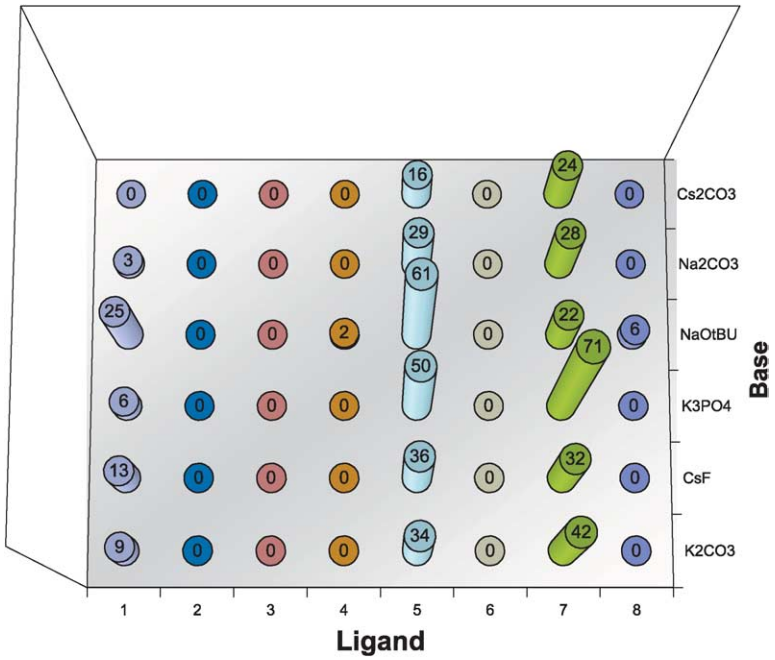


Figure 3. Screening of system C in toluene at 110 °C. Reported is the conversion of starting material. Reactions were run with 1 equiv aniline, 1 equiv methoxy-2-methylchlorobenzene, 1.4 equiv base, 0.5 mol% of $Pd_2(dba)_3$ and 2 mol% of phosphine (1 mol% of phosphine for **4** and **8**).

Since a positive effect of high temperatures for this reaction was noted in previous experiments, xylenes were chosen as the solvent and reactions were run at 120 °C. The two ligands **5** and **8** gave very high conversions with all three bases we examined, therefore all these combinations could be picked for a scale-up. Important to note is the good result again for PPh_3 **6** using sodium *tert*-butylate as base, therefore rendering another rather simple approach for MMDPA **IV**. Since, the combination of BINAP **8** and cesium carbonate represented the best screening result, we chose this one for scale up.

Reduction of the catalyst loading quickly showed that 1 mol% of catalyst is actually needed (Table 1) when reaction time was fixed to be 24 h. Lower amounts of catalyst resulted in incomplete conversion of the starting material.

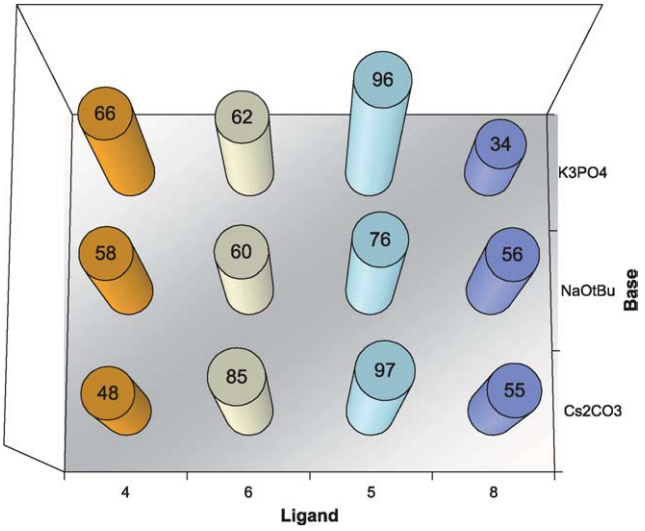


Figure 4. Screening of system C in aniline at 184 °C. Reported is the conversion of starting material. Reactions were run using 1 equiv aniline, 1 equiv methoxy-2-methylchlorobenzene, 1.4 equiv base, 0.5 mol% of $Pd_2(dba)_3$ and 2 mol% of phosphine **5**, 1 mol% of phosphine **4** and **8**, 4 mol% of phosphine **6**.

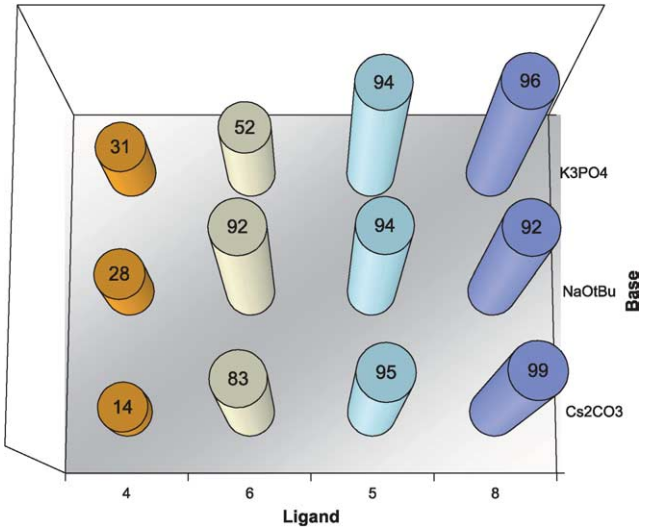


Figure 5. Screening of system D: 1 equiv bromobenzene, 1 equiv 4-methoxymethylaniline, 1.4 equiv base, xylenes, 120 °C, 24 h. Reported is the conversion of starting material. Reactions were run using 0.5 mol% of $Pd_2(dba)_3$ and 2 mol% of phosphine **5**, 1 mol% of phosphine **4** and **8**, 4 mol% of phosphine **6**.

Table 1. Reduction of catalyst loading in system D: 1 equiv bromobenzene, 1 equiv 4-methoxymethylaniline, ratio of $Pd_2(dba)_3$ to BINAP **8**:1:2, 1.4 equiv Cs_2CO_3, xylenes, 120 °C, 24 h

Entry	System	Catalyst concentration (mol%)	Conversion (%)
1	D	1	100
2	D	0.1	9
3	D	0.05	2
4	D	0.01	0

On the scale of 1 mol of reactants, using 0.5 mol% of $Pd_2(dba)_3$ with BINAP **8** as ligand and cesium carbonate as base but toluene instead of xylenes as solvent at reflux, a 95% yield of MMDPA **IV** was isolated.

The final combination of starting materials is denoted as system A in Scheme 2. The coupling of chlorobenzene **IX** and 4-methoxy-2-methylaniline **I** represents a somewhat more difficult example of a Buchwald–Hartwig Amination. It can nevertheless be regarded as the most attractive combination from an economical point of view. When checking the availability and price of all starting materials encountered so far, this combination will lead to the lowest material cost.

We therefore, conducted a screening run in xylenes at 120 °C (Fig. 6).

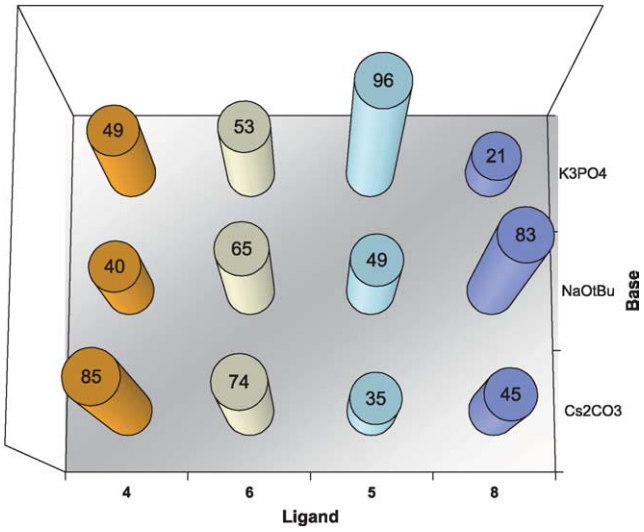


Figure 6. Screening of system A in xylenes at 120 °C. Reported is the conversion of starting material. Reactions were run using 1 equiv chlorobenzene, 1 equiv methoxy-2-methylaniline, 1.4 equiv base, 0.5 mol% of $Pd_2(dba)_3$ and 2 mol% of phosphine **5**, 1 mol% of phosphine **4** and **8**, 4 mol% of phosphine **6**.

While in general this system A gave several combinations with moderate to good yields, using ligand **5** together with potassium phosphate lead to nearly full conversion of the starting materials in the screening.

The result could be confirmed when running the reaction on the scale of 1 mol of starting material. A total of 95% of MMDPA **IV** was isolated after distillation of the crude mixture.

To complete the picture we attempted to run the reaction in a heterogeneous fashion using palladium on charcoal, cesium carbonate as base and PPh_3 **6** as ligand. We deliberately chose a ligand that was favourable rather by material cost than by chemical performance. This allowed us to set up a reaction model that was comparable to the original synthesis by Mitsui (Scheme 1) from an economical point of view. In that case, a catalyst loading of 5% (w/w) of 5% Pd/C[16] with ligand **6** present in the system resulted in poor conversion of a maximum of 12% using cesium carbonate as base. Therefore, we concluded that a heterogeneous version of this amination reaction could not compete with the homogeneous counterpart.

3. Summary

While generally speaking the cleverly designed transfer hydrogenation published by Mitsui (Scheme 1) is hard to match, we were able to generate a set of four reaction procedures that allow the production of MMDPA **IV** on the medium scale at high yield. These four procedures are summarized in Table 2.

From our point of view, a true but often underestimated strength of the Buchwald–Hartwig Amination becomes obvious in this study: not only the possibility to perform new chemical transformations that would be difficult to do otherwise, this new methodology also allows for a synthetic flexibility unknown from other chemical transformations to date. This adds a new freedom to synthesis which will help to tackle today's demanding targets from a chemical point of view.

4. Experimental

4.1. General

Industrial grade $Pd_2(dba)_3$ was purchased from Umicore. Industrial grade Cesiumcarbonate was purchased from Chemetall. Industrial grade Potassium phosphate was purchased from Guilani. All other components were

Table 2. Overview of conditions chosen for scale up runs with isolated yields: 1 equiv of arylhalide, 1 equiv of amine, 1.4 equiv of base were used

Entry	System	Conditions	Yield/%
1	A	2 mol% **5**, 0.5 mol% $Pd_2(dba)_3$, K_3PO_4, toluene, 110 °C	95
2	D	1 mol% BINAP **8**, 0.5 mol% $Pd_2(dba)_3$, Cs_2CO_3, toluene, 110 °C	95
3	C	2 mol% **5**, 0.5 mol% $Pd_2(dba)_3$, K_3PO_4, aniline, 184 °C	96
4	B	4 mol% PPh_3 **6**, 0.5 mol% $Pd_2(dba)_3$, Cs_2CO_3, aniline, 184 °C	93

either produced internally or purchased from catalogue companies.

Gas chromatographical analysis was done on a HP 5890 Serie II Gas chromatograph, using nitrogen as carrier (0.6 bar) with a SE 30, 0.32 mm ID, 0.25 mm FD column.

4.1.1. Screenings. Inorganic bases used were ground in a standard laboratory mill and dried under vacuum overnight. The bases were then weighed in individual vials and stored under nitrogen. Screenings were run in H+P Stir Blocks.[6]

The Block was fitted with oven dried 20 ml reaction tubes with magnetic stir bars and septum. The tubes were evacuated and flushed with argon three times via a needle manifold. Stock solutions of the ligands were prepared in Schlenck glassware under argon as 0.2–1.0 M solutions in degassed toluene or aniline. The stock solutions were added to the vials by means of a syringe. Stock solutions of the starting materials and dodecane as internal standard were prepared in degassed solvents (either toluene, xylenes or aniline). $Pd_2(dba)_3$ was added last to the stock solution. This stock solution was distributed by syringe. The bases were added by quickly opening the vials while flushing with argon. The block was heated for the indicated time at the indicated temperature. Heating was then discontinued and the reaction tubes were allowed to cool to 40 °C, diluted with ethylacetate and an aqueous buffer 7 solution (Riedel-de Haen, order no. 33546). Small samples of the organic solution were cleared by filtration over celite and analyzed by GC.

4.1.2. Synthesis of MMDMA according to system A. A 2 l jacketed glass reactor, fitted with reflux condenser, mechanical stirrer and an internal thermometer was heated to 90 °C and flushed with nitrogen for 30 min. The jacket was allowed to cool to room temperature and 113.7 g (99%, 1 mol) of chlorobenzene, 154.0 g (98%, 1.1 mol), 4-methoxy-2-methylaniline and 750 ml of toluene were added. The mixture was degassed with nitrogen for 20 min at room temperature. A slight nitrogen pressure was maintained on the apparatus during the reaction. 7.9 g of ligand **5** (>99%, 20 mmol) together with 4.6 g of $Pd_2(dba)_3$ (>99%, 5 mmol) were added. The apparatus was closed and the catalyst allowed to dissolve by stirring for additional 10 min. K_3PO_4 (232.0 g) (>99%, 1.4 mol) were added and the vessel was heated to a jacket temperature of 125 °C within 40 min. The temperature was maintained for 8 h. The reaction was then cooled to 50 °C and 500 ml of brine were added. The mixture was stirred for 30 min at 50 °C, the stirrer was then turned off and phases allowed to separate for 15 min. The aqueous phase was discharged through the bottom drain and the remaining organic solution concentrated by distillation under reduced pressure until the total volume of the organic phase had reached about 250 ml. The remaining organic solution was the transferred to a smaller setup for high vacuum distillation. The crude was distilled over a 50 cm column filled with 4 mm Raschig rings (approximately eight theoretical plates) at a reflux ratio of 3/1 at 0.3 mbar. The product distilled at 140–150 °C and 204.6 g (>99% by GC, 95% of theoretical yield) were collected and analyzed by GC–MS, ^{13}C and ^{1}H NMR GC–MS: $m/e=213$ (M^+), 198 (M^+-CH_3), 180 ($M^+-CH_3-H_2O$), 167 ($M^+-CH_3-CH_3O$), 154, 128, 77 ($C_6H_5^+$). ^{1}H NMR (400 MHz): $\delta=7.11$–7.21 (m, 3H); 6.68–6.83 (m, 5H); 5.18 (s, br, 1H); 3.79 (s, 3H); 2.21 (s, 3H) ppm. ^{13}C NMR (100 MHz): $\delta=156.2$ (q); 146.2 (q); 134.0 (q); 133.4; 129.2 (2C); 125.0; 118.7; 116.3; 114.7 (2C); 111.8; 55.4 (CH_3O); 18.2 (CH_3) ppm.

4.1.3. Synthesis of MMDMA according to system D. The procedure was repeated in the same apparatus as described in experiment 2 except that 158.6 g (99%, 1 mol) of bromobenzene, 6.7 g (>99%, 10 mmol) of ligand BINAP **8** and 395.2 g (>99%, 1.2 mol) of Cs_2CO_3 were used.

Of the distilled product 204.2 g (>99%, 95% of theoretical yield) were collected and identified as MMDMA by analytical comparison to the product of experiment 2.

4.1.4. Synthesis of MMDMA according to system C. The procedure was repeated in the same apparatus as described in experiment 2 except that 158.2 g (99%, 1 mol) of 4-methoxy-2-methylchlorotoluene were dissolved in 750 ml of aniline. PPh_3 **6** (10.6 g) (99%, 40 mmol) together with 4.6 g of $Pd_2(dba)_3$ (>99%, 5 mmol) were added. K_3PO_4 (254.4 g) (>99%, 1.2 mol) was added last. The mixture was heated with a jacket temperature of 190 °C for 8 h.

Of the distilled product 206.8 g (>99%, 96% of theoretical yield) was collected and identified as MMDMA by analytical comparison to the product of experiment 2.

4.1.5. Synthesis of MMDMA according to system B. The procedure was repeated in the same apparatus as described in experiment 2 except that 205.2 g 4-methoxy-2-methyl-bromotoluene (98%, 1 mol) was dissolved in 750 ml of aniline 7.9 g of ligand **5** (>99%, 20 mmol) together with 4.6 g of $Pd_2(dba)_3$ (>99%, 5 mmol) were added. Cs_2CO_3 (395.2 g) (>99%, 1.2 mol) was added last. The mixture was heated with a jacket temperature of 190 °C for 8 h.

Of the distilled product 200.3 g (>99%, 96% of theoretical yield) were collected and identified as MMDMA by analytical comparison to the product of experiment 2.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.139

References and notes

1. For recent reviews see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem.* **2003**, *115*, 5558–5607. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439.
2. Mitsui Patents: JP61218560, JP 05003867.
3. JP 2002 173607 (Yamada Patents), WO 2000 012513 (Ciba Patents), EP 1998 928794 (CIBA Patents).

4. (a) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626. (b) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim; 2004, ISBN 3-527-30518-1. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146. (d) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (e) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (f) Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (g) Hartwig, J. F. In *Modern Arene Chemistry*; Didier, A, Ed.; Wiley-VCH: Weinheim, 2002; pp 107–168. (h) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organopalladium Chemistry of Organic Synthesis*, 2002; Vol. 1, pp 1051–1096. (i) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209.
5. Rouhi, A. M. *Chem. Eng. News* **2004**, *6*, 62.
6. H+P Labortechnik GmbH, Munich/Germany, http://www.hp-lab.de
7. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.
8. (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem.* **1995**, *107*, 1456. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
9. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.
10. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.
11. U.S. Patent Appl. Publ. US 2001012906, 2001.
12. (a) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. Specialty Chemicals 1998, 18, 10, 445–450.(b) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Teterahedron Lett.* **1998**, *39*, 617. (c) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Teterahedron Lett.* **1998**, *39*, 2367.
13. (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. (b) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.
14. Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.
15. (a) Anderson, K. W.; Mendez-Perez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563–9573. Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H.; Martin, J. Q. *J. Am. Chem. Soc.* **1999**, *121*, 6090–6091.
16. A standard Hydrogenation catalyst from Heraeus, K0219 (Pd/C, dry) was used.
17. Since the use of ligand **7** is protected by Watanabe et al., Tosoh Corp. (EP 0 802 173, 1996) we chose not to pursue this result for further optimization. On the other hand Lanxess has licensed Buchwald's ligands, which are protected by WO 00/028887 and therefore is free to use them.

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Practical and highly stereoselective technology for preparation of enantiopure sulfoxides and sulfinamides utilizing activated and functionally differentiated *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide derivatives

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Abstract—A simple, general, and practical technology to prepare enantiopure 1,2,3-oxathiazolidine-2-oxide derivatives using chiral aryl *N*-sulfonyl aminoalcohol derivatives and thionyl chloride is reported. The versatility of these novel chiral building blocks (MIOO and TMPOO), was exemplified by the expedient production of a variety of unique chiral sulfoxides and valuable chiral sulfinamides in excellent yields and enantiopurities.

1. Introduction

During the past few decades, many synthetic groups have engaged in the design and development of new synthetic methods for generation of enantiopure sulfoxides, because they are highly utilized as chiral controllers for asymmetric C–C bond formation processes,[1] as ligands in catalytic asymmetric synthesis,[2] and as molecular recognition studies.[3] In addition to these synthetic utilities, chiral sulfoxide functionality plays a highly important role in a variety of medicinal targets.[4] Literature shows that two distinct approaches have been applied in the preparation of optically active sulfoxides, which are asymmetric oxidation of prochiral sulfides,[5] and organometallic addition to displacement of electrophilic sulfoxides with inversion of configuration at the sulfur atom.[6] As noted in the literatures, both methods have advantages and disadvantages. However, the latter method is widely used for the production of optically active sulfoxides. The synthesis of optically active sulfoxides was originally proposed by Gilman in 1926,[7] and a few decades later, in 1962, Andersen demonstrated the first chiral sulfinyl transfer agent as (*S*)-menthyl *p*-toluenesulfinate **1** for production of sulfoxides via organometallic addition to the S–O bond of **1** with high yield in an excellent enantioselection.[8] However, this method has limited generality. A decade later, Wudl and Lee introduced the first cyclic sulfinyl transfer agent as 1,2,3-oxathiazolidine-2-oxide derived from (−)-ephedrine **2** to prepare methyl aryl sulfoxides.[9] Later, Hiroi employed the same type of technology using a chiral benzoxathiazine derivative that produced optically active sulfoxides.[10] Sulfoxides obtained by these oxathiazolidines had low enantioselectivites and yields. Snyder and Benson modified the Wudl and Lee procedure by addition of trimethylaluminium as an additive in order to cleave the S–N bond derived from sulfinamide, to produce sulfoxide in good yield with high enantioselectivites.[11] The notable exception to this procedure is the production of hindered sulfoxides, such as *t*-butyl sulfoxides, which cannot be produced from the corresponding *t*-butyl sulfinamides. By overcoming these difficulties, Kagan introduced a more general route compared to the above discussed methods utilizing cyclic sulfite **3**.[6b,12] Compound **3**, when treated with a variety of organometallic agents, produces a regiomeric mixture of sulfinate esters. The ratio of these regiomeric mixtures is highly dependent on the nature of the organometallic agent employed. The diastereomeric mixture, then purified and upon treatment with a second organometallic agent,

Keywords: Chiral sulfinamide; Chiral sulfoxide; 1,2,3-Oxathiazolidine-2-oxide.
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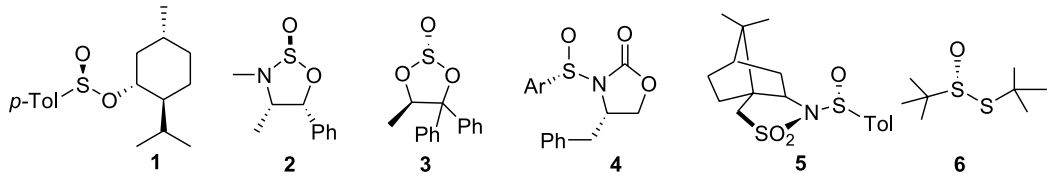
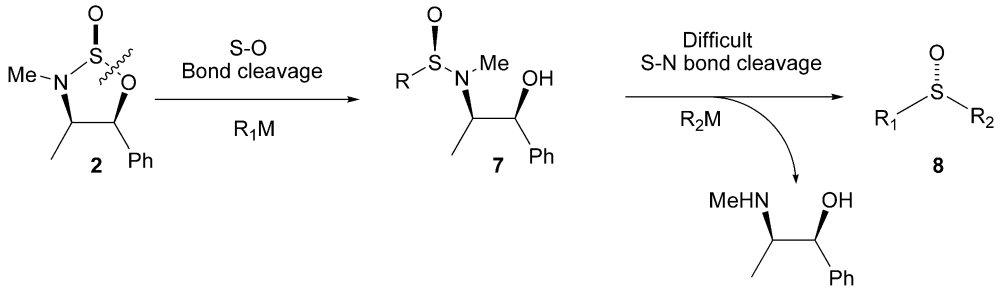


Figure 1.



Scheme 1.

produced chiral sulfoxides in excellent enantioselectivities. The major drawback of this process is that some organometallic additions to sulfite **3** proceed with low selectivities, and therefore, the overall yield is low (Fig. 1).

In 1992, Evans introduced highly reactive *N*-sulfinyloxazolidinone **4** for production of chiral sulfoxides in high enantioselectivites.[13] Later, Oppolzer demonstrated *N*-sulfinyl sultam **5** as a highly reactive sulfinyl transfer agent.[14] Recently, Ellman introduced a mole-scale synthesis of *tert*-butyl *tert*-butanethiosulfinate **6** in the production of a variety of *t*-butyl sulfoxides in excellent enantioselectivites and high yields.[15] It is important to note that extension of the Andersen method to other chiral alcohols has been used to produce optically active sulfoxides.[16] For example, Alcudia and co-workers have developed an elegant solution for preparation of optically active sulfoxides and sulfinamides utilizing racemic aryl, or alkyl sulfinyl chlorides with diacetone D-glucose (DGA) as a chiral controller.[15b,16c,17] In addition to the above discussed methods, in the last few decades there have been numerous other methods introduced for the preparation of optically active sulfoxides.[18] Surprisingly, however, there is no general and practical enantiopure synthesis of this important class of compounds utilizing single chiral template. In the present study, we disclose a highly general, selective, and practical technology for the production of a wide range of chiral sulfoxides and sulfinamides[19] in high yield and excellent enantioselectivities from newly-defined functionally differentiated aryl *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide derivatives (ASOO).

Three decades ago, Wudl and Lee demonstrated that carbon nucleophiles selectively cleave the more reactive S–O bond of (−)-ephedrine-derived 1,2,3-oxathiazolidine-2-oxide **2** in the presence of the *N*-methyl S–N bond to produce *N*-methyl sulfinamide derivatives. These acyclic sulfinamide derivatives were then treated with a second carbon nucleophile to give optically active sulfoxides with low enantioselectivites and yields.[9] The major reason this method was not widely practiced was that cleavage of the S–N bond of acyclic sulfinamide with nucleophiles was extremely difficult, unlike the S–O bond of sulfinates **1**, **2** or **3** (Scheme 1). Based on Wudl and Lee's results, we predicted that attachment of an electron donating group (ED), such as the alkyl group to the nitrogen of 1,2,3-oxathiazolidine-2-oxide (OO), should make the S–N bond stronger and weaken the S–O bond of OO. On the other hand, attachment of the electron withdrawing group (EW), such as the activator group to the nitrogen of OO, would reverse the bond strengthening order (Fig. 2). Therefore, we envisaged that activation of nitrogen of 1,2,3-oxathiazolidine-2-oxide derivatives could reverse the bond cleaving order (S–N vs S–O) to selectively cleave the more reactive S–N bond in the presence of appropriate nucleophiles (organometallic agents).

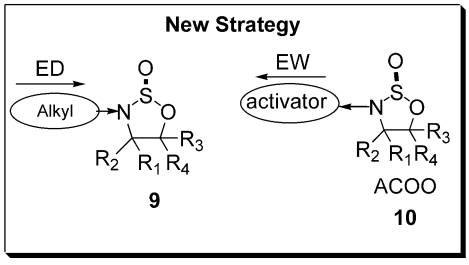
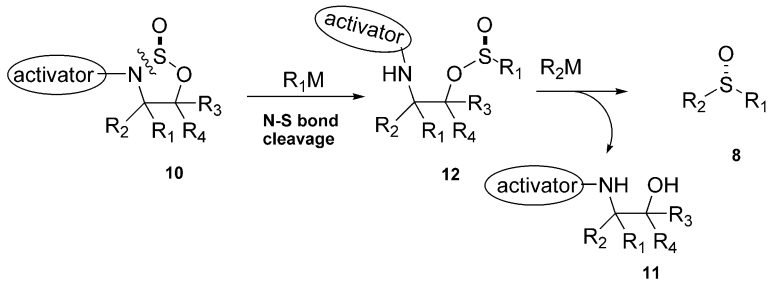
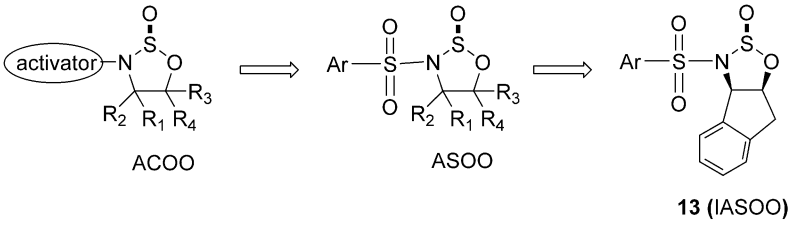


Figure 2.

Our strategy is to devise diastereopure conformationally constrained 1,2,3-oxathiazolidine-2-oxide bearing an activated group on nitrogen from thionyl chloride, and *N*-activated amino alcohol **11**. The N–S bond of activated 1,2,3-oxathiazolidine-2-oxide **10** (ACOO) could be cleaved chemoselectively with an organometallic agent with inversion of configuration at the sulfur atom of **12**, followed by mild displacement of the O–S bond with a second organometallic agent with inversion of configuration, which should lead to modular synthesis of enantiopure sulfoxides **8** (Scheme 2).



Scheme 2.



Scheme 3.

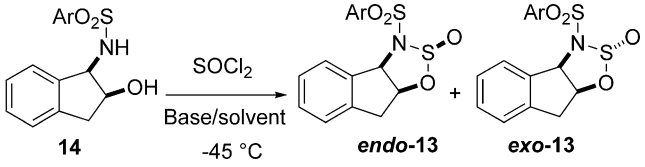
2. Results and discussion

To test this hypothesis, we envisaged as an activating group on nitrogen, the arylsulfonyl group, and a conformationally constrained backbone as the indane platform as depicted in Scheme 3.

Initial efforts for the synthesis of indane derived *p*-toluenesulfonyl 1,2,3-oxathiazolidine-2-oxide **13a** (ITSOO) met with difficulties. It was found that a 75:25 diastereomeric ratio of *endo*/*exo* **13a** can be obtained by simply treating (1*R*,2*S*)-1-*N*-tosyl-aminoindanol (**14a**) in THF at −45 °C with 1.5 equiv of thionyl chloride, followed by a slow addition of 2.5 equiv of TEA at −45 °C. Quenching with water, or acidic conditions showed immediate decomposition. However, quenching with aqueous bicarbonate at −45 °C provided a clean diastereomeric mixture of **13a** with an excellent yield (>98%).

We first explored the effect of the solvent and base on the diastereoselectivity. As depicted in Table 1, the solvent and base combination had a pronounced effect on the *endo*/*exo* ratio of **13a**. With aprotic solvents in the presence of TEA, the major isomer was *endo*-**13a** (Table 1, entries 1–3).

Table 1. Diastereoselective formation of *endo*-**13** (*endo*-IASOO)



Entry	**14**	Ar	Base (solvent)	*endo*-**13**/*exo*-**13**[a]
1	**14a**	4-Tolyl	TEA (THF)	75:25
2	**14a**	4-Tolyl	TEA (ACN)	87:13[b]
3	**14a**	4-Tolyl	TEA (EtOAc)	73:27
4	**14a**	4-Tolyl	TEA (CH_2Cl_2)	19:81[b]
5	**14a**	4-Tolyl	Imidazole (THF)	70:30
6	**14a**	4-Tolyl	1-Methylimidazole (THF)	75:25
7	**14a**	4-Tolyl	Pyridine (THF)	80:20
8	**14a**	4-Tolyl	4-Picoline (THF)	79:21
9	**14a**	4-Tolyl	4-*t*-Butylpy (THF)	83:17
10	**14a**	4-Tolyl	2,6-Lutidine(THF)	85:15
11	**14a**	4-Tolyl	3,5-Lutidine (THF)	87:13
12	**14a**	4-Tolyl	Quinaldine (THF)	87:13
13	**14a**	4-Tolyl	Lepidine (THF)	88:12
14	**14a**	4-Tolyl	2,4,6-Collidine (THF)	91:9
15	**14b**	4-*t*-Butylphenyl	2,4,6-Collidine (THF)	90:10
16	**14c**	2,4,6-Mesityl	2,4,6-collidine (THF)	93:7
17	**14d**	2,4,6-Isopropylphenyl	2,4,6-Collidine (THF)	95:5

[a] *endo*/*exo* ratio is determined by ^{1}H NMR analysis.
[b] Other by-products formed.

Table 2. Optimization of base effect for **14c** for high *endo*-selectivity

Entry	Base (THF)	*endo*-**13c**/*exo*-**13c**[a]
1	TEA	85:15
2	Triisopropylamine	66:33
3	Triphenylamine	No rn
4	Imidazole	82:18
5	2-Methylimidazole	86:14
6	2-Ethyllimidazole	66:34
7	Pyridine	90:10
8	2,4,6-Collidine	93:7
9	3,5-Lutidine	97:3

[a] *endo*/*exo* ratio is determined by ^{1}H NMR analysis.

Surprisingly, CH_2Cl_2 gave *exo*-selectivity (Table 1, entry 4) with other by-products. In THF solvent, TEA, imidazole, 1-methyl imidazole, and pyridine provided comparable selectivity (entries 1, 5–7). The selectivity can be further tuned by the alkyl substitution pattern of the pyridine ring. Mono-methyl substituted pyridine, such as 4-picoline, ascertained a similar selectivity to pyridine (entry 8). However, increasing the bulk at 4-position (*tert*-butyl group), the selectivity increased from 79:21 to 83:17. Thus, 2,6-lutidine and 3,5-lutidine provided increased selectivites (entries 10 and 11), while quinaldine and lepidine gave similar selectivites (entries 12 and 13). Interestingly, 2,4,6-collidine afforded the best *endo*-selectivity (*endo*/*exo*, 91:9; entry 14). The compound **13a** (*endo*/*exo*; 91:9), obtained from the 2,4,6-collidine/THF condition, can be crystallized to >99.9% diastereopure crystalline *endo*-**13a** with high recovery. The stereochemistry of **13a** was unambiguously established by single crystal X-ray analysis to be either *endo*, or *S*-configuration at the sulfur atom.[20]

Our attention was then focused on the optimization of the steric effect of the arylsulfonyl group on the diastereoselectivity. As illustrated in Table 1, in the THF–collidine mixture, increasing the bulk at 4-position at phenyl ring, such as 4-*tert*-butyl group, had little or no effect (entries 15 and 14). Substitution of 2 and 6 positions of the 4-methyl phenyl ring with methyl groups, the *endo*/*exo* selectivity increased to 93:7 (entry 16). Furthermore, increasing the bulk at the 2,4,6-position of the phenyl ring with triisopropyl groups gave the highest *endo*/*exo* selectivity (95:5; entry 17). In this study, it is clear that changing the base/solvent combination and aryl substitution can moderate the ratio of *endo*/*exo* selectivity.

From the careful comparison data of Table 1 for base, solvent, and the aryl substitution effect and the readily available and inexpensive nature of 2-mesitylenesulfonyl chloride, further base optimization work centered on the preparation of *endo*-**13c** (mesityl indanyl oxathiazolidine-2-oxide, *endo*-MIOO). As shown in Table 2, surprisingly, when 3,5-lutidine was used as the base in THF, the *endo*/*exo* selectivity jumped to 97:3. Gratifyingly, this process is amenable to scale-up in kilo quantity to produce *endo*-**13c** in an excellent yield.[20]

After finding a highly *endo*-selective process for **13**, our attention was focused on finding a proper complementary procedure to produce highly *exo*-selective indanyl aryl *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide (*exo*-IASOO, *exo*-**13**). After examination of many reaction conditions, it was found that high *endo*-selectivity can be switched to high *exo*-selectivity by a simple change in the pyridine substitution pattern by increasing the steric bulk at the 2,6 position. As indicated in Table 3, when compound **14a** was subjected to 2,4,6-collidine, high *endo*-selective **13a** was provided. By increasing the bulk at the 2,6 position, the *t*-butyl group provided moderately high *exo*-selectivity (Table 3, entry 2, *endo*/*exo*=20:80). Interestingly, removal of the methyl group from the 4-methyl-2,6-di-*t*-butyl pyridine provided outstanding *exo*-selectivity for **13a** (entry 3, *endo*/*exo*=2:98). *exo*-**13c** also can be obtained in high selectivity (entry 5, *endo*/*exo*=7:93), utilizing 2,6-di-*t*-butyl pyridine as the base.[20] *endo*-**13** and *exo*-**13** are highly crystalline, and can be crystallized to an enantio- and diastereopure form with excellent recovery from single antipode **14**. The stereochemistry of *endo*-**13c** and *exo*-**13c** was unambiguously established by single-crystal X-ray analysis. The *endo*- and *exo* isomers displayed *S*-configuration and *R*-configuration at the sulfur atom, respectively (Fig. 3). Furthermore, examination of bond lengths of the X-ray structures of strained bicyclic *endo*-**13c** and *exo*-**13c** showed that the S–N bond is far longer than the O–S bond, indicating that the S–N bond might have a higher reactivity compared to the S–O bond toward organometallic addition processes (Fig. 3).

Having generated large quantities of *endo*- and *exo*-MIOO in diastereo- and enantiopure form, we focused on the production of both enantiomers of chiral sulfoxides. Snyder reported that preparation of hindered *tert*-butyl derived sulfoxides are unsuccessful utilizing sulfinamide **7** derived from OO-**2**.[11] In addition, Ellman recently disclosed that hindered optically active *tert*-butyl *iso*-propyl sulfoxides can be prepared only in a modest yield utilizing sulfinyl transfer agent **6**.[15a] To highlight the power of this new synthetic methodology, we first investigated the preparation of both antipodes of *tert*-butyl *iso*-propyl sulfoxide utilizing a Chemoselective Ring Opening (CRO) of MIOO with inversion of configuration at the sulfur atom, using the *tert*-butyl organometallic reagent followed by an *iso*-propyl Grignard addition. As depicted in Scheme 4, we first evaluated the addition of *tert*-butyl Grignard to *endo*-MIOO (*endo*-**13c**) in THF at low temperature (−45 °C). We were

Table 3. Complementary diastereoselective thionylation of **14**

Entry	**14**	Ar	Base	*endo*-**13**/*exo*-**13**[a]
1	**14a**	4-Tolyl	2,4,6-Collidine	91:9[b]
2	**14a**	4-Tolyl	4-Methy-2,6-di-*t*-butyl py	20:80
3	**14a**	4-Tolyl	2,6-Di-*t*-butyl py	2:98[b]
4	**14c**	2,4,6-Mesityl	3,5-Lutidine	97:3[b]
5	**14c**	2,4,6-Mesityl	2,6-Di-*t*-butyl py	7:93[b]

[a] *endo*/*exo* Ratio is determined by ^{1}H NMR analysis.
[b] Recystallization provided diastereo- and enantiopure **13** (see Section 4 for experimental procedures).

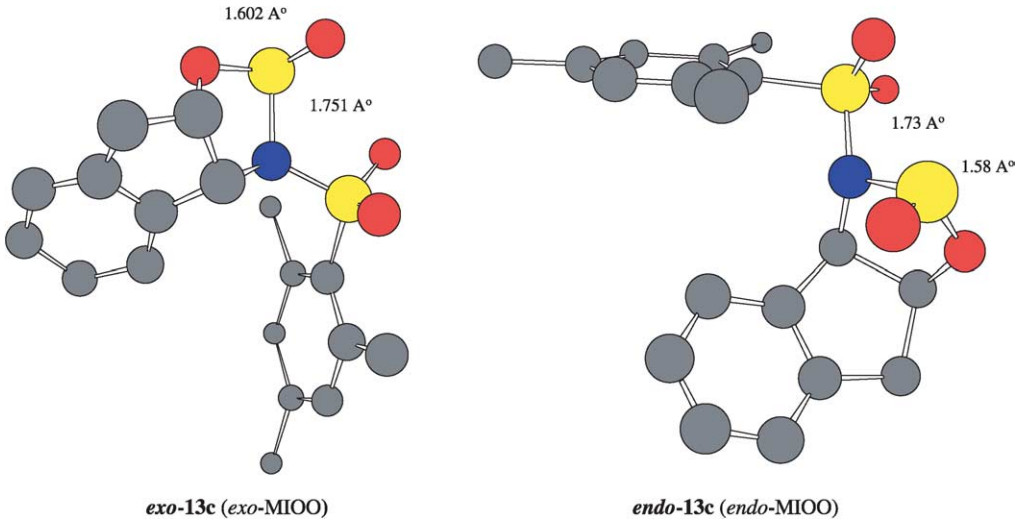
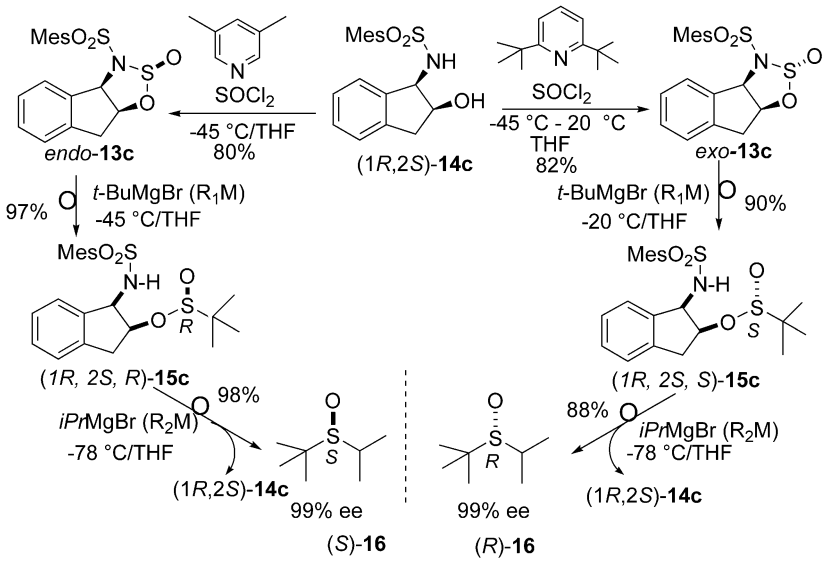


Figure 3. X-ray structures of *exo*- and *endo*-**13c**.



Scheme 4. Production of enantiopure sulfoxide **16** using double displacement of MIOO.

pleased to find that *tert*-butyl Grignard only cleaved the more reactive S–N bond in the presence of the S–O bond of MIOO to produce a stable and crystalline (1*R*,2*S*,*R*)-**15c** sulfinate ester in 97% yield. This reaction proceeds with clean inversion at S atom to produce single diastereomer (1*R*,2*S*,*R*)-**15c**, as established by single crystal X-ray analysis (Fig. 4). On the other hand, *exo*-**13c**, when exposed to *tert*-butyl Grignard at −20 °C, smoothly underwent chemoselective S–N bond cleavage with clean inversion at the S center to produce diastereopure (1*R*,2*S*,*S*)-**15c** in excellent yield (90%). Individual diastereomeric sulfinate **15c**, upon treatment with *iso*-propylMgCl, provided either enantiomer of *tert*-butyl isopropyl sulfoxide (**16**) (with inversion of configuration at the S atom) in excellent yield with an outstanding recovery of enantiopure **14c** (96%).[20,21]

Next, our attention focused on the investigation of developing readily available and inexpensive amino alcohol-based *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide derivatives. After evaluating many chiral *N*-sulfonyl aminoalcohol derivatives, we found that inexpensive *N*-tosyl-norephedrine (**17**) is an ideal template for preparation of *N*-tosyl-methyl-phenyl-1,2,3-oxathiazolidine-2-oxide

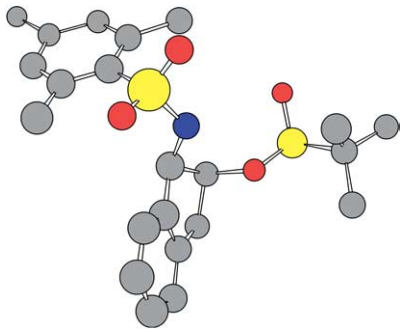
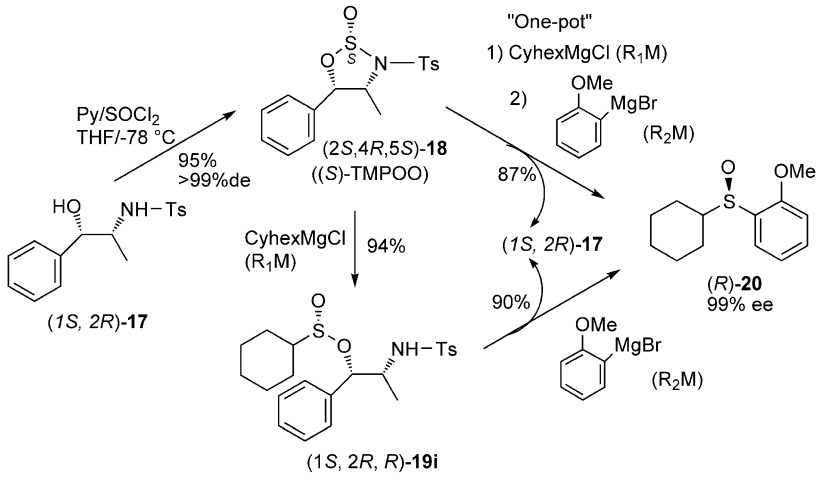


Figure 4. X-ray structure of (1*R*,2*S*,*R*)-**15c**.



Scheme 5. Production of enantiopure sulfoxide using (*S*)-TMPOO ((2*S*,4*R*,5*S*)-**18**).

(TMPOO, **18**). As shown in Scheme 5, treatment of (1*S*,2*R*)-**17** in THF with thionyl chloride and pyridine, or 4-propylphenyl pyridine (P3N) at −78 °C provided >99% de and 95% isolated yield of *N*-tosyl-phenyl-methyl-1,2,3-oxathiazolidine-2-oxide ((*S*)-TMPOO). The single crystal analysis of (*S*)-TMPOO indicated that absolute configuration of the S atom is *S* (Fig. 5). It is worth noting that (*R*)-TMPOO ((2*R*,4*S*,5*R*)-**18**) can also be generated with the same procedure utilizing antipode (1*R*,2*S*)-**17**. It is extremely gratifying to state that the preparation of kilogram quantities of either synthetically important isomer of TMPOO (**18**) is not difficult, and the procedure is amenable to scale-up.[20]

First, the application of (*S*)-TMPOO in the generation of optically active cyclohexyl 2-methoxyphenyl sulfoxide ligand was evaluated. As illustrated in Scheme 5, treatment of cyclohexylMgCl with (*S*)-TMPOO in THF at −78 °C provided 94% isolated yield of (1*S*,2*R*,*R*)-**19i** (inversion of configuration at S atom). Diastereopure **19i** was then exposed to 2-methoxyphenylMgBr at −78 °C, which underwent clean inversion of configuration at the S atom to give enantiopure (*R*)-cyclohexyl 2-methoxyphenyl sulfoxide ((*R*)-**20**) in 90% yield. Gratifyingly, the enantiopure (*R*)-**20** can also be generated in an excellent yield utilizing a one-pot operation by sequential addition of cyclohexylMgCl and 2-methoxyphenylMgBr to (*S*)-TMPOO at −78 °C.

Viability of this double inversion organometallic displacement process was extended to the production of other

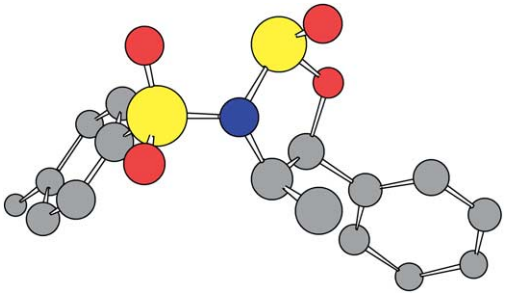
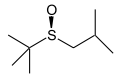
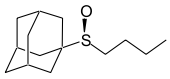
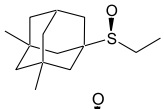
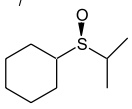
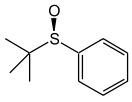
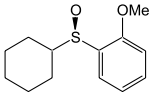
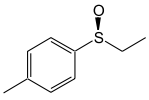
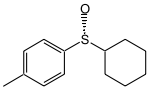
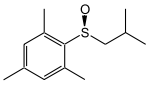
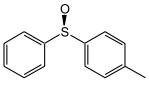
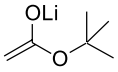
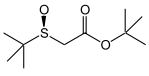
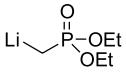
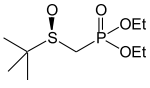


Figure 5. X-ray crystal structure of (2*S*,4*R*,5*S*)-**18** ((*S*)-TMPOO).

structurally unique optically active sulfoxides. As shown in Table 4, either enantiomer of alkyl–alkyl sulfoxides can be obtained in excellent yields (entries 1–4). It is important to note that mild reagents, such as organozinc reagents, can cleave the S–N bond of either *endo*-MIOO or (*R*)-TMPOO resulting in high yields. For example, sterically congested 1-adamantylZnBr or 3,5-dimethyl 1-adamantylZnBr can simply be added to *endo*-**13c** or (*R*)-TMPOO to provide the corresponding sulfinates, which upon treatment with *n*-BuMgBr or EtMgCl provided either enantiomer of appropriate new sulfoxides in high yields (entries 2 and 3). The success of this methodology is also exemplified by the preparation of optically active alkyl–aryl (entries 5 and 6) and aryl–alkyl (entries 7–9) sulfoxides in excellent yields. It is noteworthy to highlight that an addition of *p*-tolylMgBr, followed by EtMgCl to *endo*-**13c** provided only 90% ee. However, a sequential addition of *p*-tolylMgBr, followed by EtMgCl/CuBr·SMe_2 to *endo*-**13c** provided increased selectivity (95% ee, entry 7).[20,22] Interestingly, enantiopure phenyl *p*-tolylsulfoxide can be prepared without any complications (entry 10). As noted in the literature, a previous attempt for preparation of enantiopure *tert*-butyl (*tert*-butylsulfinyl)acetate was unsuccessful.[15a] Notably, the addition of *tert*-butyl acetate enolate to (1*R*,2*S*,*R*)-**15c**, furnished enantiopure *tert*-butyl (*tert*-butylsulfinyl)acetate in a 93% yield without any complications (entry 11).[23] Furthermore, this methodology can be applied in generation of either enantiomer of novel diethyl (*tert*-butylsulfinyl)methylphosphonates in high yields (entry 12).[24]

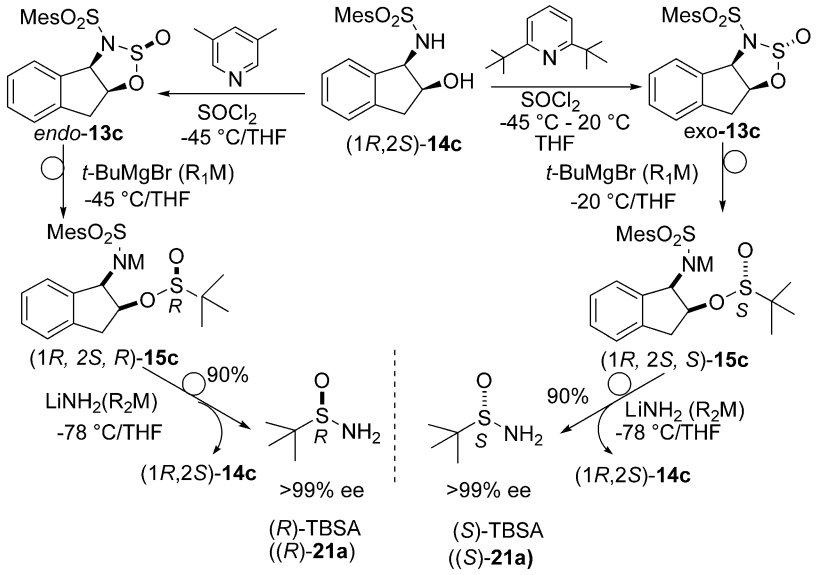
After successfully demonstrating preparation of many different types of enantiopure sulfoxides, our attention became focused on the preparation of sulfoxide derived chiral auxiliaries, such as highly valuable enantiopure sulfinamides. Literature reveals that Davis' *p*-toluenesulfinamide[25] from Andersen's menthyl sulfinate ester[8] demonstrated that the sulfinyl group serves as the first widely-used chiral synthon for the preparation of a wide range of optically active amines.[26] Recently, Ellman and co-workers demonstrated that *tert*-butanesulfinamide (TBSA) is superior to *p*-toluenesulfinamide (TOSA) for some asymmetric processes.[2f,27] They have developed a novel and elegant solution for the preparation of enantiopure

Table 4. Double nucleophilic displacement of MIOO or TMPOO to form optically active sulfoxides (see Schemes 4 and 5)

Entry	R_1M	R_2M	Product	Configuration[a] and ee%[b]	Yield %[c]
1	*t*BuMgCl	*i*BuMgCl		(*S*)-99.5[d] (*R*)-99.5[e]	90 91
2	AdZnBr	*n*-BuMgBr		(*S*)-99[d] (*R*)-99[e]	93 91
3	3,5-Di-MeAdZnBr	EtMgCl		(*S*)-96[d] (*R*)- >99[e]	90 93
4	CyhexMgCl	isoPrMgCl		(*S*)-99[d] (*R*)-98[f]	88 63
5	*t*-BuMgCl	PhMgBr		(*R*)-99[d]	77
6	CyhexMgCl	*o*-MeO-PhMgBr		(*R*)-98[g] (*S*)-99[f]	83 87
7	*p*-TolylMgBr	EtMgCl/CuBr EtMgCl		(*S*)-95[d] (*S*)-90[d]	89 83
8	*p*-TolylMgBr	CyhexMgCl		(*R*)-99[d]	97
9	2,4,6-MesitylMgBr	isoBuMgCl		(*S*)-98[g] (*R*)-99[f]	85 86
10	PhMgBr	*p*-TolylMgBr		(*R*)-99[d]	84
11	*t*BuMgCl			(*R*)-99[d] (*S*)-99[e]	93 92
12	*t*BuMgCl			(*S*)-99[d] (*R*)-98[h]	93 83

[a] Absolute configuration was deduced from the synthetic schemes involving two consecutive inversions of configuration, and by comparison to known literature optical rotations.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] Given yields are second step isolated yields.
[d] See Section 4 experimental procedures for Method A.
[e] See Section 4 experimental procedures for Method B.
[f] See Section 4 experimental procedures for Method E.
[g] See Section 4 experimental procedures for Method C.
[h] See Section 4 experimental procedures for Method D.

(*R*)-*tert*-butanesulfinamide ((*R*)-TBSA) by using *tert*-butyl disulfide with catalytic oxidation of Bolm's protocol[28] to give 91% ee, followed by a $LiNH_2$ addition, and then crystallization.[15a] From the practical point of view the (*R*)-TBSA production in large-scale was especially hampered by the malodorous odor of *tert*-butanethiol that was generated during the $LiNH_2$ addition process to *tert*-butanethiosulfinate **6** to produce (*R*)-TBSA. We recently disclosed that enantiopure *endo*-**13c** is an ideal candidate for production of tertiary alkyl and aryl sulfinamide ligands in enantiopure form.[19] As Scheme 4 shows, *endo*-MIOO (*endo*-**13c**) and *exo*-MIOO can be prepared in an optically pure form. Therefore, we anticipated that the same strategy used in the preparation of either enantiomer of sulfoxides could be applied to the preparation of (*R*)- or (*S*)-TBSA. As depicted in Scheme 6, when exposed to either diastereomer of (1*R*,2*S*,*R*)-**15c** or (1*R*,2*S*,*S*)-**15c** to $LiNH_2/NH_3$/THF at −78 °C, it underwent clean inversion displacement at the S center to produce either enantiomer of TBSA (**21a**) in quantitative conversion with excellent recovery of (1*R*,2*S*)-**14c**.



Scheme 6. Production of enantiopure sulfinamides using MIOO.

It has been discussed in literature that an enantiopure aminoindanol template is widely utilized as a chiral controller for many asymmetric processes.[29] It is important to note that (1*R*,2*S*)-aminoindanol is available in MT scale at a low cost. However, in gram quantities it is costly ($18/g from Aldrich). Due to the high expense of aminoindanol in gram quantities, we focused on all valuable sulfinamides preparations via either enantiomer of TMPOO, because TMPOO can be prepared according to Scheme 5 in multi-kilo quantities in an economical fashion compared to MIOO.[30]

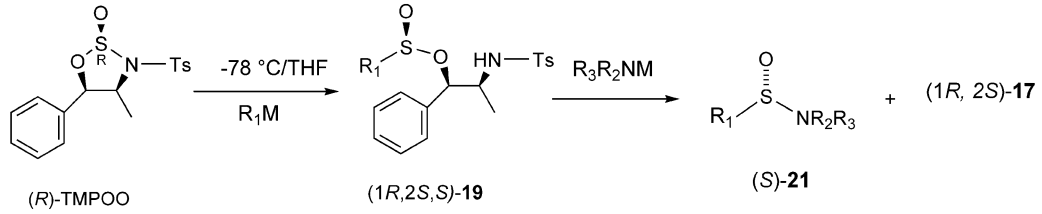
Having generated large quantities of (*R*)-TMPOO, our Immediate attention then focused on the production of (*S*)-TBSA ((*S*)-**21a**) utilizing a chemoselective ring-opening (CRO) with inversion of configuration at the sulfur atom, using a *tert*-butyl organometallic reagent followed by a lithium amide addition. We first evaluated the addition of *tert*-butyl Grignard to (*R*)-TMPOO in THF at low temperature (-78 °C). To our delight, we found that *tert*-butyl Grignard only cleaves the S–N bond in the presence of the S–O bond of (*R*)-TMPOO to produce a crystalline **19a** sulfinate ester in 98% yield with diastereopure form. The exposure of **19a** to lithium amide in liquid ammonia at −78 °C in THF led to S–O bond breakage with inversion of configuration at the S atom, giving quantitative conversions of enantiopure (*S*)-**21a** and (1*R*,2*S*)-**17**. This overall process is highly reproducible for the production of (*S*)-**21a** (94%) with regeneration of auxiliary **17**, with an excellent recovery (>96%).[31]

Generality of this stereospecific double inversion nucleophilic displacement process was extended to the production of other structurally diverse tertiary alkyl and aryl sulfinamides. As illustrated in Table 5, entry 2, addition of LHMDS to intermediate **19a** did not provide any product. On the other hand, addition of LHMDS to (*R*)-TMPOO provided the corresponding silylated sulfinamide derivative **19**, which upon treatment of *t*-butylMgBr provided (*R*)-TBSA with 90% ee (Table 5, entry 3). As depicted in Table 5, (*S*)-dimethylethylmethyl- ((*S*)-**21b**), (*S*)-triethylmethyl- ((*S*)-**21c**) and (*S*)-adamantyl ((*S*)-**21f**) sulfinamides were produced in >99%ee with excellent yields (entries 4, 5 and 9). In the cases of diastereopure **19d** and **19e** when exposed to MHMDS (M=Li or Na) at −78 to −45 °C, 99% ee with high yields of (*S*)-**21d** and (*S*)-**21e** were provided, respectively (entries 6 and 8).[32] Recent literature revealed that Ellman and co-workers have developed the first and unique multi-step synthesis of support-bound *tert*-butanesulfinamide derivative (SBS linker) via enantiopure sulfinamide precursor **21g** (precursor of support-bound *tert*-butanesulfinamide, PSBS), using (*S*)-2-amino-1,1,2-triphenyl ethanol.[33] A major drawback of the synthesis is that in constructing the precursor, **21g**, required Li/NH_3 reduction of benzylic position of (*S*)-2-amino-1,1,2-triphenyl ethanol derivative, the expensive chiral auxiliary, (*S*)-2-amino-1,1,2-triphenyl ethanol, is destroyed. We found that **21g** (precursor for SBS linker) can be prepared utilizing a newly developed double nucleophilic displacement (*R*)-TMPOO to form optically pure **21g** in an excellent yield with recovery of auxiliary (1*R*,2*S*)-**17** (Table 5, entry 10). As shown in Table 5, entry 11, we have exemplified the first novel benzyl ether derived sulfinamide **21h**, which suggests that other functionalized ether sulfinamide derivatives (for example, 4-halobenzyl or 4-halo-benzoxy) could potentially be developed as a precursor of support-bound *tert*-butanesulfinamide ether tethers.[34] To the best of our knowledge, this is the first modular synthesis for production of this valuable family of enantiopure sulfinamides.

3. Conclusion

In conclusion, we have developed a simple, general, and practical technology to prepare enantiopure 1,2,3-oxathiazolidine-2-oxide derivatives using chiral aryl *N*-sulfonyl aminoalcohol derivatives and thionyl chloride. The importance of the novel chiral building blocks, such as MIOO and TMPOO, were exemplified by the expedient production of unique sulfoxide and valuable sulfinamide ligands in excellent yields and enantiopurities. Further applications

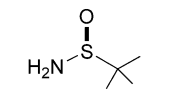
Table 5. Double nucleophilic displacement of (*R*)-TMPOO to form optically pure sulfinamides

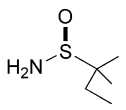


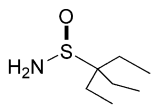
(*R*)-TMPOO (1*R*,2*S*,*S*)-**19** (*S*)-**21**

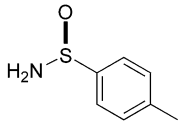
Entry	R_1M	R_2R_3NM (solvent)	Product	Configuration (%ee)	% Yield
1	*t*-ButylMgBr	$LiNH_2$ (NH_3/THF)	**21a**	(*S*), (99)	89
2	*t*-ButylMgBr	LiHMDS (THF)	**21a**	No reaction	No reaction
3	LiHMDS(THF)	*t*-ButylMgBr	**21a**	(*R*), (90)[a]	92
4	DimethylethylmethylMgBr	$LiNH_2$ (NH_3/THF)	**21b**	(*S*), (99)	90
5	TriethylmethylMgBr	$LiNH_2$(NH_3/THF)	**21c**	(*S*), (99)	87
6	4-MethylphenylMgBr	NaHMDS (THF)	**21d**	(*S*), (99)	83
7	4-MethylphenylMgBr	HMDS	**21d**	No reaction	No reaction
8	2,4,6-MesitylMgBr	MHMDS (THF) (M=Li or Na)	**21e**	(*S*), (99)	80
9	1-AdamantylZnBr	$LiNH_2$ (NH_3/THF)	**21f**	(*S*), (99)	80
10	2-Methyl-5-hexenyl MgBr	$LiNH_2$ (NH_3/THF)	**21g**	(*S*), (99)	90
11	4-Benzyloxy-2-methyl-butylMgBr	$LiNH_2$ (NH_3/THF)	**21h**	[b]	85

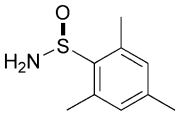
[a] This double nucleophilic displacement using *endo*-MIOO provided only 50% ee.
[b] Optical purity determination using chiral HPLC analysis was unsuccessful.

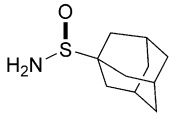

(*S*)-**21a** ((*S*)-TBSA)

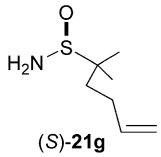

(*S*)-**21b**

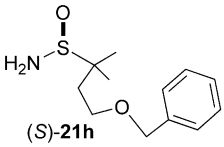

(*S*)-**21c**((*S*)-TESA)


(*S*)-**21d** ((*S*)-TOSA)


(*S*)-**21e**


(*S*)-**21f**


(*S*)-**21g**


(*S*)-**21h**

of activated 1,2,3-oxathiazolidine-2-oxide (ACOO) as the central chiral building block for many asymmetric processes are under evaluation. The behavior of these new structurally diverse sulfinamides for the biologically active amine synthesis is under investigation. Application of this new and powerful methodology for identification of sulfoxide containing novel biological targets, and sulfoxide derived chiral ligands for asymmetric catalysis will be reported in due course.

4. Experimental

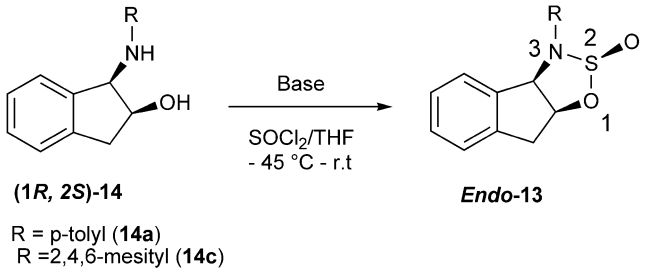
4.1. General

Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. All anhydrous solvents were used for the reaction, and were purchased from Aldrich. All reactions, unless otherwise noted, were carried out in oven-dried glassware under inert argon atmosphere. Chromatography was carried out using Silicycle 60, 230–400 mesh silica gel. Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F 254 plates, and was visualized using UV light and/or phosphomolybdic staining. ^1H NMR and proton-decoupled ^{13}C NMR spectra were obtained with a Varian Inova 300 spectrometer in $CDCl_3$ with TMS as an internal standard at room temperature. Proton and carbon spectra chemical shifts were reported using TMS and/or $CDCl_3$ as an internal standard at 0 and 77.23 ppm, respectively. Diastereomeric ratios were determined on ^1H NMR spectrum analyses. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Enantiomeric excesses were obtained by chiral HPLC analysis using Chiralpak AS, Chiralcel OB, or Chiralcel OD column.

4.2. Preparation of *endo*-13

See Scheme 7.

4.2.1. Kilogram scale procedure for *endo*-13c. To a solution of **14c** (1.50 kg, 4.53 mol) in THF (3.0 L) at −45 °C was added thionyl chloride (810 g, 6.81 mol) slowly in one portion under argon, followed by slow addition of 3,5-lutidine (1.20 kg, 11.19 mol) in THF (7.5 L) over a 5 h period. After the addition was completed, the reaction mixture was stirred, and the reaction was monitored by TLC analysis. Once the reaction was completed, the reaction was quenched with saturated $NaHCO_3$ aqueous



Scheme 7.

solution (4.50 L), and the mixture was diluted with ethyl acetate (7.5 L) and warmed to ambient temperature with stirring. The phases were allowed to separate and the aqueous phase was removed. The aqueous phase was extracted with ethyl acetate (2 L). The combined organic phases were washed with brine (3.0 L), dried, and evaporated to dryness. The residue was added to heptane (4.5 L), and the mixture was stirred for 2 h to afford a white to off-white precipitate. The slurry was filtered and the cake was washed with heptane (1.5 L). The diastereomeric ratio is 97:3 as determined by ^{1}H NMR spectrum. Crystallization of the crude product from ethyl acetate/heptane gave diastereopure crystalline *endo*-**13c** (1.36 kg) in an 80% yield. The absolute stereo-chemistry of *endo*-**13c** was established by single crystal X-ray analysis to be *S*-configuration at sulfur atom (Fig. 6). ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.77 (s, 6H), 3.40–3.66 (m, 2H), 5.57 (d, J=6.4 Hz, 1H), 5.86–5.91 (m, 1H), 6.63 (d, J=8.1 Hz, 1H), 7.08–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 21.5, 23.4, 39.6, 66.6, 96.0, 125.0, 125.8, 128.1, 129.8, 132.8, 138.8, 141.2, 145.1. Anal. Calcd for $C_{18}H_{19}NO_4S_2$: C, 57.27; H, 5.07; N, 3.71; S, 16.99. Found: C, 57.45; H, 5.14; N, 3.76; S, 16.93.

4.2.2. *endo*-13a. Diastereopure *endo*-**13a** was prepared from **14a** with 2,4,6-collidine used as the base by following the same procedure described above to give a 78% yield. ^{1}H ($CDCl_3$): δ 2.51 (s, 3H), 3.32–3.62 (m, 2H), 5.38–5.52 (m, 2H), 7.81–7.89 (m, 6H), 7.81–7.89 (m, 2H). ^{13}C ($CDCl_3$): δ 22.0, 39.7, 67.1, 93.3, 125.6, 126.0, 127.8, 128.1, 130.0, 130.6, 135.9, 138.2, 138.6, 245.6. Anal. Calcd for $C_{16}H_{15}NO_4S_2$: C, 55.00; H, 4.33; N, 4.01; S, 18.35. Found: C 55.09; H, 4.37; N, 3.92; S, 18.39. The absolute stereo-chemistry of *endo*-**13a** was established by single crystal X-ray analysis to be *S*-configuration at sulfur atom (Fig. 6).

4.3. Preparation of *exo*-13

See Scheme 8.

4.3.1. *exo*-13a. A 4-neck 250 mL round-bottom flask fitted with a mechanical stirrer, addition funnel, temperature probe, and argon inlet was charged with (1*R*,2*S*)-**14a** (10 g, 33.0 mmol) and THF (30 mL). After the reaction mixture was chilled to −45 °C, thionyl chloride (5.9 g, 49.6 mmol) was added slowly via a syringe in one portion, followed by slow addition of 2,6-di-*tert*-butylpyridine (15.8 g, 80 mmol) in THF (100 mL) over a 1–2 h period. After stirred at −45 °C for 30 min, the reaction mixture was warmed to ambient temperature, and the reaction was monitored by TLC analysis. Once the reaction was completed, the

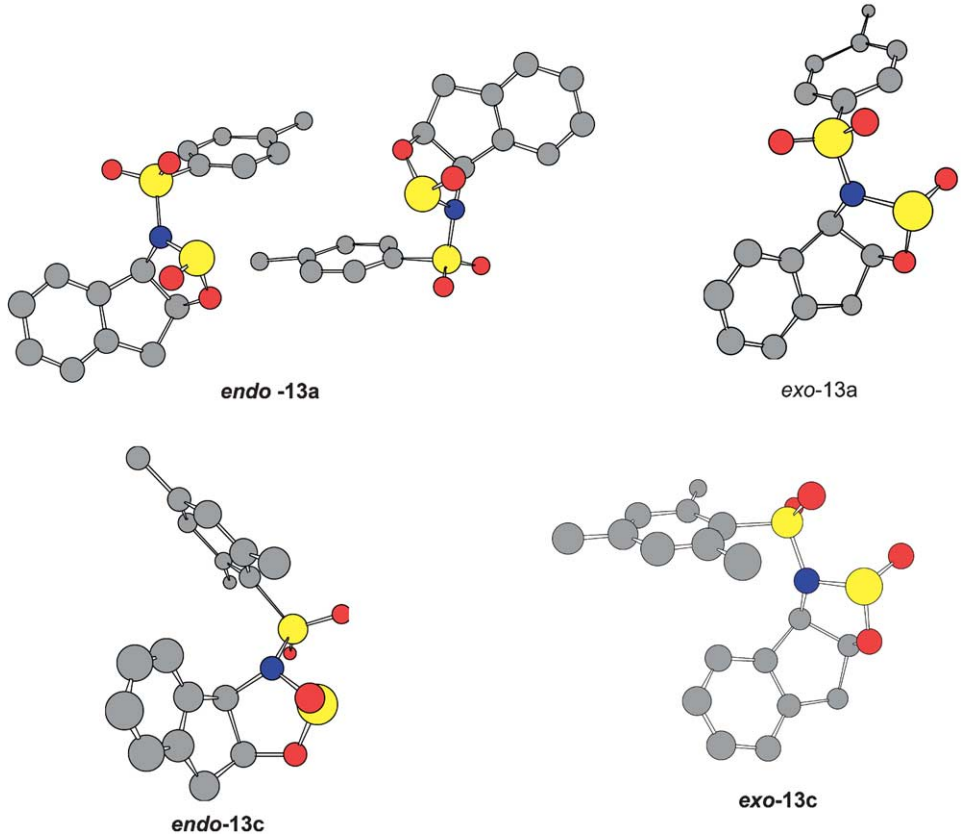
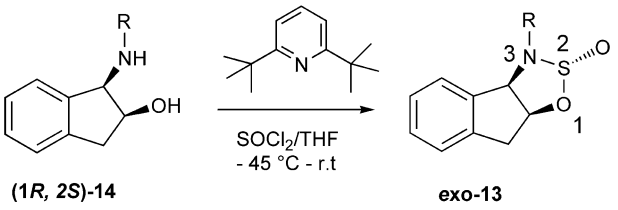


Figure 6. X-ray crystal structure of *endo*-**13a**, *exo*-**13a**, *endo*-**13c** and *exo*-**13c**.

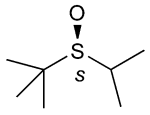


Scheme 8.

reaction was quenched with saturated $NaHCO_3$ aqueous solution (40 mL), and the mixture was diluted with ethyl acetate (100 mL) and warmed to ambient temperature with stirring. The phases were allowed to separate and the aqueous phase was removed. The aqueous phase was extracted with ethyl acetate (50 mL). The combined organic phases were washed with brine (100 mL), dried, and evaporated to dryness. The residue was added to heptane (100 mL), and the mixture was stirred for 2 h to afford a white to off-white precipitate. The slurry was filtered and the cake was washed with heptane (50 mL). The diastereomeric ratio (*endo*/*exo*) is 2:98 as determined by ^{1}H NMR spectrum. Crystallization of the crude product from ethyl acetate/heptane gave diastereopure crystalline *exo*-**13a** (9.8 g) in an 85% yield. The absolute stereo chemistry of *exo*-**13a** was established by single crystal X-ray analysis to be *R*-configuration at sulfur (Fig. 6). ^{1}H ($CDCl_3$): δ 2.46 (s, 3H), 3.31 (s, 2H), 5.02–5.04 (d, J=5.0 Hz, 1H), 5.77–5.82 (m, 1H), 7.22–7.42 (m, 5H), 7.96–8.04 (m, 3H). ^{13}C ($CDCl_3$): δ 22.0, 36.2, 65.1, 90.6, 125.2, 127.0, 128.9, 129.8, 130.2, 135.5, 137.9, 139.2, 145.5. Anal. Calcd for $C_{16}H_{15}NO_4S_2$: C, 55.00; H, 4.33; N, 4.01; S, 18.35. Found: C, 55.11; H, 4.35; N, 4.00; S, 18.40.

4.3.2. *exo*-13c. The same procedure for the preparation of *exo*-**13a** was followed to afford *exo*-**13c** in 82% yield. ^{1}H ($CDCl_3$) δ 2.41 (s, 3H), 2.75 (s, 6H), 3.34–3.541 (m, 2H), 5.68 (d, J=5.5 Hz, 1H), 6.21–6.27 (m, 1H), 6.72 (d, J=7.8 Hz, 1H), 7.04–7.14 (m, 4H), 7.24–7.34 (m, 2H). ^{13}C ($CDCl_3$) δ 21.5, 23.4, 36.3, 64.8, 91.4, 125.4, 126.1, 128.1, 129.5, 132.8, 132.9, 138.1, 139.4, 141.6, 145.1. Anal. Calcd for $C_{18}H_{19}NO_4S_2$: C, 57.27; H, 5.07; N, 3.71; S, 16.99. Found: C, 57.30; H, 4.99; N, 3.66; S, 17.12. The absolute stereochemistry of *exo*-**13a** was established by single crystal X-ray analysis to be *R*-configuration at sulfur atom (Fig. 6).

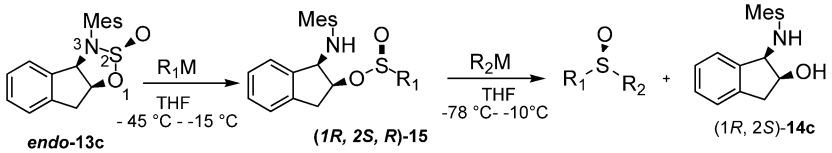
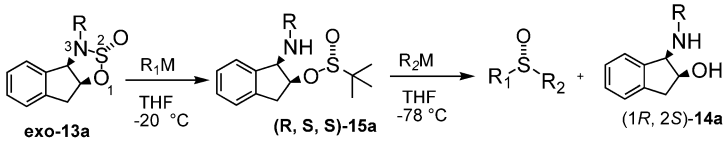
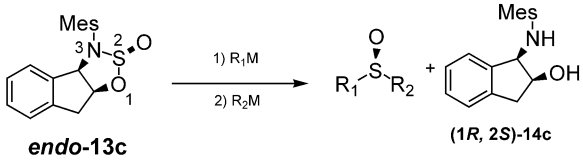
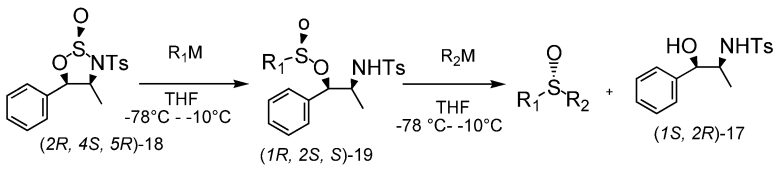
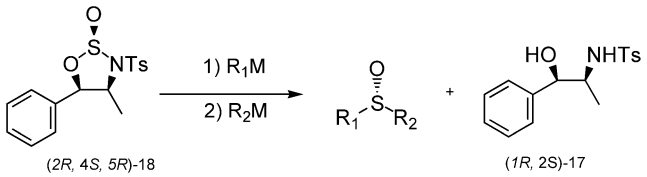
4.4. Synthesis of (*S*)-*tert*-butyl isopropylsulfoxide from *endo*-13c (Table 6, Method A)

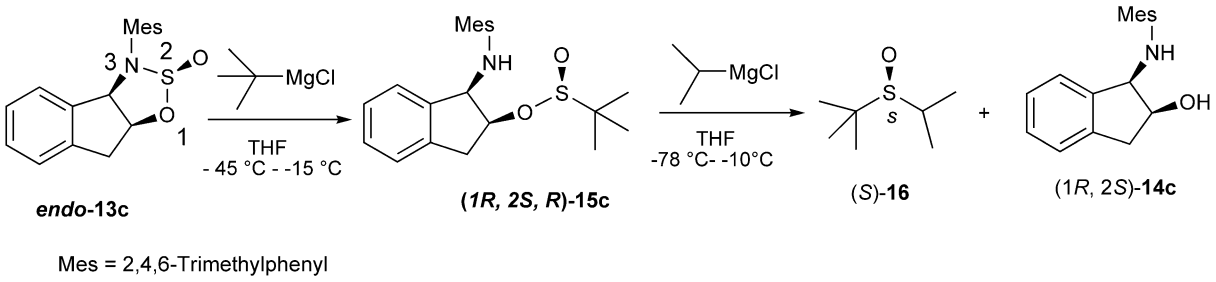


(*S*)-**16**

See Scheme 9.

Table 6. Summary of methods used for the preparation of sulfoxides

Method	Reaction
Method A (use of *endo*-**13c**)	 Mes = 2,4,6-Trimethylphenyl;
Method B (use of *exo*-**13a** or *exo*-**13c**)	 R = tosyl or mesityl
Method C (one-pot procedure. Use of *endo*-**13c**)	
Method D (use of (2*R*,4*S*,5*R*)-**18**)	
Method E (one-pot procedure. Use of (2*R*,4*S*,5*R*)-**18**)	



Scheme 9.

4.4.1. Preparation of (1*R*,2*S*,*R*)-15c from *endo*-13c. A 3-neck 100 mL round-bottom flask fitted with a stirring bar, temperature probe, and argon inlet, was charged with *endo*-**13c** (11.0 g, 29 mmol) and THF (100 mL). The mixture was stirred at ambient temperature to give a solution, and cooled to −45 °C, followed by addition of *t*-BuMgCl (32 mL, 1.0 M in THF) slowly via a syringe pump. After stirred at −45 °C for 1 h, the reaction mixture was warmed to −15 °C and the reaction was monitored by TLC analysis. The reaction was quenched with saturated $NaHCO_3$ aqueous solution (50 mL) and diluted with ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (50 mL). The organic phases were combined and washed with brine (100 mL) and water (50 mL), dried over Na_2SO_4, and concentrated to afford (1*R*,2*S*,*R*)-**15c** (12.3 g) in a 97% yield with >99% de. The absolute stereochemistry was unambiguously established by single crystal X-ray analysis to be *R*-configuration at sulfur atom with an expected inversion of configuration at the sulfinyl group[1] (Fig. 7). ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 2.32 (s, 3H), 2.71 (s, 6H), 3.06 (s, 2H), 4.75–4.85 (m, 2H), 5.64 (d, J=9.3 Hz, 1H), 6.99 (s, 1H), 7.17–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 21.1, 21.8, 37.8, 58.1, 60.5, 82.7, 124.8, 124.9, 127.8, 128.5, 132.3, 134.6, 137.8, 140.3, 142.6. Anal. Calcd for $C_{22}H_{29}NO_4S_2$: C, 60.66; H, 6.71; N, 3.22; S, 14.72. Found: C, 60.75; H, 6.72; N, 3.15; S, 14.65.

4.4.2. (*S*)-*tert*-butyl isopropylsulfoxide ((*S*)-16). A solution of (1*R*,2*S*,*R*)-**15c** (5.0 g, 11.5 mmol) in THF (20 mL) at −78 °C under argon was charged with isopropylmagnesium chloride (12 mL, 2.0 M in THF) dropwise. After stirred at −78 °C for 1 h, the reaction mixture was warmed to −10 to 0 °C, stirred, and the reaction was monitored by TLC analysis. The reaction was quenched by 20% NaCl (15 mL) aqueous solution and diluted with EtOAc (30 mL). After phase separation, the organic phase was extracted once with EtOAc. The combined organic phases was washed with 20% NaCl (10 mL) aqueous solution, dried over Na_2SO_4, and concentrated to give the sulfoxide and (1*R*,2*S*)-**14c** mixture, which was purified by flash chromatography eluted with EtOAc to afford (1*R*,2*S*)-**14c** (3.66 g, 96%) and (*S*)-*t*-butyl isopropylsulfoxide (1.6 g, 98%) in 99% ee. The enantiomeric purity was analyzed by chiral HPLC analysis. The configuration at sulfur atom was deduced from the X-ray crystal structure of (1*R*,2*S*,*R*)-**15c** with inversion of configuration with nucleophilic displacement.[2] ^{1}H NMR ($CDCl_3$): δ 1.24 (d, J=6.90 Hz, 3H), 1.26 (s, 9H), 1.32 (d, J=7.20 Hz, 3H), 2.88 (dq, J=6.9, 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 15.4, 20.6, 23.6, 44.6, 54.2. Anal. Calcd for $C_7H_{16}OS$: C, 56.70; H, 10.88; S, 21.63. Found: C, 56.27; H, 10.34; S, 22.00. Chiral HPLC method: Chiralpak AS×2 in series, 4.6×250, 10 μm; 230 nm; 0.4 mL/min. Mobile phase: hexane/EtOH, 90:10 (v/v). (*R*)-enantiomer, t_R= 24.93 min; (*S*)-enantiomer t_R=26.66 min.

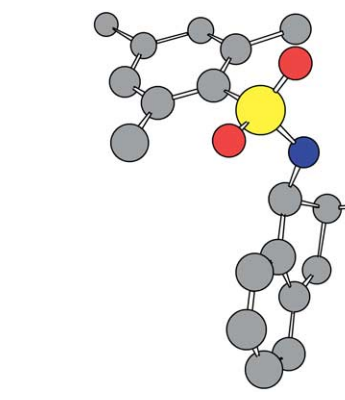
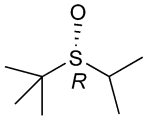


Figure 7. X-ray crystal structure of (1*R*,2*S*,*R*)-**15c**.

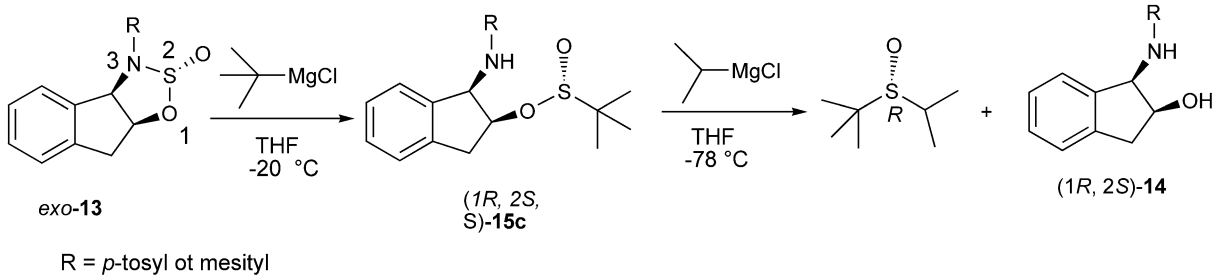
4.5. Preparation of (*R*)-*tert*-butyl isopropylsulfoxide from *exo*-13a or *exo*-13c (Table 6, Method B)



(*R*)-**16**

See Scheme 10.

4.5.1. Preparation of (1*R*,2*S*,*S*)-15c. To a solution of *exo*-**13c** (2.5 g, 6.63 mmol) in THF (20 mL) at −20 °C was added *tert*-butylmagnesium chloride (8.0 mL, 1.0 M in THF) dropwise under argon, stirred for 2 h and the reaction mixture was warmed to ambient temperature. The reaction was monitored by TLC analysis. The reaction was quenched by saturated $NaHCO_3$ aqueous solution (5 mL) and diluted with ethyl acetate (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL) and the combined organic phases were washed with brine (10 mL) and water (10 mL), dried over Na_2SO_4 and concentracted to afford (1*R*,2*S*,*S*)-**15c** (2.6 g, 90%) in >99% de. ^{1}H ($CDCl_3$): δ 1.18 (s, 9H), 2.32 (s, 3H), 2.71 (s, 6H), 3.15 (dd, J=4.89, 17.34 Hz, 1H), 3.28 (d, J=17.21 Hz, 1H), 4.83 (dd, J= 5.13, 10.50 Hz, 1H), 5.02 (dt, J=1.22, 5.00 Hz, 1H), 5.37 (d, J=10.62 Hz, 1H), 6.99 (s, 2H), 7.02–7.05 (m, 1H), 7.14–7.26 (m, 3H). ^{13}C ($CDCl_3$): δ 21.13, 21.95, 23.34, 38.67, 58.40, 60.71, 82.46, 124.10, 125.18, 127.55, 128.84, 132.22, 134.29, 138.57, 139.37, 139.47, 142.66.



Scheme 10.

4.5.2. (1*R*,2*S*,*S*)-15a. Compound (1*R*,2*S*,*S*)-**15a** was prepared by following the same procedure described above in 92% yield and 99% de. ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 9H), 2.48 (s, 3H), 2.95–3.14 (m, 2H), 4.64–4.70 (m, 1H), 4.76–4.84 (m, 1H), 5.76 (d, J=9.2 Hz, 1H), 7.16–7.50 (m, 6H), 7.94–7.97 (m, 2H). ^{13}C ($CDCl_3$): δ 21.7, 38.0, 58.2, 60.6, 83.1, 124.9, 125.0, 127.8, 128.6, 130.0, 137.5, 140.1, 143.8. Anal. Calcd for $C_{20}H_{25}NO_4S_2$: C, 58.94; H, 6.18; N, 3.44; S, 15.74. Found: C, 59.10; H, 6.22; N, 3.35; S, 15.79.

4.5.3. (*R*)-*tert*-butyl isopropylsulfoxide. The reaction was performed at −78 to −10 °C by following the same procedure for the preparation of (*S*)-**16** to afforded the title compound in an 88% yield and >99% ee by using (1*R*,2*S*,*S*)-**15c** and in an 90% yield and 99% ee using (1*R*,2*S*,*S*)-**15a**, respectively.

4.6. Kilogram scale procedure for the preparation of (*S*)-TMPOO

To a solution of (1*S*,2*R*)-**17** under argon (2.0 kg, 6.56 mol) in dry THF (11.7 L) at −70 to −75 °C was added thionyl chloride (1.09 kg, 9.16 mol) slowly in one portion, followed by addition of dry pyridine (1.30 kg, 16.4 mol) solution in THF (3.5 L) over a period of 4–6 h. After stirred at −70 to −75 °C for 30 min, the reaction mixture was warmed to −45 °C, and stirred for 1.5 h. Progress of the reaction was monitored by TLC analysis. The reaction was quenched by slow addition of saturated aqueous $KHCO_3$ solution (7.8 kg) in a controlled fashion while keep the temperature below −5 °C. Ethyl acetate (12 L) was added, the reaction mixture was allowed to warm to ambient temperature and the phases were allowed to separate. After removal of the aqueous phase, the organic phase was washed with saturated aqueous $KHCO_3$ (3 kg) and 21% NaCl (4.5 kg), followed by distillation under reduced pressure to a volume of about 13 L. Heptane (17 L) was added and the mixture was distilled further until all low boiling point solvents were removed. Then the mixture was cooled to ambient temperature, stirred for 30 min and the slurry was filtered and the wet cake was washed with a mixture of ethyl acetate/heptane (2:8, v/v, 2 L×2) and heptane (4 L). The wet cake was dried at 45 °C under reduced pressure to afford a crystalline (2*S*,4*R*,5*S*)-**18** (2.3 kg) in a 95% yield and >99% diastereomeric purity as determined by ^{1}H NMR analysis.The opposite antipode, (2*R*,4*S*,5*R*)-**18**, was prepared by following the above procedure. The absolute stereochemistry of (2*S*, 4*R*, 5*S*)-**18** was established by single crystal X-ray analysis to be *S*-configuration at sulfur atom (Fig. 8) ^{1}H NMR ($CDCl_3$): δ 0.87 (d, J=6.97 Hz, 3H), 2.54 (s, 3H), 4.21 (p, J=6.48 Hz, 1H), 5.57 (d, J=5.98 Hz, 1H), 7.28–7.39 (m, 7H), 7.86–7.89 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 16.6, 21.5, 57.1, 92.1, 126.4, 127.7, 128.9, 129.2, 130.4, 133.4, 136.6, 145.3. Anal. Calcd for $C_{16}H_{17}NO_4S_2$: C, 54.68; H, 4.88; N, 3.99; S, 18.25. Found: C, 54.76; H, 4.79; N, 3.98; S, 18.25 (Scheme 11).

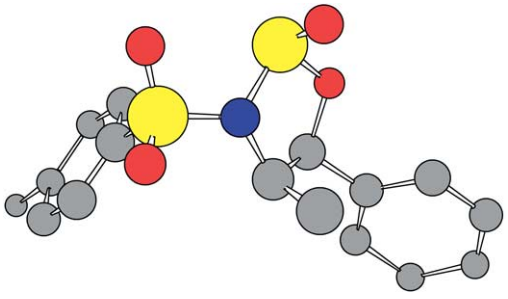
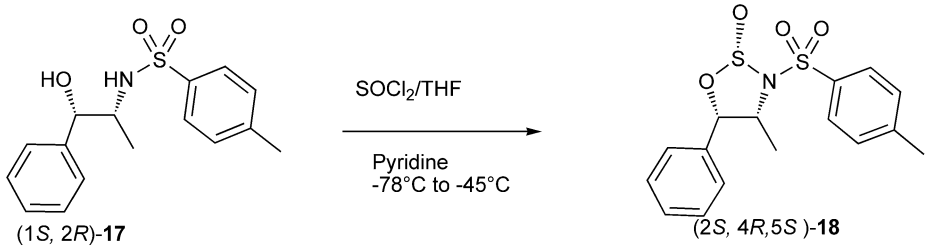


Figure 8. X-ray crystal structure of (2*S*,4*R*,5*S*)-**18**.

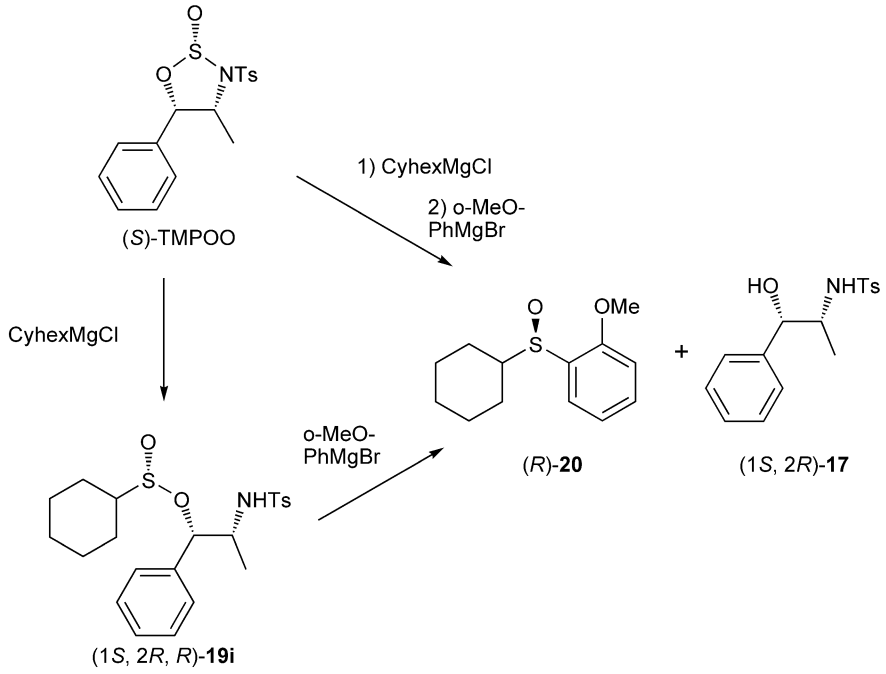
4.7. Preparation of (*R*)-cyclohexyl-2-methoxyphenyl-sulfoxide (*R*)-20 from (*S*)-TMPOO

See Scheme 12.

4.7.1. Preparation of (1*S*,2*R*,*R*)-19i (Table 6, Method D). A solution of (*S*)-TMPOO (0.5 g, 1.42 mmol) in THF (5 mL) at −78 °C under argon was added cyclohexylMgCl (0.72 mL, 2.0 M in THF) dropwise, the reaction mixture



Scheme 11.



Scheme 12.

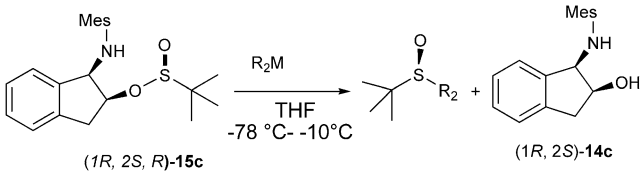
was stirred at −78 °C and the reaction was monitored by TLC analysis. The reaction was quenched with $NaHCO_3$ (5 mL) and diluted with EtOAc (15 mL), and the reaction mixture was warmed to ambient temperature. The aqueous phase was extracted with EtOAc (10 mL) and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and evaporated to dryness to afford (1*S*,2*R*,*R*)-**19i** (0.58 g, 94%) in >99% de. ^{1}H NMR ($CDCl_3$): δ 0.98 (d, J=6.84 Hz, 3H), 1.2–1.5 (m, 5H), 1.65–1.75 (m, 1H), 1.80–1.92 (m, 2H), 1.95–2.10 (m, 2H), 2.42 (s, 3H), 2.65–2.70 (m, 1H), 3.55–3.70 (m, 1H), 4.96 (d, J=1.32 Hz, 1H), 5.80 (d, J=9.26 Hz, 1H), 7.06–7.14 (m, 2H), 7.28–7.40 (m, 5H), 7.86 (d, J=8.31 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14/87, 21.66, 24.02, 24.60, 25.11, 25.21, 25.63, 54.45, 64.19, 84.77, 125.92, 127.27, 128.33, 128.65, 129.82, 137.39, 138.42, 143.41.

To a solution of (1*S*,2*R*,*R*)-**19i** (0.4 g, 0.92 mmol) in THF (3.5 mL) at −78 °C under argon was added 2-methoxyphenylmagnesium bromide (1.1 mL, 1.0 M in THF) dropwise. After addition of the Grignard, the reaction mixture was warmed to −45 to −15 °C, stirred, monitored by TLC analysis, and quenched by addition of aqueous $NaHCO_3$ (3 mL) and diluted with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (5 mL), the combined organic phase was washed with brine, dried over Na_2SO_4. The organic solvent was evaporated to dryness and the residue was purified by flash chromatography to afford (*R*)-**20** (0.20 g, 90%) in 99% ee. ^{1}H NMR ($CDCl_3$): δ 1.1–1.96 (m, 9H), 2.0–2.12 (m, 1H), 2.72–2.88 (m, 1H), 3.87 (s, 3H), 6.92 (d, J=8.30 Hz, 1H), 7.15 (t, J=7.50 Hz, 1H), 7.43 (dt, J=1.63, 7.78 Hz, 1H), 7.72 (dd, J=1.65, 7.63 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 22.4, 25.6, 26.2, 27.5, 55.9, 59.5, 110.8, 121.4, 126.6, 129.6, 131.9, 155.7. Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.63; H, 7.61; S, 13.26. Chiral HPLC method: Chiralcel OD 4.6×250 mm 10 μm, Hexane/TPA, 90:10; 1 mL/min. 220 nm. (*S*)-isomer, t_R=9.3 min; (*R*)-isomer t_R=11.3 min.

4.7.2. One-pot procedure (Table 6, Method E). A solution of (*S*)-TMPOO (2.0 g, 5.70 mmol) in THF (15 mL) at −78 °C under argon was added cyclohexylMgCl (2.85 mL, 2.0 M in THF) dropwise. The reaction mixture was stirred for 1–2 h at −78 °C and the progress of the reaction was monitored by TLC analysis. Then 2-methoxyphenylmagnesium bromide (5.7 mL, 1.0 M in THF) was added dropwise. The reaction mixture was warmed to −45 to −15 °C, stirred, monitored by TLC analysis, and quenched by addition of aqueous $NaHCO_3$ (15 mL) and diluted with EtOAc (30 mL). The aqueous phase was extracted with EtOAc (30 mL), the combined organic phase was washed with brine, dried over Na_2SO_4 and evaporated to dryness to give a product and auxiliary mixture that was purified by flash chromatography eluted with EtOAc to afford the (*R*)-**20** (1.2 g, 87%) in 99% ee. (*S*)-**20** was prepared by following the same procedure using (*R*)-TMPOO.

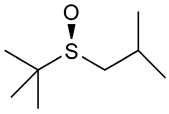
4.8. Method A (Table 6) was used for the preparation of the following sulfoxides

The following sulfoxides were prepared from (1*R*,2*S*,*R*)-**15c** (see Table 4 in the text for ee% and yield) (Scheme 13).



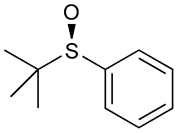
Scheme 13.

4.8.1. (*S*)-*tert*-Butyl isobutyl sulfoxide (R_2=isopropyl) (Table 4, entry 1).



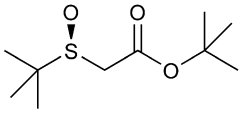
^{1}H NMR ($CDCl_3$): δ 1.10 (d, J=2.32 Hz, 3H), 1.12 (d, J=2.07 Hz, 3H), 1.16 (s, 9H), 2.12–2.22 (m, 1H), 2.30–2.38 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 21.6, 22.8, 23.3, 23.9, 52.4, 54.8. Anal. Calcd for $C_8H_{18}OS$: C, 59.20; H, 11.18; S, 19.76. Found: C, 59.39; H, 11.36; S, 19.65. Chiral HPLC method: Chiralpak AS 4.6 mm×250 mm, 10 μm; 222 nm; 0.8 mL/min; Hex/EtOH 90/10; (*R*)-isomer, t_R=6.9 min; (*S*)-isomer t_R=8.1 min.

4.8.2. (*R*)-*tert*-Butyl phenylsulfoxide (R_2=phenyl) (Table 4, entry 5).



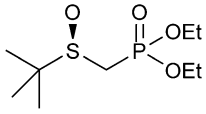
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 9H), 7.53 (m, 3H), 7.63 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.0, 56.0, 126.6, 128.6, 131.4, 140.2. Anal. Calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.74; S, 17.59. Found: C, 65.91; H, 7.78; S, 17.65. $[\alpha]_D^{22}$ +174.6 (*c*, 1, $CHCl_3$); lit.[2] +175.

4.8.3. (*S*)-*tert*-Butyl (*tert*-butylsulfinyl)acetate (R_2=$LiCH_2COOBu$-*t*) (Table 4, entry 11).



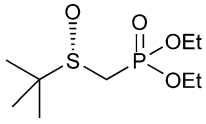
A solution of diisopropylamine (1.5 g, 14.8 mmol) in THF (4 mL) at −15 °C was added *n*-BuLi (6.0 mL, 2.5 M in hexane) slowly. The mixture was warmed to 0 °C, stirred for 30 min and cooled to −45 °C, followed by addition of *tert*-butyl acetate (2.1 g, 1.2 equiv). The reaction mixture was stirred for 30 min and transferred 5 mL (~5 mmol) of the mixture to another reaction flask. After the reaction mixture was cooled to −78 °C, a solution of (1*R*,2*S*,*R*)-**15c** (0.72 g, 1.66 mmol) in THF (3 mL) was added slowly while keeping the reaction mixture at −78 to −75 °C and the reaction was monitored by TLC analysis. The reaction was worked up and crude product was purified by flash chromatography eluted with EtOAc to afforded the title compound (0.34 g) in a 92% yield and >99% ee. ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 9H), 1.51 (s, 9H), 3.29 (d, 1H), 3.47 (d, 1H). ^{13}C NMR ($CDCl_3$): δ 22.7, 27.9, 52.8, 54.0, 83.1, 1654. Anal. Calcd for $C_{10}H_{20}O_3S$: C, 54.51; H, 9.15; S, 14.55. Found: C, 54.63; H, 9.12; N, 14.49. Chiral HPLC method: Chiralpak AS 4.6 mm×250 mm, 10 μm; 222 nm; 0.8 mL/min; Hex/EtOH 90:10; (*S*)-isomer, t_R=11.2 min; (*R*)-isomer t_R=13.2 min (99.8% ee).

4.8.4. (*R*)-Diethyl (*tert*-butylsulfinyl)methylphosphonate (R_2=$LiCH_2P(O)(OEt)_2$ (Table 4, entry 12).



The lithiated methyl-phosphonic acid diethyl ester was prepared in THF in situ with LDA by following the procedure described above. ^{1}H NMR ($CDCl_3$): δ 1.28 (9s, 9H), 1.38 (t, J=7.08 Hz, 6H), 2.82 (t, J=14.53 Hz, 1H), 3.04 (dd, $J1$=14.41 Hz, $J2$=18.30 Hz, 1H), 4.17–4.33 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 16.5, 22.6, 42.9, 44.9, 54.9, 55.0, 63.2. Anal. Calcd for $C_9H_{21}O_4PS$: C, 42.18; H, 8.26; P, 12.08. Found: C, 41.78; H, 8.32; P, 11.60. Chiral HPLC method: Chiralpak AS 4.6 mm×250 mm, 10 μm; 230 nm; 1.0 mL/min; Hex/EtOH 95:5; (*S*)-isomer, t_R=14.8 min; (*R*)-isomer t_R=17.9 min.

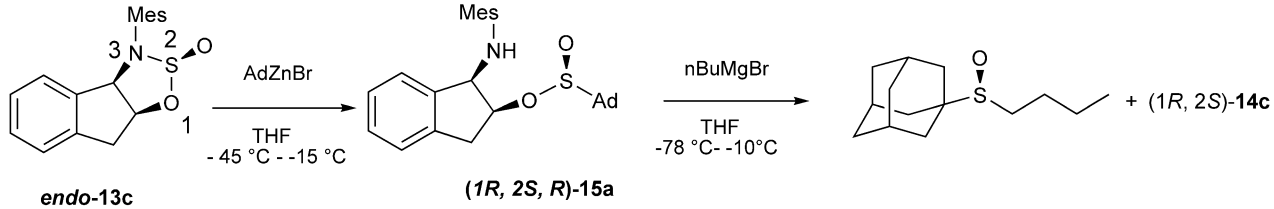
4.8.5. (*S*)-Diethyl (*tert*-butylsulfinyl)methylphosphonate (R_2=$LiCH_2P(O)(OEt)_2$ (Table 4, entry 12) was prepared from (1*S*,2*R*,*S*)-15c with Method B.



4.9. Preparation of (*S*)-1-adamantyl butylsulfoxide from (1*R*,2*S*,*R*)-15a (Table 4, entry 2)

See Scheme 14.

4.9.1. Preparation of (1*R*,2*S*,*R*)-15a. A 3-neck 100 mL round-bottom flask fitted with a stirring bar, temperature probe, and argon inlet, was charged with *endo*-**13c** (5.0 g, 13.3 mmol) and THF (30 mL). The mixture was stirred at ambient temperature to give a solution, and cooled to −45 °C. 1-Adamantylzinc bromide (40 mL, 0.5 M in THF) solution was charged in a 1 h period. After stirred at −45 °C for 2 h, the reaction mixture was warmed between −30 and −15 °C and stirred and the reaction was monitored by TLC analysis. The reaction was quenched with 20% NaCl aqueous solution (20 mL) and diluted with ethyl acetate



endo-13c (1*R*, 2*S*, *R*)-15a

Scheme 14.

(60 mL). The organic phase was washed with brine (20 mL) and water (10 mL), dried over Na_2SO_4, and concentrated to give a solid product, which was purified by flash chromatography (CH_2Cl_2/EtOAc, 96:4) to afford the compound (6.0 g) in 87% yield and >99% de. ^1H ($CDCl_3$): δ 1.57–1.84 (m, 12H), 2.02–2.19 (m, 3H), 2.33 (s, 3H), 2.53 (s, 6H), 3.08 (s, 2H), 4.77–4.88 (m, 2H), 5.70–5.736 (d, J=10 Hz, 1H), 7.02 (s, 2H), 7.16–7.49 (m, 4H). ^{13}C ($CDCl_3$): δ 21.3, 23.4, 28.4, 33.9, 36.5, 37.9, 59.9, 60.5, 82.5, 124.8, 125.0, 127.7, 128.5, 132.3, 134.6, 137.8, 139.6, 140.4, 142.6. Anal. Calcd for $C_{28}H_{35}NO_4S_2$: C, 65.46; H, 6.87; N, 2.73; S, 12.48. Found: C, 65.24; H, 7.03; N, 2.69; S, 12.56.

4.9.2. (*S*)-1-Adamantyl *n*-butylsulfoxide. Same procedure was followed in the preparation. ^1H NMR ($CDCl_3$): δ 0.97 (t, J=7.32 Hz, 3H), 1.38–1.60 (m, 2H), 1.66–1.94 (m, 14H), 2.13–2.22 (m, 3H), 2.40- 2.58 (m,2H). ^{13}C NMR ($CDCl_3$): δ 13.8, 22.3, 25.6, 28.6, 35.1, 36.4, 43.4, 54.8. Anal. Calcd for $C_{14}H_{24}OS$: C, 69.94; H, 10.06; S, 13.34. Found: C, 69.98; H, 10.06; S, 13.16. Chiral HPLC method: Chiralpak AS 4.6 mm×250 mm, 10 μm; 230 nm; 0.8 mL/min; Hex/EtOH 90/10; (*R*)-isomer, t_R=8.9 min; (*S*)-isomer t_R=16.7 min.

4.10. Preparation of (*S*)-3,5-dimethyl-1-adamantyl ethylsulfoxide from (*R*,*S*,*R*)-15b (Table 4, entry 3)

See Scheme 15.

4.10.1. Preparation of (*R*,*S*,*R*)-15b. The reaction was performed at −45 to 0 °C to afford the compound after chromatography in a 83% yield with 99% de. ^1H NMR ($CDCl_3$): δ 0.82 (s, 3H), 0.83 (s, 3H), 1.06–1.37 (m, 10H), 1.52 (d, J=2.8 Hz, 2H), 2.16 (m, 1H), 2.32 (s, 3H), 2.72 (s, 6H), 3.07 (s, 2H), 4.81 (m, 2H), 5.68 (d, J=8.8 Hz, 1H), 7.00 (s, 2H), 7.25 (m, 3H), 7.33 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.5, 21.3, 23.4, 29.5, 30.4, 31.9, 32.5, 37.9, 39.8, 39.9, 42.8, 50.7, 60.5, 61.6, 82.6, 124.8, 125.0, 127.7, 128.5, 132.3, 134.6, 137.8, 139.5, 140.4, 142.5. MS: 542, $C_{30}H_{39}NO_4S_2$ (Calcd 541.77).

4.10.2. (*S*)-3,5-Dimethyl-1-adamantyl ethylsulfoxide. ^1H NMR ($CDCl_3$) δ 0.82 (s, 6H), 1.14 (s, 2H), 1.28–1.66 (m, 11H), 1.58 (q, 11.8 Hz, 2H), 2.17 (m, 1H), 2.46 (m, 2H). ^{13}C NMR δ 8.3, 29.6, 30.2, 31.9, 33.8, 37.4, 40.9, 41.1, 42.6, 50.5, 56.5. M^+ 240. Anal. Calcd for $C_{14}H_{24}OS$: C, 69.94; H, 10.06. Found: C, 69.55, H, 9.95. Chiral HPLC method: Chiralpak AS, Hex/EtOH, 90:10. (*R*)-isomer, t_R=6.9 min; (*S*)-isomer t_R=8.7 min.

4.11. Preparation of (*S*)-cyclohexyl isopropylsulfoxide from (*R*,*S*,*R*)-15d (Table 2, entry 4)

See Scheme 16.

4.11.1. Preparation of (1*R*,2*S*,*R*)-15d. The reaction was performed at −78 °C to afford the compound in a 90% yield with >99% de. ^1H NMR ($CDCl_3$): δ 1.12–1.40 (m, 5H), 1.57–1.67 (m, 1H), 1.70–1.84 (m, 3H), 1.88–1.98 (m, 1H), 2.31 (s, 3H), 2.42–2.56 (m, 1H), 2.71 (s, 6H), 3.07 (s, 2H), 4.76–4.81 (m, 1H), 4.84–4.90 (m, 1H), 5.68 (d, J=9.27 Hz, 1H), 6.98 (s, 2H), 7.18–7.26 (m, 3H), 7.29–7.32 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 21.1, 23.3, 24.3, 24.7, 25.0, 25.1, 25.6, 37.9, 60.3, 64.0, 82.4, 124.7, 125.0, 127.7, 128.4, 132.2, 134.4, 137.8, 139.5, 140.3, 142.5. Anal. Calcd for $C_{24}H_{31}NO_4S_2$, C, 62.44; H, 6.77; N, 3.03; S, 13.89. Found: C, 62.42; H, 6.77; N, 2.88; S, 13.73.

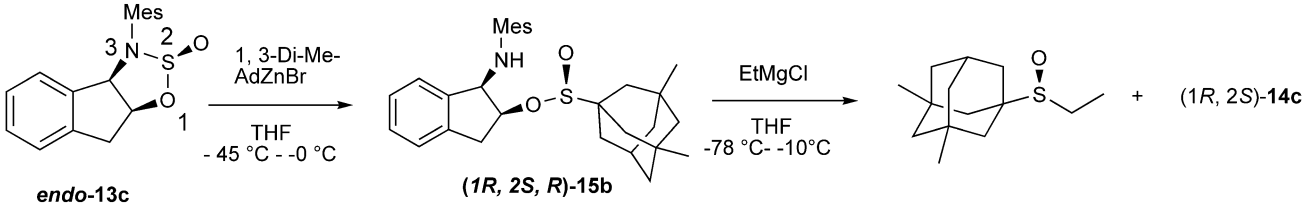
4.11.2. (*S*)-Cyclohexyl isopropylsulfoxide. ^1H NMR ($CDCl_3$): δ 1.21–1.41 (m, 9H), 1.44–1.60 (m, 2H), 1.64–1.98 (m, 4H), 2.02–2.10 (m, 1H), 2.55 (tt, $J1$=11.6 Hz, $J2$=3.8 Hz, 1H), 2.82 (heptet, J=7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 14.1, 17.6, 24.6, 25.5, 25.7, 25.8, 27.4, 46.1, 55.5. (*S*)-enantiomer: [α] +25.6° (*c* 1, $CHCl_3$), lit.[3] plus;20.5°.

Chiral HPLC method: Chiralcell OD, Hex/IPA, 95:5, (*R*)-isomer, t_R=10.3 min; (*S*)-isomer t_R=11.3 min.

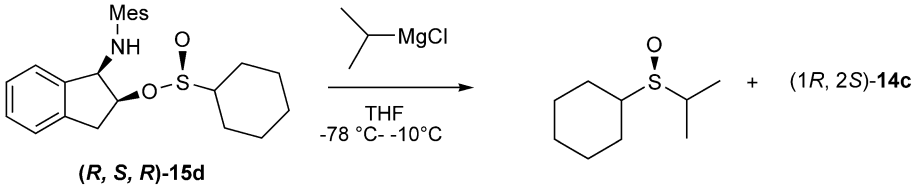
4.12. (*S*)-*p*-Tolyl ethylsulfoxide was prepared from (1*R*,2*S*,*R*)-15e (Table 4, entry 7)

See Scheme 17.

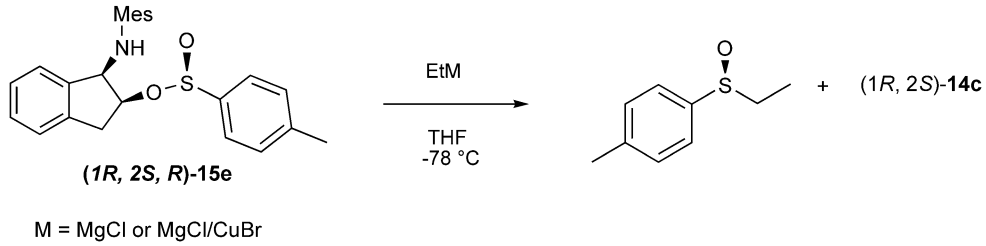
4.12.1. Preparation of (*R*,*S*,*R*)-15e. The reaction was



Scheme 15.



Scheme 16.



Scheme 17.

performed at −78 °C to afford the compound after chromatography in a 90% yield with >99% de. ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.40 (s, 3H), 2.67 (s, 6H), 3.10 (dd, J=16.8, 4.5 Hz, 1H), 3.29 (dd, J=16.8, 1.2 Hz, 1H), 4.75 (dd, J=9.6, 4.8 Hz, 1H), 4.85 (m, 1H), 5.40 (d, J=9.6 Hz, 1H), 7.00 (s, 2H), 7.10–7.30 (m, 6H), 7.45–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 21.7, 23.3, 38.4, 60.3, 80.1, 124.6, 125.2, 125.4, 127.6, 128.7, 130.0, 132.2, 134.8, 138.2, 139.3, 140.0, 141.5, 142.5, 143.4.

4.12.2. Preparation of (*S*)-*p*-tolyl ethylsulfoxide with EtMgCl/CuBr.[4] Ethyl magnesium chloride (4.92 mL, 2.0 M in THF, 9.83 mmol,9.0 equiv) was added to a slurry of copper (I) bromide–dimethyl sulfide complex (1.12 g, 5.45 mmol) in THF (5 mL) at −60 to −50 °C. The mixture was then cooled to −78 °C and stirred for 0.5 h. A solution of (*R*,*S*,*R*)-**15e** (513 mg, 1.09 mmol, 1.0 equiv) in THF (5 mL) was added to the reagent via a cannula. The reaction mixture was then stirred at −78 °C for 2 h and the reaction was monitored by TLC analysis. The reaction was then quenched with saturated $KHCO_3$ aqueous solution and extracted with ethyl acetate (2×20 mL). The organic extracts were washed with brine and evaporated. The residue was purified by flash chromatography eluted with EtOAc to afford the title compound (162 mg) in 89% yield. ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J=7.4 Hz, 3H), 2.41 (s, 3H), 2.69–2.88 (m, 2H), 7.32 (d, J=7.9 Hz, 2H), 7.50 (d, J=8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 6.0, 21.1, 50.3, 124.2, 129.8, 139.9, 140.9. Chiral HPLC method: Chiralpak AS, 90:10 Hex/EtOH, 1 min/mL, (*R*)-isomer, t_R=15.5 min; (*S*)-isomer, t_R=18.0 min).

4.13. Preparation of (*R*)-phenyl *p*-tolylsulfoxide from (1*R*,2*S*,*R*)-15f (Table 4, entry 8)

See Scheme 18.

4.13.1. Preparation of (1*R*,2*S*,*R*)-15f. The reaction was performed at −78 °C. Compound (1*R*,1*S*,*R*)-**15f** was obtained after chromatography to give a 70% yield with 99% de. ^{1}H NMR (MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.70 (s, 6H), 3.15 (dd, J=17.1, 4.5 Hz, 1H), 3.34 (d, J=17.1 Hz, 1H), 4.80 (dd, J=9.6, 4.9 Hz, 1H), 4.93 (ddd, J=4.9, 4.9, 1.6 Hz, 1H), 5.47 (d, J=9.6 Hz, 1H), 7.02 (s, 2H), 7.12–7.31 (m, 7H), 7.50–7.68 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 21.16, 23.30, 38.34, 60.27, 80.33, 124.53, 125.14, 125.42, 127.64, 128.67, 129.38, 132.23, 132.63, 134.78, 138.14, 139.26, 139.99, 142.50, 144.43. Anal. Calcd for $C_{24}H_{25}NO_4S_2$: C, 63.27; H, 5.53; N, 3.07. Found: C, 63.18; H, 5.65; N, 2.96.

4.13.2. Preparation of (*R*)-phenyl *p*-tolylsulfoxide. ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H), 7.20 (d, J=8.1 Hz, 1H), 7.38 (m, 1H), 7.55 (d, J=8.1 Hz, 1H), 7.61 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 21.28, 124.50, 124.81, 129.15, 129.93, 130.78, 141.51, 142.38, 145.71. Anal. Calcd for $C_{13}H_{12}OS$: C, 72.19; H, 5.59; S, 14.82. Found: C, 71.49; H, 5.67; S, 14.54. Chiral HPLC method: Chiralpak AS, hexane/IPA, 90:10; 1 mL/min; 220 μm; (*R*)-isomer t_R=15.5 min; (S)- isomer, t_R=13.4 min.

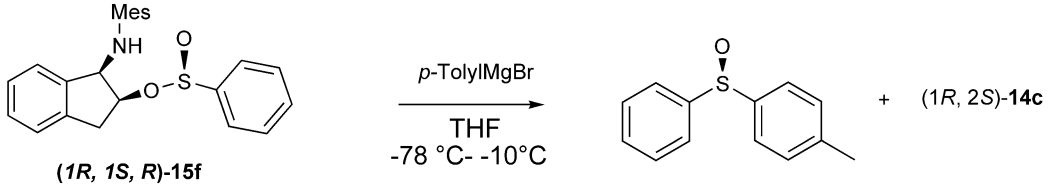
4.14. Method C: one pot procedure for the preparation of sulfoxides from *endo*-13c

See Scheme 19.

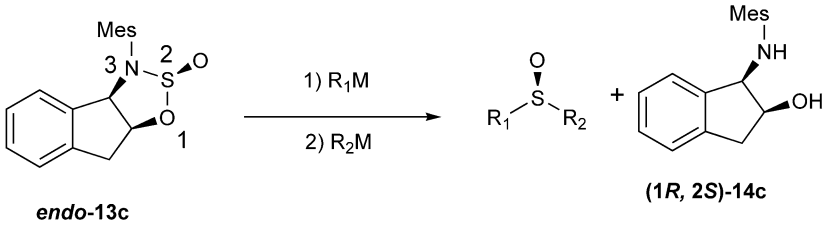
4.14.1. Preparation of (*R*)-cyclohexyl 2-methoxyphenyl-sulfoxide (Table 4, entry 6). See Scheme 20.

Typical one-pot procedure for the preparation of sulfoxide using *endo*-**13c**

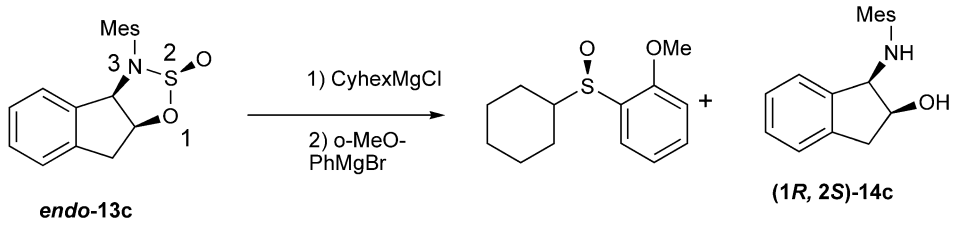
A solution of e*ndo*-**13c** (1.44 g, 3.82 mmol) in THF (10 mL) at −78 °C under argon was added cyclohexylMgCl (1.9 mL, 2.0 M in THF) dropwise. The reaction mixture was stirred for 1–2 h at −78 °C, monitored by TLC analysis. Then 2-methoxyphenylmagnesium bromide (4.5 mL, 1.0 M in THF) was added dropwise. The reaction mixture was warmed to −45 to −15 °C, stirred, monitored by TLC analysis, and quenched by addition of aqueous $NaHCO_3$ (10 mL) and diluted with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (20 mL), the



Scheme 18.



Scheme 19.



Scheme 20.

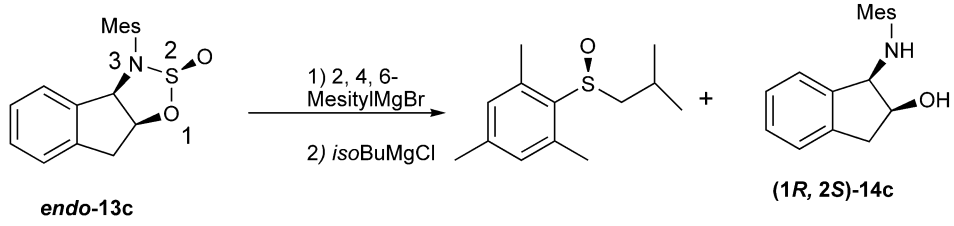
combined organic phase was washed with 20% NaCl, dried over Na_2SO_4 and evaporated to dryness to give a product and auxiliary mixture that was purified by flash chromatography eluted with EtOAc to afford the sulfoxide (0.73 g, 83%) in 98% ee. See section 4.7.1 for analytical data ((*R*)-**20**).

4.14.2. Preparation of (*S*)-2,4,6-mesityl isobutylsulfoxide (Table 4, entry 9). ^{1}H NMR ($CDCl_3$): δ 1.07 (d, J=6.6 Hz, 3H), 1.09 (d, J=6.0 Hz, 3H), 2.10–2.22 (m, 1H), 2.23 (s, 3H), 2.40–2.50 (m, 1H), 2.50 (s, 6H), 6.82 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 19.0, 20.9, 21.5, 22.8, 24.4, 61.5, 130.8, 135.3, 137.9, 140.8. Anal. Calcd for $C_{13}H_{20}OS$: C, 69.59; H, 8.98; S, 14.29. Found: C, 69.41; H, 8.98; S, 14.15. Chiral HPLC method: Chiralcel OB, 250×4.6 mm, 10 μm, hexane/IPA, 95:5, 0.2 mL/min, 222 nm, (*R*)-isomer, t_R=45.3; (*S*)-isomer t_R=53.6 min (Scheme 21).

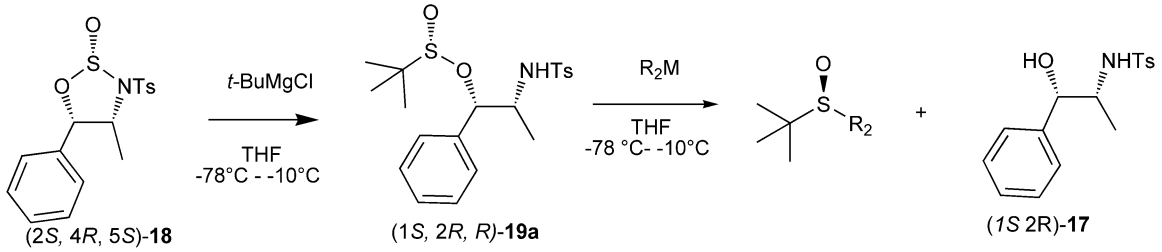
4.15. Method D: the preparation of sulfoxides from (2*S*,4*R*,5*S*)-18 ((*S*)-TMPOO) or (2*R*,4*S*,5*R*)-18 ((*R*)-TMPOO)

See Scheme 22.

4.15.1. (1*S*,2*R*,*R*)-19a. To a solution of (*S*)-TMPOO (45 g, 128 mmol) in THF (300 mL) at −78 °C was added *t*-butyl magnesium chloride (145 mL, 1.0 M) in THF dropwise via syringe for 30 min under argon. After stirred for 1–2 h, as monitored by TLC for the disappearance of the starting material, the reaction was quenched with aqueous $NaHCO_3$ (300 mL), and diluted with EtOAc (400 mL). The aqueous phase was extracted with EtOAc (200 mL) and the combined organic phases were washed with brine (400 mL), dried with (Na_2SO_4) and concentrated to afford a crystalline product, (1*S*,2*R*,*R*)-**19a** (52 g, 99%)



Scheme 21.



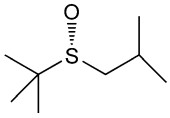
Scheme 22.

with >99% de. ^{1}H NMR ($CDCl_3$): δ 0.98 (d, J=6.84 Hz, 3H), 1.25 (s, 9H), 2.43 (s, 3H), 3.56–3.68 (m, 1H), 4.96 (d, J=2.32 Hz, 1H), 5.84 (d, J=9.77 Hz, 1H), 7.07–7.11 (m, 2H), 2.27–7.35 (m, 5H), 7.85–7.88 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 14.9, 21.7, 21.9, 54.6, 58.3, 84.8, 125.9, 127.3, 128.4, 128.7, 129.8, 137.4, 138.5, 143.5. Anal. Calcd for $C_{20}H_{27}NO_4S_2$: C, 58.65; H, 6.64; N, 3.42; S, 15.66. Found: C, 58.56; H, 6.61; N, 3.40; S, 15.69.

4.15.2. (1*R*,2*S*,*S*)-19a. Compound (1*R*,2*S*,*S*)-**19a** was prepared from (*R*)-TMPOO by following same procedure described above to afford (1*R*,2*S*,*S*)-**19a** in 98% yield and >99% de.

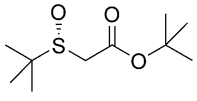
The following sulfoxides were prepared from (1*R*,2*S*,*S*)-**19a**.

4.15.2.1. Preparation of (R)-tert-butyl isobutylsulfoxide (Table 4, entry 1) (R_2M=isoBuMgCl) from (1*R*,2*S*,*S*)-19a.



Refer (*S*)-enantiomer for analytical data (section 4.8.1).

4.15.2.2. Preparation of (R)-tert-Butyl (tert-butylsulfinyl)acetate (Table 4, entry 11) (R_2M=$LiCH_2COOBu$-t) from (1*R*,2*S*,*S*)-19a.



Refer (*S*)-enantiomer for analytical data (section 4.8.3).

4.16. Typical procedure for the reaction of (*R*)-TMPOO with RZnBr reagent for the preparation of sulfoxide

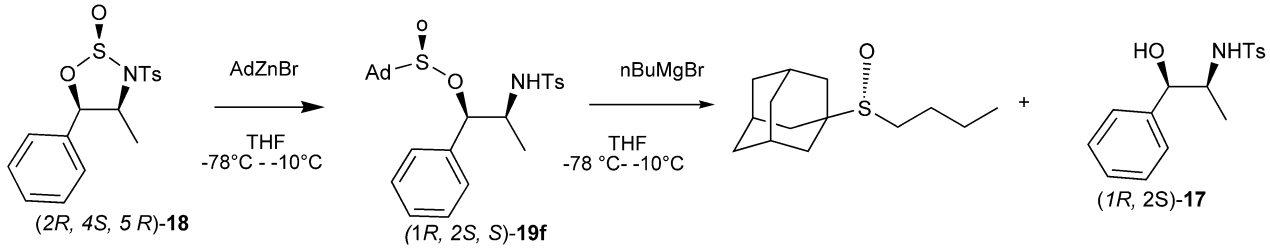
4.16.1. Preparation of (*R*)-1-adamantyl *n*-butylsulfoxide from (1*R*,2*S*,*S*)-17b (Table 4, entry 2). See Scheme 23.

4.16.1.1. Preparation of (1*R*,2*S*,*S*)-19f. The compound was prepared by following the same procedure as described in Method A to afford the compound with 85% yield and 99% de. ^{1}H (δ $CDCl_3$): 0.98 (d, J=6.83, Hz, 3H), 1.66–1.83 (m, 7H), 1.83–1.98 (m, 5H), 2.14–2.23 (m, 3H), 2.42 (s, 3H), 3.58–3.68 (m, 1H), 4.92 (d, J=2.08 Hz, 1H), 5.86 (d, J=9.64 Hz, 1H), 7.07–7.13 (m, 3H), 7.26–7.38 (m, 4H), 7.84–7.90 (m, 2H). ^{13}C (δ $CDCl_3$): 14.9, 21.7, 28.4, 34.0, 36.5, 54.6, 60.2, 84.4, 126.0, 127.4, 128.3, 128.7, 129.9, 137.6, 138.5, 143.4. Anal. Calcd for $C_{26}H_{33}NO_4S_2$, C, 64.03; H, 6.82; N, 2.87; S, 13.15. Found: C, 63.97; H, 6.78; N, 2.69; S, 12.94.

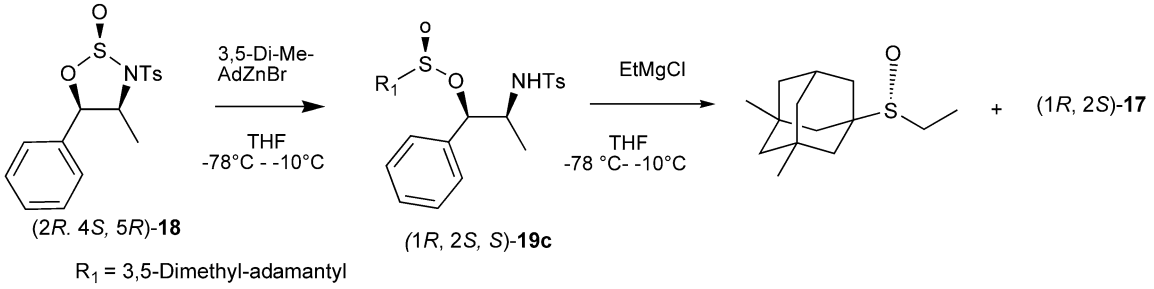
4.16.1.2. (R)-1-Adamantyl butylsulfoxide (Table 4, entry 2). The sulfoxide was prepared from (1*R*,2*S*,*S*)-**19f** by following Method A. Refer (*S*)-enantiomer for analytical data (section 4.9.2).

4.16.2. Preparation of (*R*)-3,5-dimethyl-adamantyl ethylsulfoxide from (1*R*,2*S*,*S*)-19c (Table 4, entry 3). See Scheme 24.

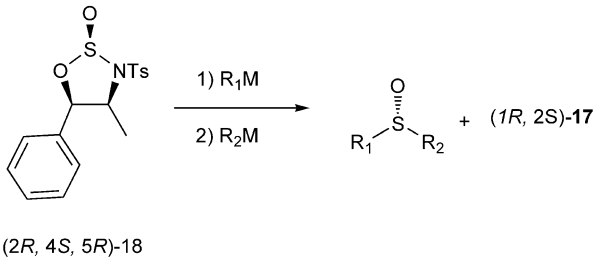
4.16.2.1. Preparation of (1*R*,2*S*,*S*)-19c. The compound was prepared in an 83% yield and >99% de. ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 6H), 0.98 (d, J=6.8 Hz, 2H), 1.21 (m, 3H), 1.38 (s, 3H), 1.50 (m, 3H), 1.71 (m, 2H), 2.23 (m, 2H), 3.61 (m, 1H), 4.91 (d, J=2.3 Hz, 1H), 5.93 (d, J=9.5 Hz, 1H), 7.08 (d, J=6.6 Hz, 2H), 7.29 (m, 5H), 7.83 (d, J=6.6 Hz, 2H). ^{13}C NMR δ 14.2, 14.9, 21.0, 21.5, 29.3, 30.3, 31.7, 32.7, 39.5, 40.0, 42.6, 42.7, 50.5, 54.4, 60.4, 61.7, 84.3, 125.9, 126.3, 127.0, 127.2, 128.2, 128.5, 129.7, 137.3, 138.3, 143.3. M^+ 516.



Scheme 23.



Scheme 24.



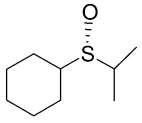
Scheme 25.

4.16.2.2. (R)-3,5-Dimethyl-adamantyl ethylsulfoxide. The sulfoxide was prepared from (1*R*,2*S*,*S*)-**19c** by following Method A. Refer (*S*)-enantiomer for analytical data (section 4.10.2).

4.17. Method E: one-pot procedure for the preparation of sulfoxides from (*R*)-TMPOO

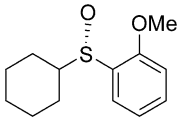
See Scheme 25.

4.17.1. (*R*)-Cyclohexyl isopropylsulfoxide (Table 4, entry 4).



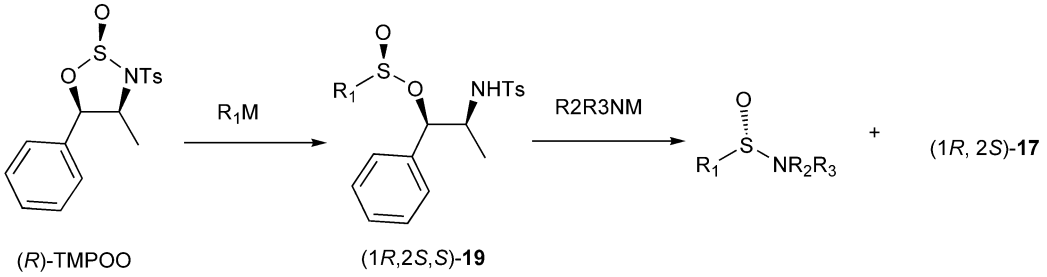
The compound was prepared from cyclohexylmagnesium chloride (R_1M) and isopropylmagnesium chloride (R_2M) by following the procedure described for (*R*)-**20**. Refer (*S*)-enantiomer for analytical data (section 4.11.2).

4.17.2. Preparation of (*S*)-cyclohexyl-2-methoxyphenyl-sulfoxide (Table 4, entry 6).

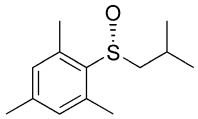


The compound was prepared from cyclohexylmagnesium chloride (R_1M) and 2-methoxyphenylmagnesium bromide (R_2M) by following the procedure described for (*R*)-**20**. Refer (*R*)-**20** for analytical data (section 4.7.1).

4.17.3. Preparation of (*R*)-2,4,6-mesityl isobutylsulfoxide (Table 2, entry 9).



Scheme 26.

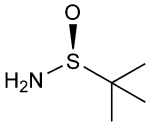


The compound was prepared form 2,4,6-mesitylmagnesium bromide (R_1M) and isobutylmagnesium chloride (R_2M) by following the procedure described for (*R*)-**20**. Refer (*S*)-enantiomer for analytical data (section 4.14.12).

4.18. Preparation of sulfinamides from (*R*)- or (*S*)-TMPOO

See Scheme 26.

4.18.1. Preparation of (*S*)-*tert*-butanesulfinamide ((*S*)-21a).



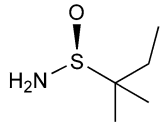
(*S*)-**21a**

4.18.1.1. Compound (1*R*,2*S*,*S*)-19a. To a solution of (*R*)-TMPOO (5 g, 14.2 mmol) in THF (30 mL) at −78 °C was added *t*-butyl magnesium chloride (15 mL, 1.0 M) in THF dropwise via syringe for 30 min under argon and the reaction mixture was stirred for 1–2 h. The reaction was monitored by TLC analysis for the disappearance of the starting material. The reaction was quenched with aqueous $NaHCO_3$ (30 mL), and diluted with EtOAc (40 mL). The aqueous phase was extracted with EtOAc (25 mL) and the combined organic phases were washed with brine (30 mL), dried with (Na_2SO_4) and concentrated to afford a crystalline product, (1*R*,2*S*,*S*)-**19a** (5.8 g, 99%) with >99% de. ^{1}H NMR ($CDCl_3$): δ 0.98 (d, J=6.84 Hz, 3H), 1.25 (s, 9H), 2.43 (s, 3H), 3.56–3.68 (m, 1H), 4.96 (d, J=2.32 Hz, 1H), 5.84 (d, J=9.77 Hz, 1H), 7.07–7.11 (m, 2H), 2.27–7.35 (m, 5H), 7.85–7.88 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 14.9, 21.7, 21.9, 54.6, 58.3, 84.8, 125.9, 127.3, 128.4, 128.7, 129.8, 137.4, 138.5, 143.5. Anal. Calcd for $C_{20}H_{27}NO_4S_2$: C, 58.65; H, 6.64; N, 3.42; S, 15.66. Found: C, 58.56; H, 6.61; N, 3.40; S, 15.69.

4.18.1.2. Compound (*S*)-21a. ((*S*)-TBSA). To an ammonia solution (30 mL) at −45 °C was added a few crystals of $Fe(NO_3)_3$, followed by addition of lithium wire (0.05 g, 7.1 mmol) in a controlled manner by keeping the internal temperature around −45 °C. When all the lithium

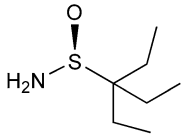
was added and a gray suspension was formed, the reaction mixture was cooled to −78 °C and a solution of (1*R*,2*S*,*S*)-**19a**, (0.45 g, 1.10 mmol) in THF (1 mL) was added slowly over a course of 20 min. Once the addition was complete, the mixture was warmed to −45 °C and stirred for 1 h, followed by addition of NH_4Cl (0.5 g). The cold bath was removed, and stirring continued until the mixture reached ambient temperature. The remaining volatile material was removed under reduced pressure. To the remaining residue was added 2 mL water and stirred. EtOAc (5 mL) was added to the mixture and stirred. After separation of the phases, the organic phase was washed with brine (2 mL×2). After removal of the organic solvent, the residue was purified by chromatography eluted with EtOAc to afforded (*S*)-TBSA (**21a**) (0.12 g, 90%) with 99% ee. ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 9H), 3.82 (br, s, 2H). ^{13}C NMR ($CDCl_3$): δ 22.1, 55.3. Chiral HPLC analysis; Chiralpak AS column, 90:10 hexane/ethanol; 1.2 mL/min, 222 nm; (*R*)-TBSA, t_R=6.6 min; (*S*)-TBSA, t_R=9.4 min).

4.18.1.3. Sulfinamides (*S*)-21b–h. These were prepared by following the same procedure described above for the preparation of (*S*)-TBSA. The enantiomeric purity was determined by chiral HPLC analysis (see Table 5 for yield and enantiomeric excess data).[5]



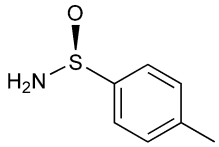
(*S*)-**21b**

4.18.2. (*S*)-2-Methyl butanesulfinamide ((*S*)-21b). ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J=7.44 Hz, 3H), 1.165 (d, J=6.23 Hz, 6H), 1.62 (ds, J=4.6, 7.45 Hz, 2H), 3.99 (b, 2H). ^{13}C NMR ($CDCl_3$) δ 8.05, 18.60, 18.70, 28.61, 58.75. Anal. Calcd for $C_5H_{13}NOS$: C, 44.41; H, 9.69; N, 10.36; S, 23.71. Found: C, 44.58; H, 9.57; N, 10.13; S, 23.57. Chiral HPLC condition: Chiralpak AS column, 4.6 mm×250 mm, 10 μm; 90:10 hexane/ethanol, 1.2 mL/min; 222 nm; (*R*)-**21b**, t_R=8.1 min; (*S*)-**21b**, t_R=10.9 min.



(*S*)-**21c**

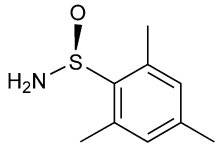
4.18.3. (*S*)-3-Ethyl pentanesulfinamide((*S*)-21c). ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J=7.6 Hz, 9H), 1.69 (m, 6H), 3.97 (s, 2H). ^{13}C NMR δ 8.39, 23.75, 63.61. M^+ 164.1. Anal. Calcd for $C_7H_{17}NOS$: C, 51.49; H, 10.49; N, 8.58; S, 19.64. Found: C, 51.79; H, 10.76; N, 8.40; S, 19.74. Chiral HPLC condition: Chiralcel OD, 4.6 mm×250 mm, 10 μm; 90:10 hexane/isopropanol, 1.0 mL/min; 222 nm; (*R*)-**21c**, t_R=14.0 min; (*S*)-**21c**, t_R=21.4 min.



(*S*)-**21d**

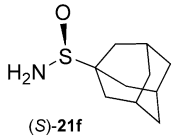
4.18.4. (*S*)-*p*-Toluenesulfinamide (*S*)-21d. ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 4.40 (s, 2H), 7.30 (d, J=8.7 Hz, 2H), 7.62 (d, J=8.7 Hz, 2H). ^{13}C NMR δ 21.3, 125.3, 129.5, 141.4, 143.3.

Chiral HPLC condition: Chiralcel OD, 4.6×250 mm, 10 μm; 90:10 hexane/ethanol, 1.0 mL/min; 230 nm; (*R*)-**21d**, t_R=10.2 min; (*S*)-**21d**, t_R=12.3 min.



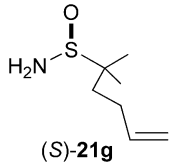
(*S*)-**21e**

4.18.5. (*S*)-2,4,6-Trimethylphenylsulfinamide ((*R*)-21e). ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H), 2.60 (s, 6H), 4.42 (b, 2H), 6.86 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 19.45, 21.20, 131.07, 136.41, 139.07, 140.98. Calcd for $C_9H_{13}NOS$; 183.27, M^+, 183.20. Chiral HPLC condition: Chiralcel OD, 4.6×250 mm, 10 μm; 90:10 hexane/isopropanol, 1.0 mL/min; 220 nm; (*R*)-**21e**, t_R=24.5 min; (*S*)-**21e**, t_R=17.0 min.



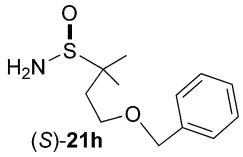
(*S*)-**21f**

4.18.6. (*S*)-1-Adamantylsulfinamide ((*R*)-21f). ^{1}H (δ $CDCl_3$): 1.4–2.2 (m, 15H), 4.02 (s, 2H). ^{13}C (δ $CDCl_3$): 28.7, 34.5, 36.6, 57.1 Anal. Calcd for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60; N, 7.03; S, 16.09. Found: C, 60.28; H, 8.59; N, 6.93; S, 16.09. Chiral HPLC condition: Chiralpak AD, 4.6 mm×250 mm, 10 μm; 90:10 hexane/isopropanol; 1 mL/min; 222 nm; (*R*)-**21f**, t_R=9.4 min, (*S*)-**21f**, t_R=14.5 min.



(*S*)-**21g**

4.18.7. (*S*)-2-Methyl-hex-5-enesulfinamide. ^{1}H NMR ($CDCl_3$): δ 0.82 (s, 6H), 1.14 (s, 2H), 1.28–1.66 (m, 11H), 1.58 (q, J=11.8 Hz, 2H), 2.17 (m, 1H), 2.46 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 19.1, 19.2, 27.8, 34.9, 57.9, 114.8, 138.0. M^+ 162. Anal. Calcd for $C_7H_{15}NOS$: C, 52.13; H, 9.38. Found: C, 52.26; H, 9.49. Chiral HPLC analysis: Chiralcel OD, 4.6 mm×250 mm, 10 μm; 230 nm; 1.0 mL/min; Hex/IPA, 90:10; (*R*)-**21g**, t_R=15.8; (*S*)-**21g**, t_R=4.0 min.



(*S*)-**21h**

4.18.8. (*S*)-4-Benzyloxy-2-methyl-butanesulfinamide. ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 3H), 1.24 (s, 3H), 1.93 (dt, $J1=$ 2.77 Hz, $J2=6.60$ Hz, 2H), 1.71 (t, $J=6.59$ Hz, 2H), 3.97 (s, 2H), 4.50 (m, 2H), 7.26–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 20.2, 20.3, 34.8, 57.7, 66.3, 73.2, 127.8, 128.5, 138.5. Anal. Calcd for $C_{12}H_{19}NO_2S$; C, 59.72; H, 7.93; N, 5.80; S, 13.29. Found: C, 60.12; H, 8.09; N, 5.79; S, 13.63.

4.19. Unoptimized chromatography free process for the preparation of (*S*)-TBSA

4.19.1. Preparation of (1*R*,2*S*,*S*)-19a. To a solution of (2*R*,4*S*,5*R*)-**18** (62 g, 171 mmol) in THF (350) at −45 °C was added *t*-butyl magnesium chloride (200 mL, 1.0 M) dropwise over 1–1.5 h under argon. After the reaction mixture was stirred for 1.5 h, aqueous solution of NH_4Cl (20%) (150 mL) was added to quench the reaction (keep the temperature below −10 °C). The reaction mixture was diluted with THF (150 mL) and allowed to warm to ambient temperature. After removal of the aqueous phase, the organic phase was washed once with aqueous solution of NaCl (24%) (75 mL) and concentrated under reduced pressure. Then heptane was added to the mixture and the mixture was further distilled under reduced pressure until the mixture reached a KF value of <0.02%. Then the concentration of the product (1*R*,2*S*,*S*)-**19a** was adjusted to 0.2 to 0.3 g/mL by adding anhydrous THF (95–98% reaction yield).

4.19.2. Preparation of (*S*)-TBSA. To an ammonia (600 mL) solution at −45 °C containing catalytic amount of $Fe(NO_3)_3$ was added lithium (5.25 g) portionwise under argon and the resulting mixture was stirred at −45 °C for 1.5 h. The mixture was then cooled to −78 °C and a solution of (1*R*,2*S*,*S*)-**19a** prepared above was added in 1.5 h. After stirring for 20 min, the reaction mixture was warmed to −45 °C and stirred for 30–60 min to furnish the reaction. After the quenching of the reaction by slow addition of solid ammonium chloride (60 g) portionwise, the mixture was warmed to 20–25 °C while the released ammonia gas was trapped by water. The mixture was diluted with isopropyl acetate (IPAC) (500 mL) and the resulting mixture was distilled under reduced pressure to remove the low boiling point solvent (THF). Water (140 mL) and IPAC (300 mL) was added to the residue and stirred to give a clear phase separation. The organic phase was washed once with aqueous solution of NH_4Cl (24%) (30 mL). The aqueous phase was extracted with IPAC (150 mL×2) and the organic phases were combined ((*S*)-TBSA is very soluble in water). The combined organic phases were conducted solvent switch under pressure to water (80 mL) and stirred to give a slurry. The slurry was filtered and wet cake was washed twice with water (15 mL). The wet cake was dried and recovered as the starting material (1*R*,2*S*)-**17** (50.5 g 97%), leaving the (*S*)-TBSA in the aqueous solution. The aqueous solution of (*S*)-TBSA was vacuum concentrated, heptane (150 mL) was added and the distillation was performed under azotropic condition with a Dean–Stark trap until all the water was removed. The resulting mixture was then cooled to 0 °C and stirred for 1 h. The slurry was filtered to afford (*S*)-TBSA (15.7 g, 76%) in 99% ee.

References and notes

1. (a) Solladie, G. *Synthesis* **1981**, 185. (b) Posner, G. H. In Morrison, J. D., Ed.; Asymmetric Synthesis; Academic: New York, 1983; Vol. 2, Chapter 3, p 225. (c) Barbachyn, M. R.; Johnson, C. R. In Morrison, J. D., Scott, J. W., Eds.; Asymmetric Synthesis; Academic: New York, 1983; Vol 4, Chapter 3, p 227. (d) Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717. (e) Kagan, H. B.; Diter, P. In Page, P. C. B., Ed.; Organosulfur Chemistry; Academic: New York, 1998; Vol. 2, Chapter 3, p 1. (f) Khiar, N.; Fernandez, I.; Alcudia, A.; Alcudia, F. In Rayner, C. M., Ed.; Advances in Sulfur Chemistry; JAJ: Stamford, 2000; Vol 2. (g) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Spina, G.; Tortorella, P. *J. Org. Chem.* **2001**, *66*, 5933.
2. (a) James, B. R.; McMillan, R. S. *Can. J. Chem.* **1977**, *55*, 3927. (b) Khiar, N.; Fernandez, I.; Alcudia, F. *Tetrahedron Lett.* **1993**, *34*, 123. (c) Carreno, M. C.; Garcia-Ruano, J. L.; Maestro, M. C.; Martin Cabrejas, L. M. *Tetrahedron: Asymmetry* **1993**, *4*, 727. (d) Tokunoh, R.; Sodeoka, M.; Aoc, K.; Shibasaki, M. *Tetrahedron Lett.* **1995**, *36*, 8035. (e) Ordonez, M.; Rosa, V. G.; Labastida, V.; Llera, J. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2675. (f) Owens, D. T.; Hollander, J. F.; Oliver, A. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 1539.
3. (a) Savage, P. B.; Holmgren, S. K.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 7900. (b) Savage, P. B.; Holmgren, S. K.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 10448.
4. (a) Iimori, T.; Takahashi, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 1965. (b) Davis, F.; Kern, J. R.; Kurtz, L. J.; Pfister, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 7873. (c) Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717. (d) Matsugi, M.; Fukuda, N.; Muguruma, Y.; Yamaguchi, T.; Minamikawa, J.; Otsuka, S. *Tetrahedron* **2001**, *57*, 2739. (e) Cotton, H.; Elebring, T.; Larsson, M.; Li, L.; Sorensen, H.; Unge, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3819.
5. Kagan, H. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed. 2nd ed.; Wiley-VCR: New York, 2000; Chapter 6c.
6. (a) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; AP: UK, 1994. (b) Kagan, H. B.; Rebiere, F. *Synlett* **1990**, 643.
7. Gilman, H.; Robinson, J.; Beaber, N. H. *J. Am. Chem. Soc.* **1926**, *48*, 2715.
8. Andersen, K. K. *Tetrahedron Lett* **1962**, *3*, 93.
9. (a) Wudl, F.; Lee, T. B. K. *J. Chem. Soc., Chem. Commun.* **1972**, 61. (b) Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349.
10. Hiroi, K.; Sato, S.; Kitayama, R. *Chem. Lett.* **1980**, 1595.
11. Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5885.
12. Rebiere, F.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991.
13. Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977.

14. Oppolzer, W.; Froelich, O.; Wiaux-Zamar, C.; Bernardinell, G. *Tetrahedron Lett.* **1997**, *38*, 2825.
15. (a) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011. (b) For racemic synthesis of **6**, see: Khiar, N.; Fernandez, I.; Alcidia, F. *Tetrahedron Lett.* **1994**, *35*, 5719. (c) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317.
16. (a) Whitesell, J. K.; Wong, M. S. *J. Org. Chem.* **1991**, *56*, 4552. (b) Whitesell, J. K.; Wong, M. S. *J. Org. Chem.* **1994**, *59*, 597. (c) Fernandez, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789.
17. (a) El Ouazzani, H.; Khiar, N.; Fernandez, I.; Alcudia, F. *J. Org. Chem.* **1997**, *62*, 287. (b) Khiar, N.; Araujo, C. S.; Alcudia, F.; Fernandez, I. *J. Org. Chem.* **2002**, *67*, 345.
18. (a) Colonna, S.; Gaggero, N.; Pasta, P.; Ottolina, G. *Chem. Commun.* **1996**, 2303. (b) Khiar, N.; Alcudia, F.; Espartero, J.-L.; Rodriguez, L.; Fernandez, I. *J. Am. Chem. Soc.* **2000**, *122*, 7598 and references therein. (c) Bolm, C.; Muniz, K.; Hildebrand, J. P. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999.
19. (a) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880. (b) Han, Z.; Krishnamurthy, D.; Grover, P.; Wilkinson, H. S.; Fang, Q. K.; Su, X.; Lu, Z-H. ; Magiera, D.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2032.
20. For the detailed experimental procedure and single crystal X-ray data, see Section 4.
21. Absolute configuration of **16** was deduced from the synthetic Scheme 4, involving two consecutive inversions of configuration, and X-ray analysis of (1*R*,2*S*,*R*)-**15c**.
22. Addition of *p*-tolylMgBr, followed by EtMgCl/$CeCl_3$ to *endo*-**13c** at low temperature obtained a 93% ee of *p*-tolyl ethyl sulfoxide.
23. Use of *tert*-butyl (*p*-tolylsulfinyl)acetate in asymmetric synthesis: Solladia, G.; Bauder, C.; Arce-Dubois; Jacope, P. Y. *Tetrahedron Lett.* **2001**, *42*, 2923.
24. Capozzi, M. A. M.; Cardellicchio, C.; Fracchiolla, G.; Naso, F.; Tortorella, P. *J. Am. Chem. Soc.* **1999**, *121*, 4708.
25. Davis, F. A.; Zhang, Y.; Andemichael; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403 and references therein.
26. (a) Fanelli, D. L.; Szewczyk, J. M.; Zhang, G.; Reddy, V.; Burns, D. M.; Davis, F. A. *Org. Synth.* **1999**, *77*, 50. (b) Davis, F. A.; Zhou, P.; Chen, B-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (c) Zhou, P.; Chen, B.-C.; Davis, F. A. In Rayner, C. M., Ed.; Advances in sulfur chemistry; JAL, 2000; Vol. 2, p 249.
27. Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.
28. Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2640.
29. (a) Senanayake, C. H. *Aldrichim. Acta* **1998**, *31*, 3. (b) Ghosh, A. K.; Fidanze, S.; Senanayake, C. H. *Synthesis* **1998**, 937.
30. Direct comparison of raw material cost of *endo*-MIOO (*end*-**13c**) and (*R*)-TMPOO indicated that (*R*)-TMPOO is much more inexpensive to prepare in multi kilo scale compared to *endo*-MIOO.
31. Unoptimized chromatography free process has been devised for isolation of (*S*)-TBSA with high recovery of (1*R*,2*S*)-**17**. For the detailed experimental procedure, see Section 4.[19]
32. Different enantioselectivity between Na and LiHMDS was observed by Davis' group. Davis, F. A.; Ramachandar, T.; Wu, Y. *J. Org. Chem.* **2003**, *68*, 6894.
33. Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127.
34. Review of solid-phase linkers: James, I. W. *Tetrahedron* **1999**, *55*, 4855.

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Exploring structural effects of ketone catalysts on asymmetric epoxidation of olefins

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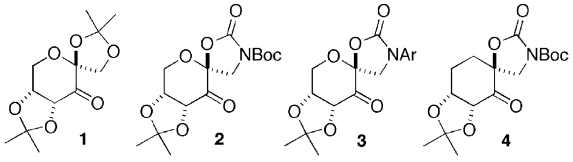
Abstract—Several ketone catalysts containing spiro ethers and lactones have been investigated for the asymmetric epoxidation of olefins. The results showed that substituents on the spiro ring of the ketone catalysts have profound effects on enantioselectivity. Results also suggested that the high enantioselectivities previously observed for conjugated *cis*-olefins with oxazolidinone containing ketones could be partially due to attractive interactions between the R_π group of the olefin and the carbonyl group of the oxazolidinone. In addition, nonbonding interactions such as van der Waals forces and/or hydrophobic interactions between the olefin substituents and the nitrogen substituents of the oxazolidinone may also be involved in stereodifferentiation. The information gained provides additional understanding of factors important for ketone catalyzed epoxidations.

1. Introduction

Dioxiranes are a powerful and versatile class of oxidizing agents.[1] Chiral dioxiranes generated in situ from chiral ketones have recently been shown to be viable reagents for asymmetric epoxidation of olefins.[2,3] During the course of our studies, we found that fructose-derived ketone **1** gives high ees for a variety of *trans*- and trisubstituted olefins (Scheme 1).[2b,c,4] However, enantioselectivity was found to be poor for *cis*- and terminal olefins with this ketone.[4b] Our continuing studies showed that ketones **2** and **3** containing a spiro oxazolidinone ring gave encouragingly high ees for *cis*-olefins and styrenes (Scheme 1).[5] Subsequently, we found that the enantioselectivity for styrenes could be further enhanced using carbocyclic oxazolidinone-containing ketone **4** (Scheme 1).[6]



Scheme 1.

Spiro and planar models represent the two extreme transition state geometries for epoxidation with dioxiranes (Fig. 1). It is believed that spiro transition states are generally favored over the planar ones presumably due to the geometric feasibility of stabilizing secondary orbital interactions of an oxygen lone pair of the dioxirane with the π^* orbital of the reacting alkene in the spiro transition state.[1c,2,3d,i,4a,b,7,8] Our studies showed that the origin of the enantioselectivity of ketone **1** is consistent with steric effects. Among possible competing transition states, spiro **B**–**D** and planar **E**–**G** are sterically disfavored (Fig. 2). Studies showed that the epoxidation primarily proceeds through spiro **A**, with potentially minor contributions from **B**, **E**, and **F**. In many cases, the minor enantiomer of the epoxide product mainly results from planar transition state **H**, with other competing transition states **C**, **D**, and **G** being possibly involved as well.[4a,b] The extent of the competition among various transition states is significantly influenced by the steric nature of the substituents on the olefins.[4b] However, the origin of the enantioselectivity for ketones **2**–**4** for *cis*- and terminal olefins is more likely due to non-steric interactions. Our studies suggest that the stereodifferentiation of ketones **2**–**4** may result from an attraction

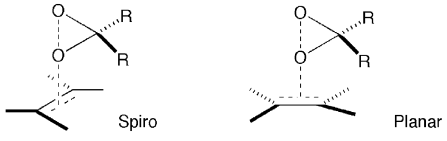


Figure 1. Spiro and planar transition states for the dioxirane epoxidation.

Keywords: Asymmetric epoxidation; Chiral dioxirane; Chiral ketone; Organocatalysis.
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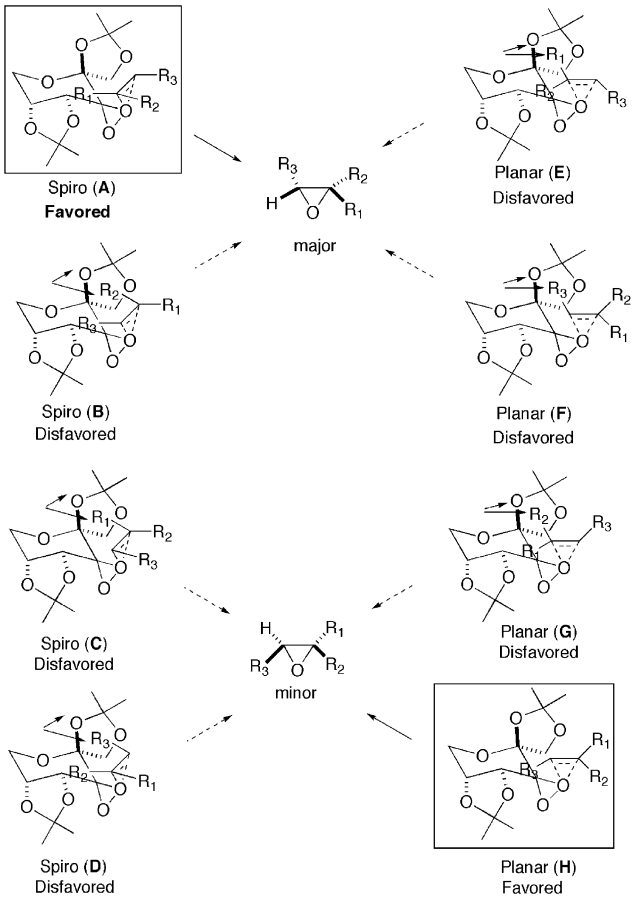


Figure 2. Spiro and planar transition states for ketone **1** catalyzed epoxidation.

between the R_π group of the conjugated *cis*-olefin and the oxazolidinone moiety of the ketone catalyst in the transition state, thus favoring spiro **I** (Fig. 3).[5,6]

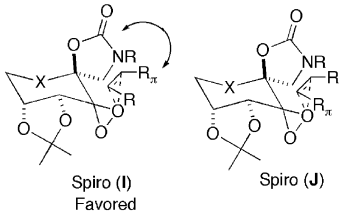
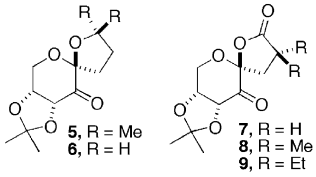


Figure 3. Competing spiro transition states for the epoxidation of *cis*-olefins catalyzed by ketones **2**–**4**.

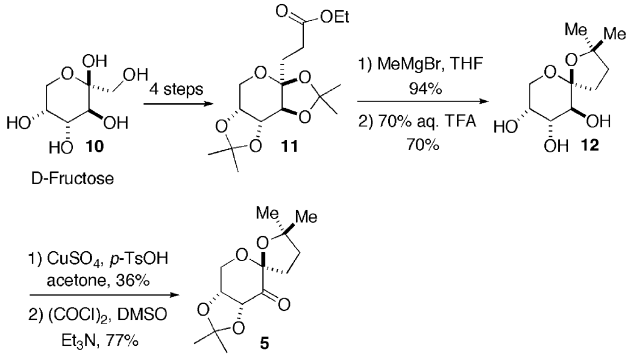
These very different results obtained for ketones **1**–**4** show that the spiro rings in these ketones are extremely important for the stereodifferentiation of the epoxidation, which prompted us to further explore the effects of different spiro ring substitution patterns on enantioselectivity for different olefin classes. Therefore, ketones **5**–**9** have been investigated (Scheme 2). Herein we wish to report our studies on this subject.



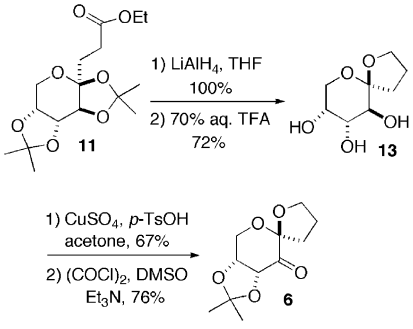
Scheme 2.

2. Results and discussion

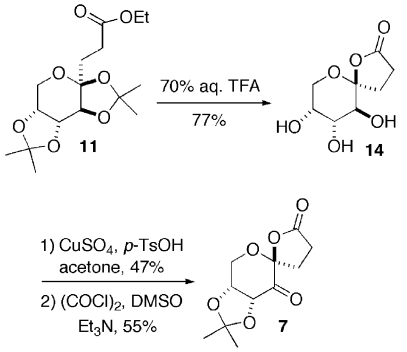
Ketone **5** is very similar to **1** with the only difference being replacement of one of the oxygens in the spiro ring with a carbon atom. Ketone **6** has the same spiro ring as **5**, but lacks the methyl groups. Ketones **7**–**9** replace the oxazolidinone of **2** with a lactone and ketones **8**–**9** contain alkyl groups α to the lactone carbonyl. Ketones **5** and **6** were synthesized as shown in Schemes 3 and 4. Ester **11**, prepared from D-fructose in four steps according to a literature procedure,[9,10] reacted with MeMgBr or $LiAlH_4$ to form an alcohol which was treated with trifluoroacetic acid to form triol **12** or **13**.[11] Ketones **5** and **6** were obtained by subsequent ketalization[11]



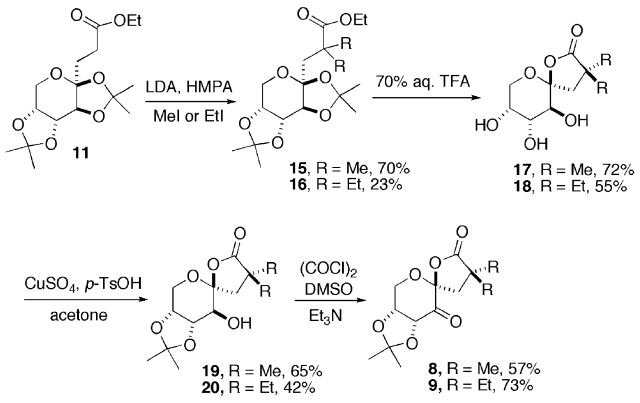
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

and Swern oxidation.[12] Ketone **7** was also prepared from ester **11** by acidic ring closure, ketalization, and Swern oxidation (Scheme 5). Ketones **8** and **9** were prepared similarly (Scheme 6). Ester **11** was alkylated with MeI and EtI to form esters **15** and **16**[13] which were converted to ketones **8** and **9** again by the same sequence of acidic ring closure, ketalization, and Swern oxidation. The X-ray structures of ketones **5**, **6**, **7**, and **9** are shown in Figures 4–7.

The catalytic properties of ketones **5**–**9** were evaluated with *trans*-β-methylstyrene, *cis*-β-methylstyrene, 1-phenylcyclohexene, and styrene. The epoxidation results are shown in Table 1. Method A uses CH_3CN–DMM (dimethoxymethane) (1:2 v/v) at pH 10.5–11.0, reaction conditions similar to those for ketone **1**.[4] Epoxidations with Methods B and C were carried out in DME-DMM (3:1 v/v), which is similar to the conditions for ketones **2**–**4**.[5,6] The reaction pH of Method C is slightly lower than in Method B.

As shown in Table 1 (entries 1 and 2), the ees obtained for *trans*-β-methylstyrene with ketone **5** are similar to those with ketone **1**,[4b] suggesting that the simple replacement of the oxygen in ketone **1** with a carbon leads to no appreciable change in enantioselectivity. However, when the two methyl groups of ketone **5** were replaced by two hydrogens as ketone **6** (Table 1, entries 3 and 4), the enantioselectivity decreased significantly for *trans*-β-methylstyrene, indicating that transition states like spiro **L** (corresponding to the

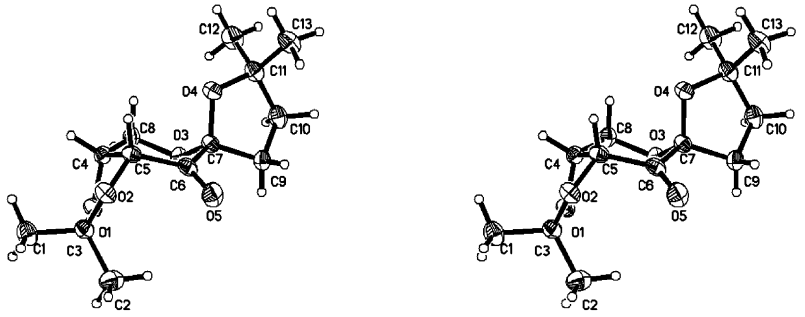


Figure 4. The X-ray structure of ketone **5** (stereoview).

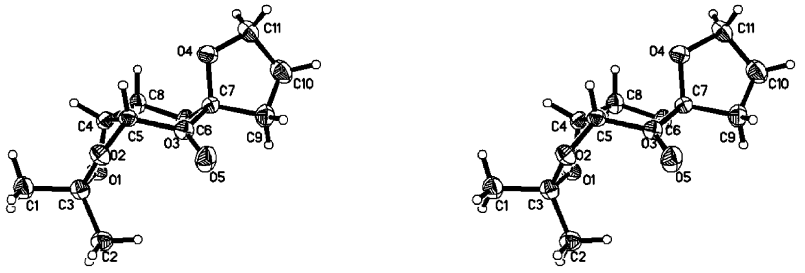


Figure 5. The X-ray structure of ketone **6** (stereoview).

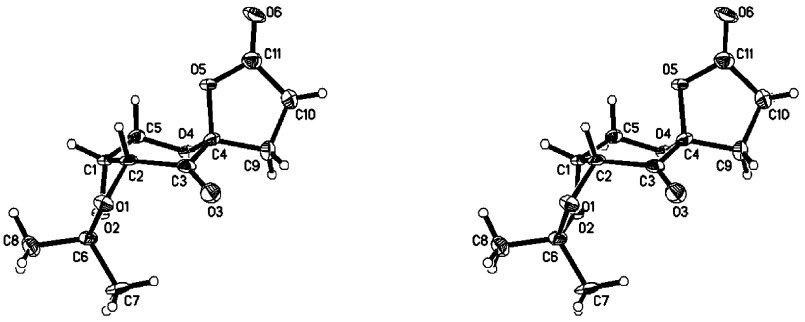


Figure 6. The X-ray structure of ketone **7** (stereoview).

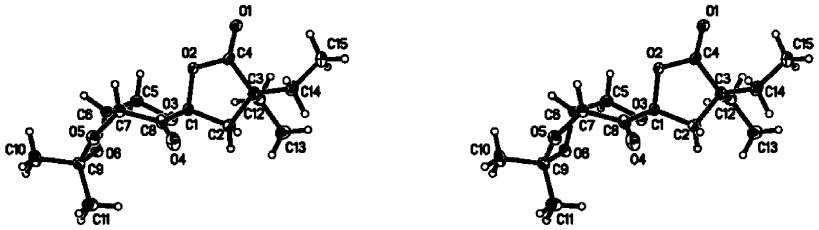


Figure 7. The X-ray structure of ketone **9** (stereoview).

sterically disfavored spiro **C**, and **D** in the case of ketone **1**) became more competitive for ketone **6** and/or planar **M** (Fig. 8). Relatively low ees for certain *trans*-olefins with ketones **2**[5a,c] and **7–9** could also be rationalized similarly as shown in Figure 9. For ketones **2**, and **7–9**, spiro transition state **O** and/or planar **P** could substantially compete with the major transition state spiro **N**, thus lowering the enantioselectivity. These results show that the methyl groups in ketone **1** and **5** are very important for the enantioselectivity with *trans*-olefins.[14] The lower ees observed with ketones **8**

Table 1. Asymmetric epoxidation of olefins by ketones **5–9**

Entry	Ketones	Method[a]	Conversion (ee)[b] (%) (config.)[c]			
			Ph	Ph	Ph	Ph
1		A	76 (96)	87 (12)	100 (97) (*R*,*R*)	50 (19)
2		B	69 (95)	86 (33)	92 (95) (*R*,*R*)	48 (38)
	5					
3		A	91 (76)	100 (45)	96 (38) (*R*,*R*)	100 (41)
4		B	98 (72)	100 (61)	86 (29) (*R*,*R*)	93 (55)
	6					
5		A	66 (73)	55 (61)	45 (18) (*S*,*S*)	34 (60)
6		B	62 (71)	62 (72)	70 (17) (*S*,*S*)	39 (62)
7		C	86 (67)	100 (74)	80 (24) (*S*,*S*)	89 (62)
	7					
8		A	76 (83)	89 (70)	89 (88) (*R*,*R*)	93 (63)
9		C	52 (71)	100 (80)	85 (81) (*R*,*R*)	70 (73)
	8					
10		A	100 (80)[d]	100 (68)[e]	100 (87) (*R*,*R*)[d]	100 (52)[d]
11		B	88 (76)	100 (81)	85 (85) (*R*,*R*)	99 (64)
12		C	96 (75)	100 (81)	86 (86) (*R*,*R*)	100 (65)
	9					

[a] Method A. Reactions were carried out with olefin (0.10 mmol), ketone (0.03 mmol), Oxone (0.212 M, 0.65 mL), and K_2CO_3 (0.892 M, 0.65 mL), in CH_3CN/DMM (1:2 v/v) (1.5 mL) and buffer (0.1 M K_2CO_3–AcOH, pH 9.3) (1.0 mL) at 0 °C. The reactions were stopped after 1.5 h. Method B. Reactions were carried out with olefin (0.10 mmol), ketone (0.03 mmol), Oxone (0.212 M, 0.84 mL), and K_2CO_3 (0.892 M, 0.84 mL) in DME/DMM (3:1 v/v) (1.5 mL) and buffer (0.1 M K_2CO_3–AcOH, pH 9.3) (1.0 mL) at 0 °C. The reactions were stopped after 1.5 h. Method C. Reactions were carried out with olefin (0.10 mmol), ketone (0.015 mmol), Oxone (0.212 M, 0.84 mL), and K_2CO_3 (0.479 M, 0.84 mL) in DME/DMM (3:1 v/v) (1.5 mL) and buffer (0.1 M K_2CO_3–AcOH, pH 8) (1.0 mL) at 0 °C. The reactions were stopped after 3.5 h.

[b] Enantioselectivity was determined by chiral GC (Chiraldex B-DM column).

[c] The absolute configurations were determined by comparing the GC data with those observed for ketones **1** and **2**. For *trans*-β-methylstyrene, all epoxides have the (*R*,*R*) configuration. For *cis*-β-methylstyrene, all epoxides have the (1*R*,2*S*) configuration. For styrene, all epoxides have the (*R*) configuration.

[d] Reactions were carried out on 0.25 mmol (olefin) scale.

[e] Reactions were carried out on 0.20 mmol (olefin) scale.

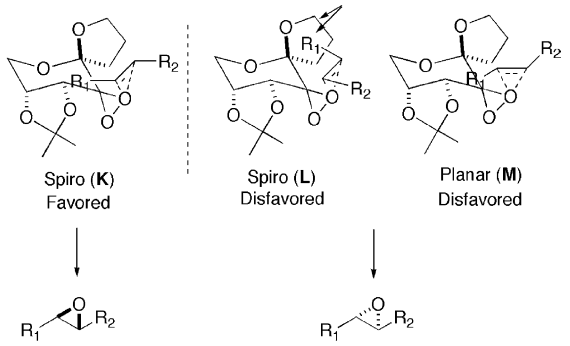


Figure 8. Competing transition states for the epoxidation of *trans*-olefins with ketone **6**.

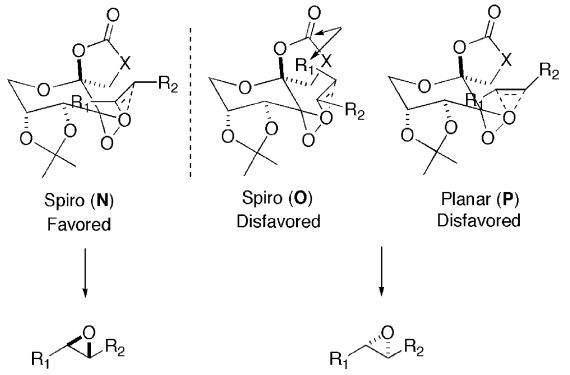


Figure 9. Competing transition states for the epoxidation of *trans*-olefins with ketones **2** and **7–9**.

and **9** further indicate that the location of the alkyl group substitution in the spiro ring is also important.

Earlier studies have shown that oxazolidinone-containing ketones **2–4** gave high ees for certain conjugated *cis*-olefins. The high enantioselectivity appears to arise primarily from electronic differentiation (Fig. 3). Current studies show that ketones **7–9** bearing carbonyl functionality in the spiro ring provide higher enantioselectivity for *cis*-β-methylstyrene when compared to the chiral ketones without carbonyl groups in their spiro rings (Table 1). This suggests that the carbonyl group is at least partially responsible for the attraction between the phenyl group of the olefin and the spiro ring of the ketone catalysts **2–4** and **7–9** (Fig. 10). The higher ees obtained for *cis*-β-methylstyrene with ketone **2** as compared to lactone ketones **7–9** suggest that in addition to the attraction between the phenyl groups of the olefins and the carbonyl groups of the spiro rings of the catalysts, further nonbonding interactions such as van der Waals forces and/or hydrophobic interactions between the

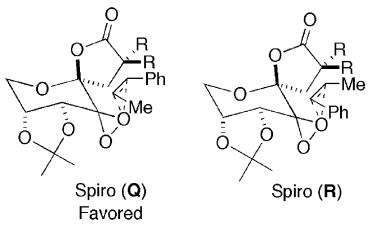


Figure 10. Competing spiro transition states for the epoxidation of *cis*-β-methylstyrene catalyzed by ketones **7–9**.

phenyl group and the nitrogen substituents of the oxazolidinone further enhance enantioselectivity (Fig. 3).

The sensitivity of the electronic and steric effects on enantioselectivity is also revealed by the epoxidation results of 1-phenylcyclohexene. Earlier studies showed that the attractive interaction between the phenyl group of 1-phenylcyclohexene and the oxazolidinone moiety of ketones **2** and **3** could make a planar transition state compete with or even override the inherent bias of the spiro transition state.[5c,d] The (*S*,*S*) epoxide obtained for 1-phenylcyclohexene (Table 1, entries 5–7) with ketone **7** also supports the presence of an attraction between the phenyl group of the olefin and the spiro lactone of the ketone catalyst, thus favoring planar transition state **T** (Fig. 11). However, the opposite enantiomer was obtained with ketones **8** and **9** (Table 1, entries 8–12). The reversal of the epoxide configuration could be due to the fact that the α-alkyl groups of the lactones of these two ketones sterically disfavor planar transition state **V** (Fig. 12). These results along with the data obtained from *cis*- and *trans*-β-methylstyrene give an idea of the functionality requirements responsible for the observed enantioselectivity for the different olefin classes.

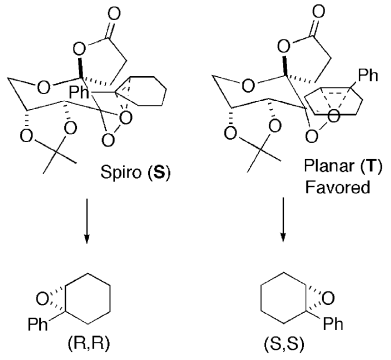


Figure 11. Competing transition states for the epoxidation of 1-phenylcyclohexene by ketone **7**.

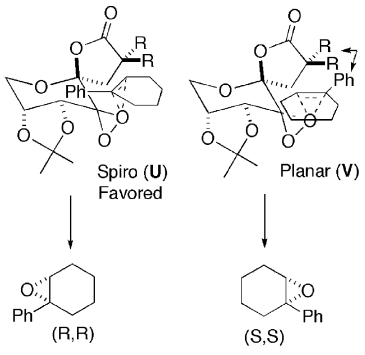


Figure 12. Competing transition states for the epoxidation of 1-phenylcyclohexene by ketones **8** and **9**.

3. Conclusion

Several ketone catalysts with spiro ethers and lactones have been prepared and investigated for the asymmetric epoxidation of olefins. Studies showed that substituents on the spiro

ring of ketone catalysts have profound effects on the enantioselectivity both sterically and electronically. Substituents smaller than methyl groups on the spiro ring of the catalyst decreased the ee due to increased competition from disfavored spiro and/or planar transition states for *trans*-olefins. The results obtained with lactone-containing ketones suggest that attractive interactions between the R_{π} group of the olefin and the carbonyl group of the oxazolidinone significantly contribute to the high enantioselectivity previously observed for conjugated *cis*-olefins with oxazolidinone ketones (**2**–**4**). In addition, nonbonding interactions such as van der Waals forces and/or hydrophobic interactions between the olefin substituents and the nitrogen substituents of the oxazolidinone make significant contributions to stereodifferentiation. The information gained in this study provides us with further understanding of steric and electronic effects on ketone catalyzed epoxidation and will aid in the design of new ketone catalysts.

4. Experimental

4.1. General methods

Oxone was purchased from Aldrich (it has been found that the oxidation activity of the purchased Oxone occasionally varies with different batches). All glassware used for the epoxidation was carefully washed with soap water to be free of any trace metals which catalyze the decomposition of Oxone. High-resolution mass spectra were performed at the mass spectrometry facility of Colorado State University. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ). X-ray crystallographic analyses were performed at the X-ray Crystallographic Laboratory of Colorado State University. Column chromatography was done with 60 Å 230–400 mesh Whatman silica gel.

4.1.1. Preparation of ketone 5. To a solution of ester **11**[10] (2.52 g, 7.6 mmol) in THF (40.0 mL) at 0 °C was added MeMgBr (10.0 mL, 31.7 mmol, 3.17 M in ether) slowly. The reaction was stirred at rt overnight until complete as judged by TLC (1:1 hexanes/ethyl acetate). The reaction was then taken back to 0 °C and was slowly diluted with water. The mixture was extracted with ethyl acetate, washed with saturated NH_4Cl and brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (1:1 hexanes/ethyl acetate) to give the alcohol as a clear oil (2.25 g, 94%). IR (NaCl film) 3454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.58 (dd, J=8.0, 2.4 Hz, 1H), 4.23 (d, J=8.0 Hz, 1H), 4.12 (d, J=2.4 Hz, 1H), 3.86 (dd, J=13.0, 1.6 Hz, 1H), 3.73 (d, J=13.0 Hz, 1H), 2.03–2.00 (m, 1H), 1.88–1.75 (m, 3H), 1.53 (s, 3H), 1.50 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.1, 107.7, 104.3, 74.3, 71.0, 70.8, 70.5, 61.2, 36.8, 35.8, 29.6, 29.4, 26.6, 26.0, 25.3, 24.3.

A solution of the above alcohol (2.25 g, 7.12 mmol) in aqueous TFA (70%) (14.2 mL) was stirred at rt overnight.[11] The solvent was removed by rotovap under high vacuum. The resulting residue was purified by flash chromatography (ethyl acetate, 20:3 ethyl acetate/methanol) to give impure triol **12** as a white solid (1.09 g, 70%). The product was taken on without further purification and characterization.

To a solution of the above triol **12** (1.09 g, 5.0 mmol) in acetone (50.0 mL) at rt was added *p*-TsOH (0.1 g, 0.53 mmol) and $CuSO_4$ (1.5 g, 9.4 mmol). After stirring at rt for 50 h,[11] solid K_2CO_3 (excess) was added until the pH of the reaction was made slightly basic. The reaction mixture was filtered over a glass frit and a compressed plug of celite, concentrated, and purified by flash chromatography (2:3 hexanes/ether) to give the alcohol as a solid (0.47 g, 36%). IR (NaCl film) 3459 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.17 (dd, J=5.6, 2.4 Hz, 1H), 4.08 (dd, J=13.6, 2.4 Hz, 1H), 4.02 (dd, J=7.2, 5.6 Hz, 1H), 3.94 (d, J=13.6 Hz, 1H), 3.58 (d, J=7.2 Hz, 1H), 2.39–2.34 (m, 1H), 2.01–1.94 (m, 2H), 1.77–1.70 (m, 1H), 1.69 (brs, 1H), 1.56 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.4, 107.8, 84.8, 78.5, 74.1, 72.2, 59.6, 36.6, 34.2, 29.7, 28.7, 28.4, 26.4.

To a solution of oxalyl chloride (0.16 mL, 1.83 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C was added DMSO (0.27 mL, 3.80 mmol).[12] After the reaction was stirred at −78 °C under argon for 5 min, the cold bath was removed for 3 min. and then the reaction was taken back to −78 °C. A solution of the above alcohol (0.44 g, 1.7 mmol) in CH_2Cl_2 (17.0 mL) was added. After stirring for 1 h, Et_3N (0.8 mL, 5.7 mmol) was added. The reaction mixture was slowly brought to rt over 45 min, quenched with water, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (1:1 hexanes/ether) to give ketone **5** as a white solid (0.34 g, 77%). IR (NaCl film) 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.72 (d, J=5.6 Hz, 1H), 4.53–4.51(m, 1H), 4.39 (dd, J=13.6, 2.4 Hz, 1H), 4.02 (d, J=13.6 Hz, 1H), 2.72–2.65 (m, 1H), 2.01–1.93 (m, 2H), 1.83–1.78 (m, 1H), 1.47 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.7, 110.4, 107.7, 86.7, 78.5, 76.2, 59.3, 36.4, 31.7, 29.6, 28.5, 27.5, 26.4. HRMS calcd for $C_{13}H_{21}O_5$ (M+1): 257.1389, found: 257.1390.

4.1.2. Preparation of ketone 6. To a solution of $LiAlH_4$ (0.3 g, 7.9 mmol) in THF (30.0 mL) at 0 °C was slowly added a solution of ester **11** (1.32 g, 4.0 mmol) in THF (10.0 mL).[10] The ice bath was removed, and the reaction was stirred at rt until complete as judged by TLC (3:2 hexanes/ether). The reaction was then taken back down to 0 °C, diluted with ether (5.0 mL), quenched with water (1.2 mL), 15% NaOH (1.2 mL), and water (4.0 mL). The solution was vigorously stirred until the gray color gave way to an off-white color. The reaction was filtered over a glass frit and celite and concentrated to give the alcohol as a clear oil (1.27 g, quantitative). The product was taken on without any further purification. IR (NaCl film) 3447 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.57 (dd, J=7.6, 2.4 Hz, 1H), 4.22 (dd, J=7.6, 2.1 Hz, 1H) 4.11 (d, J=2.4 Hz, 1H), 3.86 (dd, J=12.9, 2.1 Hz, 1H), 3.74–3.66 (m, 3H), 2.05–1.97 (m, 1H), 1.91–1.78 (m, 4H), 1.52 (s, 3H), 1.49 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.1, 107.8, 104.0, 74.2, 70.9, 70.7, 63.1, 61.1, 37.8, 26.5, 26.0, 25.2, 24.3.

The cyclization of the above alcohol was carried out as previously described with the alcohol (1.68 g, 5.8 mmol)

and aqueous TFA (70%) (12.0 mL) to give impure triol **13**[11] as a white solid (0.79 g, 72%).

The ketalization of triol **13** was carried out as previously described with the triol (0.79 g, 4.2 mmol), acetone (42.0 mL), *p*-TsOH (0.06 g, 0.3 mmol), and $CuSO_4$ (1.3 g, 8.1 mmol) to give the alcohol[11] as a white solid (0.65 g, 67%). IR (NaCl film) 3457 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.20 (dd, $J=5.6$, 1.6 Hz, 1H), 4.10 (dd, $J=7.6$, 5.6 Hz, 1H), 4.04–3.92 (m, 4H), 3.70 (d, $J=7.6$ Hz, 1H), 2.29–2.21 (m, 1H), 2.10–1.85 (m, 4H), 1.56 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.4, 107.5, 78.3, 74.1, 72.3, 69.0, 59.9, 33.7, 28.4, 26.4, 24.1.

The Swern oxidation was carried out as previously described with oxalyl chloride (0.26 mL, 3.0 mmol), DMSO (0.43 mL, 6.1 mmol), the alcohol (0.62 g, 2.7 mmol), and Et_3N (1.3 mL, 9.3 mmol) to give ketone **6** as a white solid (0.47 g, 76%). IR (NaCl film) 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.73 (d, $J=5.6$ Hz, 1H), 4.54 (dd, $J=5.6$, 1.6 Hz, 1H), 4.34 (dd, $J=13.6$, 2.0 Hz, 1H), 4.11–4.00 (m, 3H), 2.60–2.53 (m, 1H), 2.10–2.03 (m, 1H), 2.00–1.89 (m, 2H), 1.48 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.6, 110.6, 107.8, 78.4, 76.3, 70.3, 59.7, 31.4, 27.5, 26.3, 24.1. HRMS calcd for $C_{11}H_{17}O_5$ (M+1): 229.1076, found: 229.1073.

4.1.3. Preparation of ketone 7. The cyclization of ester **11** was carried out as previously described with the ester (3.28 g, 9.93 mmol) and aqueous TFA (70%) (20.0 mL) to give impure triol **14** as a white solid (1.57 g, 77%).

The ketalization of triol **14** was carried out as previously described with the triol (1.57 g, 7.7 mmol), acetone (77.0 mL), *p*-TsOH (0.1 g, 0.6 mmol), and $CuSO_4$ (2.3 g, 14.4 mmol) to give the alcohol as a white solid (0.88 g, 47%). IR (NaCl film) 3443, 1783 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.28–4.26 (m, 1H), 4.20–4.15 (m, 3H), 3.72 (d, $J=7.6$ Hz, 1H), 2.76–2.54 (m, 3H), 2.18–2.05 (m, 2H), 1.56 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1, 110.0, 108.0, 77.1, 73.5, 72.8, 62.0, 29.9, 28.4, 27.9, 26.3.

The Swern oxidation was carried out as previously described with oxalyl chloride (0.33 mL, 3.8 mmol), DMSO (0.53 mL, 7.5 mmol), the above alcohol (0.84 g, 3.6 mmol), and Et_3N (1.7 mL, 12.2 mmol) to give ketone **7** as a white solid (0.48 g, 55%). IR (NaCl film) 1804, 1752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.76 (d, $J=5.6$ Hz, 1H), 4.62–4.60 (m, 1H), 4.41 (dd, $J=13.8$, 2.0 Hz, 1H), 4.19 (d, $J=13.8$ Hz, 1H), 2.97–2.89 (m, 1H), 2.81–2.72 (m, 1H), 2.62 (ddd, $J=17.6$, 10.4, 3.4 Hz, 1H), 2.17–2.10 (m, 1H), 1.48 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.8, 174.4, 111.3, 105.9, 75.7, 61.6, 27.3, 27.2, 27.1, 26.1; HRMS calcd for $C_{11}H_{15}O_6$ (M+1): 243.0869, found: 243.0870.

4.1.4. Preparation of ketone 8. To a solution of *N*,*N*-diisopropylamine, (3.2 mL, 22.8 mmol) in THF (3.0 mL) at 0 °C was added *n*-BuLi (13.3 mL, 21.3 mmol, 1.6 M in hexanes) slowly. After stirring at 0 °C for 45 min, a solution of ester **11** (5.0 g, 15.1 mmol) in THF (7.6 mL) was added. The mixture was stirred at 0 °C for 1 h and then cooled to −78 °C. Upon addition of a mixture of HMPA (2.3 mL, 13.2 mmol) and MeI (1.5 mL, 24.1 mmol) in THF (3.3 mL), the reaction mixture was stirred at −78 °C for 2 h, warmed to rt, and stirred at rt until most of the starting material was gone (by GC).

To a solution of *N*,*N*-diisopropylamine (3.8 mL, 27.1 mmol) in THF (2.0 mL) was added *n*-BuLi (16.0 mL, 25.6 mmol, 1.6 M in hexanes) at 0 °C. After stirring at 0 °C for 45 min, the above reaction mixture containing the monoalkylated ester was introduced at 0 °C. The resulting mixture was stirred at rt for 2 h, then cooled to 0 °C. Upon addition of a mixture of MeI (1.9 mL, 30.5 mmol) and HMPA (2.5 mL, 14.4 mmol), the reaction mixture was stirred at 0 °C for 2 h and at rt overnight until complete as judged by GC, quenched with water, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), filtered, concentrated, purified by flash chromatography (2:3 ether/hexanes) to give ester **15** as a white solid (3.8 g, 70%). IR (NaCl film) 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.56 (dd, $J=6.1$, 1.8 Hz, 1H), 4.18–4.08 (m, 3H), 3.99 (d, $J=2.1$ Hz, 1H), 3.75 (dd, $J=9.7$, 1.5 Hz, 1H), 3.61 (d, $J=9.7$ Hz, 1H), 2.38 (d, $J=10.6$ Hz, 1H), 1.84 (d, $J=10.6$ Hz, 1H), 1.53 (s, 3H), 1.47 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.25 (t, $J=5.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.2, 109.2, 108.1, 103.8, 75.1, 70.9, 70.8, 60.9, 60.4, 51.0, 41.0, 27.6, 26.7, 26.5, 26.0, 25.1, 24.4, 14.4.

The cyclization of ester **15** was carried out as previously described with the ester (1.5 g, 4.2 mmol) and aqueous TFA (70%) (8.4 mL) to give triol **17** as a white solid (0.7 g, 72%).

The ketalization of triol **17** was carried out as previously described with the triol (0.63 g, 2.71 mmol), acetone (27.0 mL), *p*-TsOH, (0.036 g, 0.19 mmol), and $CuSO_4$ (0.82 g, 5.13 mmol) to give alcohol **19** as a white solid (0.48 g, 65%). IR (NaCl film) 3493, 1775 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 400 MHz) δ 4.76 (d, $J=7.0$ Hz, 1H, OH), 4.34–4.32 (m, 1H), 4.15–4.02 (m, 3H), 3.58 (dd, $J=7.6$, 7.0 Hz, 1H), 2.56 (d, $J=13.4$ Hz, 1H), 1.97 (d, $J=13.4$ Hz, 1H), 1.44 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ 182.0, 109.9, 105.5, 77.3, 73.5, 72.3, 61.6, 43.7, 39.8, 28.5, 27.3, 26.4, 26.0.

The Swern oxidation was carried out as previously described with oxalyl chloride (0.03 mL, 0.34 mmol), DMSO (0.06 mL, 0.84 mmol), alcohol **19** (0.10 g, 0.37 mmol), and Et_3N (0.2 mL, 1.4 mmol) to give ketone **8** as a white solid (0.062 g, 57%) (the ketone and its hydrate showed two different spots on TLC). IR (NaCl film) 1792, 1752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.77 (d, $J=5.6$ Hz, 1H), 4.62–4.60 (m, 1H), 4.44 (dd, $J=13.5$, 2.0 Hz, 1H), 4.19 (d, $J=13.5$ Hz, 1H), 2.85 (d, $J=14.2$ Hz, 1H), 2.02 (d, $J=14.2$ Hz, 1H), 1.48 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.8, 180.3, 111.2, 103.4, 75.7, 61.3, 40.9, 39.5, 27.3, 26.7, 26.2, 25.9. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.41; H, 6.51.

4.1.5. Preparation of ketone 9. To a solution of *N*,*N*-diisopropylamine (0.62 mL, 4.42 mmol) in THF (0.6 mL) at 0 °C was added *n*-BuLi (2.59 mL, 4.14 mmol, 1.6 M in hexanes) slowly. After stirring at 0 °C for 45 min, a solution of ester **11** (0.98 g, 2.97 mmol) in THF (1.5 mL) was added.

The mixture was stirred at 0 °C for 1 h and then cooled to −78 °C. Upon addition of a solution of EtI (0.39 mL, 4.88 mmol) and HMPA (0.44 mL, 2.53 mmol) in THF (0.9 mL), the reaction mixture was stirred at −78 °C for 2 h and at rt overnight, quenched with water, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (3:1 hexanes/ether) to give the mono-alkylated product (0.54 g, 51%).

A solution of the above mono-alkylated product (0.54 g, 1.5 mmol) in THF (1.0 mL) was added to LDA [prepared from *N*,*N*-diisopropylamine (0.32 mL, 2.3 mmol), *n*-BuLi (1.3 mL, 2.1 mmol, 1.6 M in hexanes), and THF (0.4 mL) as above] at 0 °C. The reaction was then stirred at 0 °C for 2 h. Upon addition of a solution of EtI (0.19 mL, 2.4 mmol) and HMPA (0.22 mL, 1.26 mmol) in THF (0.6 mL), the reaction mixture was warmed to rt, stirred overnight, quenched with water, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (3:1 hexanes/ether) to give ester **16** as yellow oil (0.26 g, 44%) (the yellow oil became a white solid after storing in the freezer for 4 days.). IR (NaCl film) 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.51 (dd, J=7.8, 2.4 Hz, 1H), 4.18–3.96 (m, 4H), 3.71 (dd, J=13.0, 2.0 Hz, 1H), 3.56 (d, J=13.0 Hz, 1H), 2.31 (d, J=14.4 Hz, 1H), 1.85 (d, J=14.4 Hz, 1H), 1.87–1.78 (m, 2H), 1.78–1.63 (m, 2H), 1.54 (s, 3H), 1.47 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.25 (t, J=6.9 Hz, 3H), 0.79 (t, J=7.5 Hz, 3H), 0.76 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2, 108.9, 108.0, 103.7, 75.2, 70.7, 70.6, 60.8, 60.1, 48.3, 45.7, 27.4, 26.6, 25.8, 25.3, 24.9, 24.1, 14.4, 8.24, 8.2.

The cyclization of ester **16** was carried out as previously described with the ester (2.96 g, 7.65 mmol) and aqueous TFA (70%) (15.3 mL) to give triol **18** as a clear oil (1.1 g, 55%).

The ketalization of triol **18** was carried out as previously described with the triol (1.1 g, 4.2 mmol), acetone (42.0 mL), *p*-TsOH (0.05 g, 0.3 mmol), and $CuSO_4$ (1.3 g, 8.1 mmol) to give alcohol **20** as a clear oil (0.53 g, 42%). IR (NaCl film) 3490, 1778 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.25–4.07 (m, 4H), 3.65 (d, J=7.2 Hz, 1H), 2.59 (d, J=13.6 Hz, 1H), 1.97 (d, J=13.6 Hz, 1H), 1.72 (q, J=7.4 Hz, 2H), 1.65 (q, J=7.4 Hz, 2H), 1.55 (s, 3H), 1.39 (s, 3H), 0.95 (t, J=7.4 Hz, 3H), 0.91 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.7, 109.8, 105.2, 77.4, 73.5, 72.8, 61.5, 48.1, 38.5, 30.3, 28.7, 28.4, 26.4, 8.9, 8.8.

The Swern oxidation was carried out as previously described with oxalyl chloride (0.38 mL, 4.4 mmol), DMSO (0.62 mL, 8.7 mmol), alcohol **20** (1.21 g, 4.0 mmol), and Et_3N (2.0 mL, 14.3 mmol) to give ketone **9** as a yellow oil (a white solid was obtained after subjecting to high vacuum) (0.87 g, 73%). IR (NaCl film) 1788, 1752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.75 (d, J=5.2 Hz, 1H), 4.59–4.57 (m, 1H), 4.41 (dd, J=13.6, 2.0 Hz, 1H), 4.15 (d, J=13.6 Hz, 1H), 2.93 (d, J=14.6 Hz, 1H), 1.91 (d, J=14.6 Hz, 1H), 1.71 (q, J=7.4 Hz, 2H), 1.60 (q, J=7.4 Hz, 2H), 1.45 (s, 3H), 1.39 (s, 3H), 0.94 (t, J=7.4 Hz, 3H), 0.85 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.8, 179.1, 111.1, 103.5, 77.7, 75.7, 61.3, 48.0, 35.4, 30.2, 29.4, 27.3, 26.2, 8.8, 8.6; HRMS calcd for $C_{15}H_{23}O_6$ (M+1): 299.1494, found: 299.1493.

4.2. Representative asymmetric epoxidation procedure (Table 1, entry 8, Method A)

To a solution of *trans*-β-methylstyrene (0.012 g, 0.1 mmol) and ketone **8** (0.008 g, 0.03 mmol) in CH_3CN/DMM (1:2 v/v) (1.5 mL) were added buffer (0.1 M K_2CO_3–AcOH in 4×10^{-4} M aqueous EDTA, pH 9.3) (1.0 mL) and Bu_4NHSO_4 (0.001 g, 0.003 mmol) with stirring. After the mixture was cooled to 0 °C (bath temperature), a solution of Oxone (0.212 M in 4×10^{-4} M aqueous EDTA) (0.65 mL) and a solution of K_2CO_3 (0.892×10^{-4} M aqueous EDTA) (0.65 mL) were added dropwise separately via syringe pump over a period of 1.5 h. The reaction mixture was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting mixture was analyzed by GC to determine the conversion and enantiomeric excess.

4.3. Representative asymmetric epoxidation procedure (Table 1, entry 9, Method C)

To a solution of *cis*-β-methylstyrene (0.012 g, 0.1 mmol) and ketone **8** (0.0045 g, 0.015 mmol) in DME/DMM (3:1 v/v) (1.5 mL) were added buffer (0.2 M K_2CO_3–AcOH in 4×10^{-4} M aqueous EDTA, pH 8.0) (1.0 mL) and Bu_4NHSO_4 (0.001 g, 0.003 mmol) with stirring. After the mixture was cooled to 0 °C (bath temperature), a solution of Oxone (0.212 M in 4×10^{-4} M aqueous EDTA) (0.84 mL) and a solution of K_2CO_3 (0.479 M $\times10^{-4}$ M aqueous EDTA) (0.84 mL) were added dropwise separately over a period of 3.5 h via syringe pump. The reaction mixture was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting mixture was analyzed by GC to determine the conversion and enantiomeric excess.

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References and notes

1. For general leading references on dioxiranes see: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811. (d) Clennan, E. L. *Trends Org. Chem.* **1995**, *5*, 231. (e) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Org. React.* **2002**, *61*, 219.
2. For reviews on chiral ketone catalyzed asymmetric epoxidations see: (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. (c) Shi, Y. *Acc.*

Chem. Res. **2004**, *37*, 488. (d) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497.

3. For selected examples of asymmetric epoxidation mediated in situ by chiral ketones see: (a) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. (b) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831. (c) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (d) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (e) Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S. G.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921. (f) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995. (g) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (h) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621. (i) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (j) Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659. (k) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749. (l) Solladie-Cavallo, A.; Bouerat, L. *Org. Lett.* **2000**, *2*, 3531. (m) Solladie-Cavallo, A.; Bouerat, L.; Jierry, L. *J. Org. Chem.* **2001**, 4557. (n) Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1113. (o) Seki, M.; Furutani, T.; Imashiro, R.; Kuroda, T.; Yamanaka, T.; Harada, N.; Arakawa, H.; Kusama, M.; Hashiyama, T. *Tetrahedron Lett.* **2001**, *42*, 8201. (p) Matsumoto, K.; Tomioka, K. *Tetrahedron Lett.* **2002**, *43*, 631. (q) Shing, T. K. M.; Leung, G. Y. C. *Tetrahedron* **2002**, *58*, 7545. (r) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Forlani, R.; Maietti, S.; Pedrini, P. *J. Org. Chem.* **2002**, *67*, 5802. (s) Stearman, C. J.; Behar, V. *Tetrahedron Lett.* **2002**, *43*, 1943. (t) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479. (u) Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B. R.; Wailes, J. S. *J. Org. Chem.* **2002**, *67*, 8610. (v) Chan, W.-K.; Yu, W.-Y.; Che, C.-M.; Wong, M.-K. *J. Org. Chem.* **2003**, *68*, 6576. (w) Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* **2003**, *44*, 7403.
4. For examples of asymmetric epoxidation mediated by fructose-derived ketone **1** see (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213. (d) Tu, Y.; Frohn, M.; Wang, Z.-X.; Shi, Y. *Org. Synth.* **2003**, *80*, 1. (e) Wang, Z.-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Synth.* **2003**, *80*, 9.
5. (a) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (b) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929. (c) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435. (d) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293. (e) Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004**, *45*, 8115.
6. Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5794.
7. Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311.
8. For leading references on calculation studies, see: (a) Bach, R. D.; Andres, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1992**, *114*, 7207. (b) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. (c) Jenson, C.; Liu, J.; Houk, K. N.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 12982. (d) Armstrong, A.; Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 6297. (e) Deubel, D. V. *J. Org. Chem.* **2001**, *66*, 3790.
9. Brady, R. F. *Carbohydr. Res.* **1970**, *15*, 35.
10. Aamlid, K. H.; Hough, L.; Richardson, A. C. *Carbohydr. Res.* **1990**, *202*, 117.
11. Cubero, I. I.; Lopez-Espinosa, M. T. P.; Richardson, A. C.; Aamlid, K. H. *Carbohydr. Res.* **1993**, *242*, 281.
12. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
13. Cregge, R. J.; Herrmann, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2425.
14. Earlier studies suggested that substituents larger than methyl groups could also lower the enantioselectivity, see: Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475.

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Intermolecular reductive coupling of hindered *N*-aryl imines towards the modular synthesis of chiral *N*-heterocyclic carbenes

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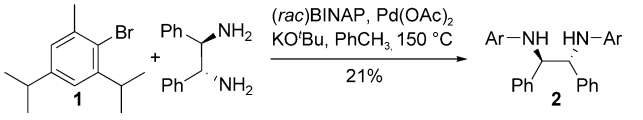
Abstract—We describe a simple method for the synthesis of hindered *N*-aryl diamines. The diastereoselectivity for these processes are relatively low but the diamines can be separated using either chromatography or selective crystallization. Separation of enantiomers can be accomplished using HPLC equipped with a chiral stationary phase.

1. Introduction

Catalysts that incorporate *N*-heterocyclic carbenes (NHC) as ligands have been applied to a broad range of reactions including olefin metathesis, hydrosylilation, and Pd-catalyzed cross coupling reactions.[1] Attractive features of NHC's are the strong σ-donor bonding with metals and their greater stability toward heat, air, and moisture compared to common phosphine ligands.[2] While some success in asymmetric catalysis using NHC-based systems has been reported,[3] the diversity and accessibility to enantiomercially enriched derivatives has been a limiting factor for general application of NHC's to asymmetric catalysis.

Our interest in the use of chiral NHC's stems from developing catalysts for Pd-catalyzed enantioselective aerobic oxidations. For the general catalytic aerobic oxidation of alcohols, the NHC, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (I*i*Pr), in combination with $Pd(OAc)_2$ has proven exceptionally effective with up to 1000 turnovers for activated substrates.[4] With this success, attention was turned toward the development of an asymmetric variant which utilizes an NHC ligand. Initial screening resulted in no catalysis when using easily accessible chiral NHC ligands (Fig. 1). Observable catalysis generally requires, an N-aryl substituent with substitution of both *ortho* sites on the aryl ring. Therefore, we set out to explore synthetic routes to hindered *N*-aryl vicinal diamines.



(1)

The common approach used for the synthesis of *N*-aryl substituted diamines is Pd-catalyzed cross coupling of the requisite aryl halide to a commercially available chiral diamine (Eq. 1). When introducing the aryl group of **1** with substitution at both *ortho* positions on the ring, the cross coupling required forcing conditions and yielded the desired product **2** in only 21%. Using larger groups, no measurable coupling is observed. The resulting Pd complex of the NHC derived from **2** was found to promote the oxidative kinetic resolution of *sec*-phenethyl alcohol with a promising initial k_{rel} value of 3.3. Considering this result, an alternative strategy for the synthesis of hindered *N*-aryl vicinal diamines was sought.

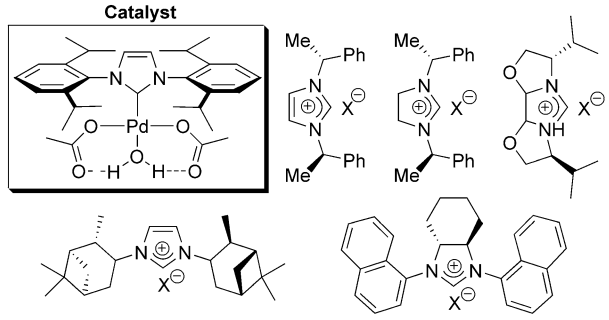


Figure 1. Chiral NHC's which failed to promote a Pd(II)-catalyzed oxidative kinetic resolution of secondary alcohols.

Keywords: *N*-Aryl; Cross coupling; Reductive coupling.
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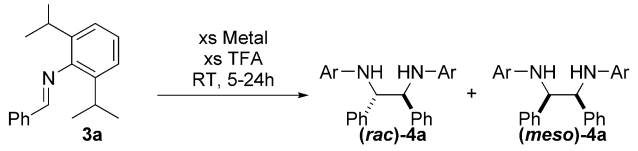
One possible approach is to submit an *N*-aryl imine to a metal-mediated reductive coupling or pinacol type reaction. Various imines have been successfully coupled using this approach but no examples of the coupling of hindered *N*-aryl imines have been reported.[5–18] If successful, this strategy offers two significant advantages over cross coupling: (a) *N*-aryl imine substrates can be synthesized easily and (b) both the *N*-aryl group and the imine substituent can be tuned simultaneously. Herein, we report the synthesis of hindered *N*-aryl vicinal diamines via imine reductive coupling.

2. Results and discussion

We previously reported the combination of Mn(0) and a Brønsted acid effectively mediate a diastereoselective intramolecular reductive coupling of tethered imines.[19,20] Using the conditions developed for this previous system, we evaluated substrate **3a**. As is observed with many imine pinacol type couplings, a mixture of diastereomers is produced under the coupling conditions (Table 1, entry 1). The *meso* diastereomer was found to be preferred ~3:1 as determined by X-ray crystallographic analysis of the major product (Fig. 2). A survey of reaction conditions (metal, acids, and solvent) allowed for an enhancement in diastereoselectivity to ~1:1 by using a combination of Mg(0) and TFA in benzene (entry 9). Hexanes proved to give the greatest selectivity for the preferred diastereomer but a significantly lower yield made this process unusable (entry 10). Interestingly, ethereal solvents such as THF, promote a highly *meso* selective reductive dimerization of **3a** (entries 3 and 7). The use of zinc lead to a slight reduction in isolated yield (entry 11). Overall, the nature of the solvent had the most profound effect on diastereoselectivity with Mg allowing for a modest improvement of yield. The nature of the acid had little effect on the outcome of this transformation.

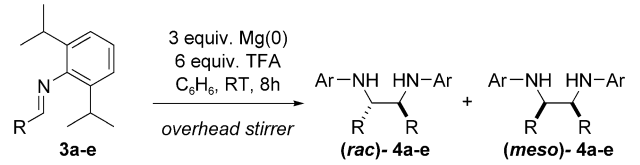
Table 1. Optimization of reaction parameters



Entry	Metal	Solvent	*racemic*: *meso*	Yield (%)
1	Mn(0)	Acetonitrile	25:75	81
2	Mn(0)	Dimethoxyethane	9:61	69
3	Mn(0)	THF	5:95	95
4	Mn(0)	Toluene	45:55	53
5	Mg(0)	Acetonitrile	26:74	93
6	Mg(0)	Dimethoxyethane	14:86	90
7	Mg(0)	THF	5:95	95
8	Mg(0)	Touene	48:52	50
9	Mg(0)	Benzene	49:51	74
10	Mg(0)	Hexanes	63:37	22
11	Zn(0)	Toluene	42:58	42

Further optimization of these initial conditions lead to the evaluation of various aryl substrates for this transformation. A key improvement of the method is the use of a mechanical stirrer to insure effective stirring of the heterogeneous mixture. Aryl imines with 2,6-diisopropylaniline are generally good substrates for this transformation (Table 2). In all cases, similar levels of diastereoselectivity are observed. The diastereomeric ratios were all determined by ^{1}H NMR and each diastereomer was assigned by correlating the ^{1}H shift of the benzylic proton (*meso* downfield), and the isopropyl methine (*meso* upfield). For further confirmation, a single crystal of (*rac*)-**4e** was found suitable for crystallographic analysis (Fig. 3). Separation of the diastereomers can be accomplished either by chromatography using Brockman 1 basic alumina or by selective crystallization.

Table 2. Substrate scope



Entry	R	Product	*racemic*: *meso*	Yield (%)[a]
1	Ph	**4a**	45:55	75
2	2,5-$(CH_3)_2C_6H_3$	**4b**	45:55	67
3	*p*-BrC_6H_4	**4c**	47:53	75
4	2-Naphthyl	**4d**	40:60	55
5	*p*-$CF_3C_6H_4$	**4e**	48:52	72

[a] Average of a least two experiments.

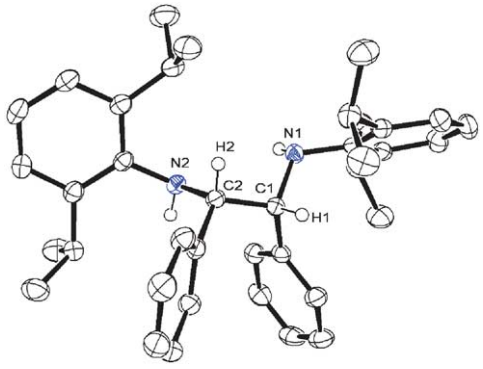


Figure 2. ORTEP diagrm of the molecular structure of *meso*-**4a** (50% thermal ellipsoid probability).

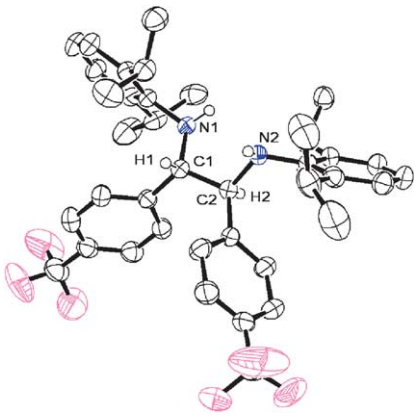


Figure 3. ORTEP diagram of the molecular structure of *rac*-**4e** (50% thermal ellipsoid probability).

Separation of enantiomers using traditional crystallization of the diastereomeric acid salts proved prohibitive. However, enantiomers for the majority of the compounds synthesized can be readily separated using HPLC equipped with a chiral stationary phase. This also confirms the assignment of the *trans* diastereomer.

Two other substrates were evaluated to continue in determining the scope of this transformation (Fig. 4). An aliphatic imine **3f** leads mainly to the reduced product.[21] While changing the nature of the *N*-aryl group to an unsymmetrical aniline **3g** resulted in the preferred outcome to provide diamine **4g** with a slightly enhanced diastereoselectivity for the desired diastereomer.

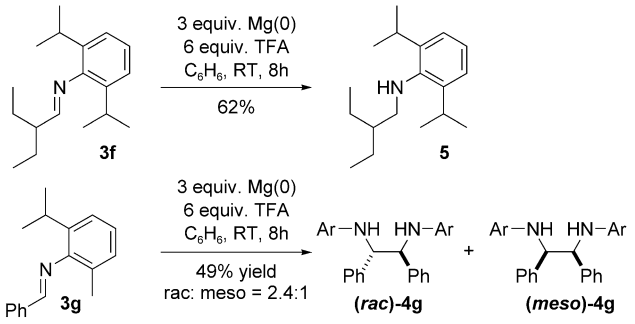


Figure 4. Evaluation of an aliphatic and an unsymmetrical *N*-aryl substrate for reductive coupling.

3. Conclusions

In conclusion, we have described a simple method for the synthesis of hindered *N*-aryl diamines which would be difficult to access using other procedures. The diastereoselectivity for these processes are relatively low but the diastereomers can be separated using either chromatography or selective crystallization. Separation of enantiomers can be accomplished using HPLC equipped with a chiral stationary phase. Diamines containing unsymmetrically substituted *N*-aryl groups can be prepared using this methodology. Diamines can be converted easily to the NHC salts as previously reported.[4a] Evaluation of these new NHC's in palladium-catalyzed asymmetric oxidations is currently ongoing.

4. Experimental

4.1. General methods

All reactions were run under a N_2 atmosphere. CH_3CN, benzene, and toluene were degassed and purified through an activated alumina solvent purification column. THF and DME were distilled from the Na/ketyl of benzophenone. Trifluoroacetic acid was freshly distilled prior to use and stored with its respective anhydride (~5% by volume) under nitrogen, to avoid significant water accumulation. All amines and carbonyl compounds were obtained from Sigma-Aldrich and used without further purification. Mn(0) (325 mesh) and Mg(0) powder (325 mesh) were obtained from Strem. All melting points are uncorrected and were recorded on an Electrothermal Melting Point apparatus. IR spectra were recorded using a Mattson Satellite FTIR instrument. NMR spectra were recorded using either a Varian Unity-300 spectrometer, or a Varian XL-300 spectrometer. HRMS were recorded using a Finnigan MAT 95 spectrometer. Imine **3a** was prepared and purified as described below, and has a ^1H NMR identical to the reported values.[22]

4.2. Preparation of aryl bromide

4.2.1. 2-Bromo-1,5-diisopropyl-3-methylbenzene (1). 1,3-Diisopropyl-5-methyl-benzene (746 mg, 4.23 mmol, 1.0 equiv) was dissolved in CCl_4 (1.0 mL) in a 10 mL round bottom flask. The reaction mixture was put under nitrogen, and the flask was chilled in an ice/water bath. In a separate vial, CCl_4 (1.0 mL) and Br_2 (676 mg, 4.23 mmol, 1.0 equiv) were combined. The Br_2 solution was then added drop-wise over 15 min to the reaction flask. After 4 h, the ice/water bath was removed and the reaction was allowed to stir overnight at room temperature. The reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was collected and the aqueous layer extracted twice more with CH_2Cl_2. The organic layers were combined, washed with 2 N NaOH and 1 M $NaSO_3$ solutions, and dried over $MgSO_4$. Removal of the solvent gave 1.079 g (91% yield) of **1** as a yellow oil. IR (salt plate): 2962, 2870, 1464, 1018; ^1H NMR: (300 MHz, $CDCl_3$) δ 6.99 (bs, 2H), 3.48 (sp, $J=6.9$ Hz, 1H), 2.87 (sp, $J=6.9$ Hz, 1H), 2.45 (s, 3H), 1.27 (d, $J=6.9$ Hz, 6H), 1.26 (d, $J=6.9$ Hz, 6H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 128.0, 126.4, 125.0, 124.0, 122.2, 33.8, 33.2, 24,4, 24.0, 23.0; HRMS (EI) calculated for $C_{13}H_{19}Br$ (M^+) 254.0670, found 254.0664.

4.3. Cross coupling of 1 with (*R*,*R*)-diphenylethylene diamine

4.3.1. *N*,*N*′-Bis-(2,4-diisopropyl-6-methyl-phenyl)-1,2-diphenyl-ethane-1,2-diamine (2). In a drybox, $Pd(OAc)_2$ (10 mg, 0.045 mmol, 0.063 equiv), BINAP (55 mg, 0.088 mmol, 0.125 equiv), and NaO^{t}Bu (200 mg, 2.08 mmol, 2.9 equiv) were dissolved in toluene (6 mL) in a screw cap vial. This solution was allowed to stir while turning from orange to bright red. After 30 min, (*R*,*R*)-diphenylethylene diamine (152 mg, 0.716 mmol, 1.0 equiv) and **1** (457 mg, 1.79 mmol, 2.5 equiv) were each dissolved in 3 mL of toluene and added to the catalyst solution. The vial was sealed, removed from the drybox, and heated to 150 °C. After 40 h, the reaction was cooled to ambient temperature and the solvent removed. The product was purified by flash chromatography (30% CH_2Cl_2/hexanes) to give 84 mg (21% yield) of a viscous oil. Optical rotation: $[\alpha]_D^{20}$ −137 (*c* 0.88, $CHCl_3$); IR (salt plate): 3505 (br), 3304 (br), 2958, 2867, 1479, 1454; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.11–7.05 (m, 3H), 7.05–6.98 (m, 2H), 6.86 (bs, 1H), 6.76 (bs, 1H) 4.64 (s, 1H), 4.12 (s, 1H), 3.20 (apparent sp, 6.7 Hz, 1H), 2.78 (apparent sp, 6.8 Hz, 1H), 2.14 (s, 3H), 1.21–1.13 (m, 9H), 0.91 (d, 6.7 Hz, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 142.8, 141.6, 140.9, 140.5, 130.8, 128.5, 127.7, 126.9, 126.4, 121.8, 67.8, 33.5, 27.6, 24.3, 24.1, 23.5, 19.8; HRMS (CI) calculated for $C_{40}H_{52}N_2$ (M^+) 560.4130, found 560.4116.

4.4. Preparation of imines 3b–3e,3g

Compound **3a**. Anhydrous magnesium sulfate (ca. 3 g) was added to a flask along with isopropyl alcohol (32 mL, 0.5 M solution) and allowed to stir for 2 min. 2,6-diisopropyl-aniline (3 mL, 15.9 mmol) and benzaldehyde (1.62 mL, 15.9 mmol) were then added to the flask. The mixture was stirred under a N_2 atmosphere overnight. The heterogeneous mixture was filtered through celite and washed with isopropyl alcohol (2×20 mL). The filtrate was reduced to a concentrated solution ca. 10 mL and placed in the freezer (−20 °C) overnight. The resulting yellow crystals were decanted and washed with cold methanol (5 mL) to produce the desired imine (3.6 g, 85%yield).

Compound **3f** was prepared as described above. The resulting liquid was purified by chromatography using Brockman I activated alumina (hexanes).

4.4.1. (2,6-Diisopropyl-phenyl)-(2,5-dimethyl-benzyl-idene)-amine (3b). Yield: 78%, white crystalline solid; mp 56–62 °C; IR (KBr) 2960, 2925, 2866, 1632, 1605; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.95 (bs, 1H), 7.26–7.11 (m, 5H), 3.02 (sp, J=6.9 Hz, 2H), 2.51 (s, 3H), 2.43 (s, 3H), 1.21 (d, J=6.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 143.7, 137.8, 136.1, 135.5, 132.0, 131.0, 128.0, 124.1, 123.0; HRMS (CI, isobutane) *m/z* calcd for ($C_{21}H_{27}N+H^+$)=294.2143, found: 294.2227.

4.4.2. (4-Bromo-benzylidene)-(2,6-diisopropyl-phenyl)-amine (3c). Yield: 58%, yellow crystalline solid; mp 108–113 °C; IR (KBr) 2963, 2923, 2867, 1641, 1586, 1570, 1484; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.78 (d, J=8.7 Hz, 2H), 7.64 (d, J=8.3 Hz, 2H), 7.19–1.08 (m, 3H), 2.93 (sp, J=6.9, 2H), 1.16 (d, J=6.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7, 148.9, 137.4, 134.8, 132.1, 129.9, 126.0, 124.2, 123.0, 27.9, 23.4; HRMS (CI, isobutane) *m/z* calcd for ($C_{19}H_{22}BrN+H^+$)=344.0936, found: 344.1010.

4.4.3. (2,6-Diisopropyl-phenyl)-naphthalen-2-ylmethyl-ene-amine (3d). Yield: 61%, reddish crystalline solid; mp 125–133 °C; IR (KBr) 2959, 2930, 2866, 1596, 1459, 1440; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.23, (d, J=8.3 Hz, 1H), 8.17 (s, 1H), 7.97 (d, J=8.7 Hz, 1H), 7.94–7.89 (m, 2H), 7.61–7.52 (m, 2H), 7.22–7.09 (m, 3H), 3.03, (sp, J=6.9 Hz, 2H), 1.19 (d, J=6.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 149.5, 137.9, 135.3, 133.9, 133.3, 131.2, 128.9, 128.2, 127.8, 126.9, 124.3, 123.9, 123.3, 28.2, 23.8; HRMS (CI, isobutane) *m/z* calcd for ($C_{23}H_{25}N+H^+$)=316.1987, found: 316.2062.

4.4.4. (2,6-Diisopropyl-phenyl)-(4-trifluoromethyl-benzylidene)-amine (3e). Yield: 55%, white solid; mp 111–116 °C; IR (KBr) 2960, 2926, 2871, 1644; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H), 8.02 (d, J=8.1 Hz, 2H), 7.75 (d, J=8.1 Hz, 2H), 7.22–7.1 (m, 3H), 2.9 (sp, J=7.0 Hz, 2H), 1.15 (d, J=7.0 Hz, 12H; ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 160.0, 137.4, 129.5, 128.2, 126.5, 125.2, 123.9, 122.5, 28.5, 27.5, 23.9, 21.9; HRMS (CI, isobutane) *m/z* calcd for ($C_{20}H_{22}F_3N+H^+$)=334.1704, found: 334.1764.

4.4.5. (2,6-Diisopropyl-phenyl)-(2-ethyl-butylidene)-amine (3f). Yield: 60%, yellow liquid; IR (salt plate) 2958, 2931, 2871, 1661, 1460; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J=6.0 Hz, 1H), 7.16–7.06 (m, 3H), 3.01 (sp, J=6.9 Hz, 2H), 2.36 (q, J=6.9 Hz, 1H), 1.74–1.61 (m, 4H), 1.19, (d, J=6.9 Hz, 12H), 1.06 (t, J=7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 148.9, 137.6, 123.8, 122.8, 49.1, 27.5, 24.5, 23.5, 11.7; HRMS (CI, isobutane) *m/z* calcd for ($C_{18}H_{29}N+H^+$)=260.2300, found: 260.2372.

4.4.6. Benzylidene-(2-isopropyl-6-methyl-phenyl)-amine (3g). Yield: 53%, white solid; mp 48–54 °C; IR (KBr) 3060, 2959, 2923, 2913, 1644, 1454; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.95–7.90 (m, 2H), 7.53–7.49 (m, 3H), 7.19–7.15 (m, 1H), 7.10–7.00 (m, 2H), 3.03 (sp, J=6.9 Hz, 1H), 2.14 (s, 3H), 1.18 (d, J=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8, 138.1, 131.7, 129.0, 128.8, 128.1, 124.1, 123.4, 28.1, 23.5, 18.9; HRMS (CI, isobutane) *m/z* calcd for ($C_{17}H_{19}N+H^+$)=238.1517, found: 238.1583.

4.5. General method for reductive coupling

4.5.1. *N,N′*-Bis-(2,6-diisopropyl-phenyl)-1,2-bis-(4-trifluoromethyl-phenyl)-ethane-1,2-diamine (4e). Mg(0) (325 mesh) (72 mg, 3.0 mmol) was added to a flame dried three-neck 25 mL round-bottom flask. The imine (330 mg, 1.0 mmol) dissolved in benzene (5 mL, 0.2 M) was added to the flask with stirring by an overhead stirrer (250 rpm). After 5 min of mixing, trifluoroacetic acid (450 μL, 6.0 mmol) was added by syringe pump (30 min). The reaction was allowed to stir at room temperature under nitrogen for eight hours. An aliquot of aqueous sodium carbonate (10% w/v ca. 10 mL) was added by syringe while stirring continued for an additional ten minutes. The biphasic solution was transferred to a separatory funnel. The organic layer was removed, and the aqueous layer extracted by ethyl acetate (3×30 mL). The combined organic layers were dried by anhydrous sodium sulfate with stirring over 30 min and concentrated in vacuo. The crude product was purified by chromatography using Brockman I activated basic alumina (0.5% ethyl acetate/hexanes). A clear highly viscous liquid was recovered (236 mg., 71.5%, 1:1.1, *rac*:*meso*)

Separation of the diastereomers of **4e**. The mixture of **4e** (210 mg, 0.31 mmol) was dissolved in methanol (500 μL) and placed in the freezer overnight (−20 °C). Crystals of the *meso* diastereomer were isolated from the mother liquor (96 mg). The mother liquor on standing at room temperature for several hours produced unique crystals of the *racemic* diastereomer (87 mg). These crystal were used for X-ray diffraction analysis.

Compound (*rac*)-**4e**. White solid; mp 136–138 °C; IR (KBr) 2962, 2928, 2871, 1459; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, J=8.3 Hz, 4H), 7.07 (d, J=7.8 Hz, 4H), 7.06–6.97 (m, 6H), 4.6 (d, J=4.1 Hz, 2H), 4.28–4.21 (bs, 2H), 3.18 (sp, (J=6.9 Hz), 4H), 1.23 (d, J=6.9 Hz, 12H), 0.88 (d, J=6.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 143.4, 140.3, 130.9, 128.5, 125.1, 124.6, 123.6, 27.9, 24.3, 23.4; HRMS (CI, isobutane) *m/z* calcd for ($C_{40}H_{46}F_6N_2+H^+$)=669.3565, found: 669.3655.

Compound (*rac*)-**4e**. White solid; mp 152–154 °C; IR (KBr) 2962, 2928, 2871, 1459; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J=7.8 Hz, 4H), 7.14 (d, J=7.8 Hz, 4H), 7.06–6.90 (m, 6H), 4.65 (d, J=8.3 Hz, 2H), 3.92 (d, J=8.7 Hz, 3H), 2.76 (sp, J=6.9 Hz, 4H), 1.04 (d, J=6.9 Hz, 12H), 0.95 (d, J=6.4 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 140.5, 128.8 125.4, 125.3, 124.8, 123.9, 68.8, 28.1, 24.6, 23.7; HRMS (CI, isobutane) m/z calcd for ($C_{40}H_{46}F_6N_2+H^+$)=669.3565, found: 669.3655.

4.5.2. *N*,*N*′-Bis-(2,6-diisopropyl-phenyl)-1,2-diphenyl-ethane-1,2-diamine (4a). Yield: 75%, *rac*:*meso*=1:1.2 Diastereomers were separated by chromatography using an alumina stationary phase activated to Brockman I, and a mobile phase of 0.5% ethyl acetate/hexanes (*rac*-**4a** elutes first). The racemic diastereomer was further purified by recrystallized from hot isopropanol/methanol (1:10).

Compound (*rac*)-**4a**. White solid; mp 127–132 °C; IR (KBr) 3062, 3027, 2958, 2929, 2866, 1454, 1442; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11–6.95 (m, 16H), 4.59 (s, 2H), 4.25 (s, 2H), 3.3 (sp, J=6.9 Hz, 4H), 1.23 (d, J=6.9 Hz, 12H), 0.90 (d, J=6.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 141.4, 140.2, 128.3, 127.5, 124.1, 123.8, 123.0, 68.9, 28.6, 28.0, 24.3; HRMS (CI, isobutane) m/z calcd for ($C_{38}H_{48}N_2+H^+$)=533.3817, found: 533.3914.

Compound (*meso*)-**4a**. White crystalline solid; mp 130–134 °C; IR (KBr) 3062, 3027, 2958, 2929, 2866, 1454, 1442; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.18, (m, 6H), 7.03–6.88, (m, 10H), 4.66 (bs, 2H), 4.14, (bs, 2H), 3.02, (sp, J=6.6 Hz, 4H), 1.09 (d, J=6.9 Hz, 12H), 1.0 (d, J=6.4 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 140.5, 139.7, 128.0, 127.4, 126.9, 123.2, 69.77, 27.5, 27.0, 23.4; HRMS (CI, isobutane) m/z calcd for ($C_{38}H_{48}N_2+H^+$)=533.3817, found: 533.3914.

4.5.3. *N*,*N*′-Bis-(2,6-diisopropyl-phenyl)-1,2-bis-(2,5-dimethyl-phenyl)-ethane-1,2-diamine (4b). Yield: 67%, *rac*:*meso*=1:1.2. Diastereomers were separated by chromatography using an alumina stationary phase activated to Brockman I, and a mobile phase of 0.5% ethyl acetate/hexanes (*rac*-**4b** elutes first).

Compound (*rac*)-**4b**. White solid; mp 184 °C (decomp.); IR (KBr) 2959, 2925, 2866, 1459, 1444; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.36 (bs, 2H), 7.03 (bs, 6H), 6.27 (d, J=7.8 Hz, 2H), 6.59 (d, J=7.8 Hz, 2H), 4.76 (bs, 2H), 4.42 (bs, 2H), 3.49 (sp, J=6.9 Hz, 4H), 2.26 (s, 6H), 1.55 (s, 6H), 1.27 (d, J=6.9 Hz, 12H), 0.85 (d, J=6.4 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ143.7, 137.1, 134.8, 133.4, 129.6, 127.3, 124.0, 123.3, 96.6, 68.0, 27.8, 24.0, 23.7, 18.9; HRMS (CI, isobutane) m/z calcd for ($C_{42}H_{56}N_2+H^+$)=589.4443, found: 589.4493.

Compound (*meso*)-**4b**. Viscous liquid; IR (salt plate) 2959, 2925, 2866, 1459, 1444; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18–6.78 (m, 12H), 4.89 (s, 2H), 3.30 (sp, J=6.9 Hz, 4H), 2.19 (s, 6H), 1.75 (s, 6H), 1.19 (d, J=6.9 Hz, 12H), 0.98 (d, J=6.9 Hz, 12H); HRMS (CI, isobutane) m/z calcd for ($C_{42}H_{56}N_2+H^+$)=589.4443, found: 589.4493.

4.5.4. 1,2-Bis-(4-bromo-phenyl)-*N*,*N*′-bis-(2,6-diisopropyl-phenyl)-ethane-1,2-diamine (4c). Yield: 75%, *rac*:*meso*=1:1.15. The crude product was purified by chromatography using an alumina stationary phase activated to Brockman I, and a mobile phase of 0.5% ethyl acetate in hexanes. The mixture of diastereomers was separated by crystallization from hot isopropanol in methanol (1:10). The *meso* diastereomer crystallized on standing and the *racemic* diastereomer was obtained by concentration of the filtrate.

Compound (*rac*)-**4c**. White solid; mp 65–70 °C; IR (KBr) 2961, 2928, 2867, 1487, 1460, 1444; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, J=8.3 Hz, 4H), 7.03 (bs, 6H), 6.82 (d, J=8.3 Hz, 4H), 4.49 (s, 2H), 4.14 (bs, 2H), 3.21 (sp, J=6.9 Hz, 4H), 1.21 (d, J=6.9 Hz, 12H), 0.92 (d, J=6.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.9, 146.2, 143.4, 131.4, 130.2, 124.5, 123.8, 121.4, 68.7, 28.1, 24.5, 23.8; HRMS (CI, isobutane) m/z calcd for ($C_{38}H_{46}N_2Br_2+H^+$)=689.2028, found: 689.2125.

Compound (*meso*)-**4c**. White solid; mp 183–188 °C; IR (KBr) 2961, 2928, 2867, 1487, 1460, 1444; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J=8.3 Hz, 4H), 7.03–6.92 (m, 6H), 6.89 (d, J=8.3 Hz, 4H), 4.54 (s, 2H), 2.85 (sp, J=6.9 Hz, 4H), 1.06 (d, J=6.9 Hz, 12H), 0.99 (d, J=6.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 139.5, 139.4, 131.0, 129.6, 123.7, 122.3, 121.3, 94.1, 69.3, 27.9, 23.9; HRMS (CI, isobutane) m/z calcd for ($C_{38}H_{46}N_2Br_2+H^+$)=689.2028, found: 689.2125.

4.5.5. *N*,*N*′-Bis-(2,6-diisopropyl-phenyl)-1,2-di-naphthalen-2-yl-ethane-1,2-diamine (4d). Yield: 55%, *rac*:*meso*=1:1.5. Diastereomers were separated by chromatography using an alumina stationary phase activated to Brockman I, and a mobile phase of 0.5% ethyl acetate/hexanes (*rac*)-**4d**: elutes first.

Compound (*rac*)-**4d**. White solid; mp 71–77 °C; IR (KBr) 2960, 2927, 2866, 1458, 1443; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71–7.54 (m, 6H), 7.4–7.26 (m, 8H), 7.0 (s, 6H), 4.85 (s, 2H), 4.26 (bs, 2H), 3.26 (sp, J=6.9 Hz, 4H), 1.22 (d, J=6.9 Hz, 12H), 0.79 (d, J=6.4 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 132.8, 132.6, 127.8, 127.6, 127.3, 125.9, 125.6, 123.6, 123.5, 94.1, 69.3, 27.8, 24.3, 23.6; HRMS (CI, isobutane) m/z calcd for ($C_{46}H_{52}N_2+H^+$)=633.4130, found: 633.4214.

4.5.6. *N*,*N*′-Bis-(2-isopropyl-6-methyl-phenyl)-1,2-diphenyl-ethane-1,2-diamine (4g). Yield: 49%, *rac*:*meso*=2.4:1. Diastereomers were separated by chromatography using an alumina stationary phase activated to Brockman I, and a mobile phase of 0.5% ethyl acetate in hexanes (*rac*-**4g** elutes first). Enriched fractions of the *racemic* diastereomer were collected and then recrystallized from isopropanol: methanol (1:10).

Compound (*rac*)-**4g**. White solid; mp 113–117 °C; IR (KBr) 3031, 2958, 2925, 2864, 1456; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12–6.82 (m, 16H), 4.72 (s, 2H), 4.17 (s, 2H), 3.14 (sp, J=6.9 Hz, 2H), 2.17, (s, 6H), 1.15 (d, J=6.9 Hz, 6H), 0.96 (d, J=6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.6, 143.0, 141.3, 140.7, 130.7, 128.9, 128.6, 128.0, 127.4, 124.0, 122.7, 67.7, 27.8, 24.4, 23.6, 20.0; HRMS (CI,

isobutane) *m/z* calcd for ($C_{34}H_{40}N_2+H^+$)=477.3191, found: 477.3261.

Compound (*meso*)-**4g** (*isolated as a mixture*). Glassy solid; IR (KBr) 3031, 2958, 2925, 2864, 1456; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.30 (m, 6H), 7.21–6.98 (m, 10H), 4.87 (s, 2H), 2.93 (sp, J=6.9 Hz, 2H), 2.13 (s, 6H), 1.28 (d, J=6.4 Hz, 6H), 1.07 (d, J=6.9 Hz, 6H); HRMS (CI, isobutane) *m/z* calcd for ($C_{34}H_{40}N_2+H^+$)=477.3191, found: 477.3261.

4.5.7. (2,6-Diisopropyl-phenyl)-(2-ethyl-butyl)-amine (5). Yield: 62%, yellow liquid; IR (salt plate) 2960, 2932, 2871, 1661, 1460; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14–7.03 (m, 3H), 3.27 (sp, J=6.9 Hz, 2H), 2.76 (d, J=5.5 Hz, 2H), 1.54–1.42 (m, 4H), 1.25 (d, J=6.9 Hz, 6H), 0.94 (t, J=7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.8, 142.4, 123.4, 122.8, 54.9, 42.5, 24.3, 24.0, 11.7, 11.1; HRMS (CI, isobutane) *m/z* calcd for ($C_{18}H_{31}N+H^+$)=262.2456, found: 262.2547.

4.6. Separation of enantiomers

Entry	Diamine	Mobile phase	Retention times (min)
1	**4a**	0.1% Diethylether in hexane	10, 11.5
2	**4c**	Hexane	20.8, 24.9
3	**4d**	0.1% Isopropanol in hexane	11.6, 13.5
4	**4e**	0.1% Isopropanol in hexane	6.5, 7.9
5	**4g**	0.1% Isopropanol in hexane	12.5, 14

Separation of enantiomers was performed by HPLC equipped with a chiralphase OD column from Diacel Chemical Industries Ltd.

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Supplementary data

Supplementary data associated with this article can be found at 10.1016/j.tet.2005.03.124

References and notes

1. For a review, see: Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309.
2. Ludovic, B. G.; Douthwaite, R. E.; Hodgson, R. *Organometallics* **2003**, 4384–4386 and references therein.
3. For examples, see: ring closing metathesis: (a) Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288–12290. (b) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225–3228. Allylic alkylation: (c) Bonnet, L. G.; Douthwaite, R. E. *Organometallics* **2003**, *22*, 4187–4189. α-Arylation of amides: (d) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415. (e) For a review, see: Burgess, K. In *New methodologies in asymmetric catalysis*; Malhotra, S., Ed.; ACS Publications, 2004; pp 61–84.
4. (a) Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63–65. (b) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810–3813. (c) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724–9734.
5. Mg and alkali metals: (a) Bachmann, W. E. *J. Am. Chem. Soc.* **1931**, *53*, 2672–2676. (b) Smith, J. G.; Veach, C. D. *Can. J. Org. Chem.* **1966**, *44*, 2497–2502. (c) Eisch, J. J.; Kaska, D. D.; Peterson, C. J. *J. Am. Chem. Soc.* **1966**, *88*, 453–456. (d) Smith, J. G.; Ho, I. *J. Org. Chem.* **1972**, *37*, 653–656.
6. Photolysis: Beak, P.; Payet, C. R. *J. Org. Chem.* **1970**, *35*, 3281–3286.
7. Zn: (a) Smith, J. G.; Boettger, T. J. *Synth Commun.* **1981**, *11*, 61–64. (b) Alexakis, A.; Aujard, I.; Kanger, T.; Mangeney, P. *Org. Synth.* **1999**, *76*, 23. (c) Tsukinoki, T.; Nagashima, S.; Mitoma, Y.; Tashiro, M. *Green Chem.* **2000**, *2*, 117–119. (d) Ortega, M.; Rodríguez;, M. A.; Campos, P. J. *Tetrahedron* **2004**, *60*, 6475.
8. Sm(II): (a) Annuziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett* **1998**, *39*, 3333. (b) Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synth. Commun. 20* **1990**, 981–987. (c) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141–1142. (d) Aurrecoechea, J. M.; Fernández-Acebes, A. *Tetrahedron Lett.* **1992**, *33*, 4763–4766.
9. Pb/Al: Tanaka, H.; Dhimane, H.; Fujita, H.; Ikemoto, Y.; Torii, S. *Tetrahedron Lett.* **1988**, *29*, 3811–3814.
10. Rieke Mn: Rieke, R. D.; Kim, S. *J. Org. Chem.* **1998**, *63*, 5235–5239.
11. Yb: Takaki, K.; Tsubaki, Y.; Tanaka, S.; Beppu, F.; Fujiwara, Y. *Chem. Lett.* **1990**, 203–204.
12. In: Kalyanam, N.; Rao, G. V. *Tetrahedron Lett.* **1993**, *34*, 1647–1648.
13. Ti: Talukdar, S.; Banerji, A. *J. Org. Chem.* **1998**, *63*, 3468–3470.
14. V: Hatano, B.; Ogawa, A.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 9421–9424.
15. Zr: Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486–4494.
16. Electrochemically: Siu, T.; Li, W.; Yudin, A. K. *J. Comb. Chem.* **2001**, *3*, 554–558.
17. For *d/l* selective protocols, see: (a) Al/Sm: Yanada, R.; Okaniwa, M.; Kaieda, A.; Ibuka, T.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 1283–1286. (b) . Mo: Cameron, T. M.; Ortiz, C. G.; Abboud, K. A.; Boncella, J. M.; Baker, R. T.; Scott, B. L. *Chem. Commun.* **2000**, 573–574. (c) Zn/Cu: Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609–610. (d) Ti: Mangeney, P.; Tjero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255–257. (e) Nb: Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152–3154.
18. For a very recent example of a highly diastereoselective SmI_2 mediated dimerization using a chiral auxiliary see: Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 4747–4750.
19. Mercer, G. J.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 1591–1594.
20. For other methods of intramolecular reductive dimerization of imines, see: (a) Rita Annunziata, R.; Benaglia, M.; Caporale,

M.; Raimondi, L. *Tetrahedron: Asymmetry* **2002**, *13*, 2727. (b) Kise, N.; Oike, H.; Okazaki, E.; Yoshimoto, M.; Shono, T. *J. Org. Chem.* **1995**, *60*, 3980–3992. (c) Shono, T.; Kise, N.; Oike, H.; Yoshimoto, M.; Okizaki, E. *Tetrahedron Lett.* **1992**, *33*, 5559–5562. (d) Shono, T.; Kise, N.; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *J. Org. Chem.* **1991**, *56*, 3063–3067. (e) Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999–2021.

21. When Mn(0) is used, no reaction occurs.
22. Cantrell, G. K.; Meyer, T. Y. *J. Am. Chem. Soc.* **1998**, *120*, 8035–8042.

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A highly active catalyst for the reductive cyclization of *ortho*-nitrostyrenes under mild conditions

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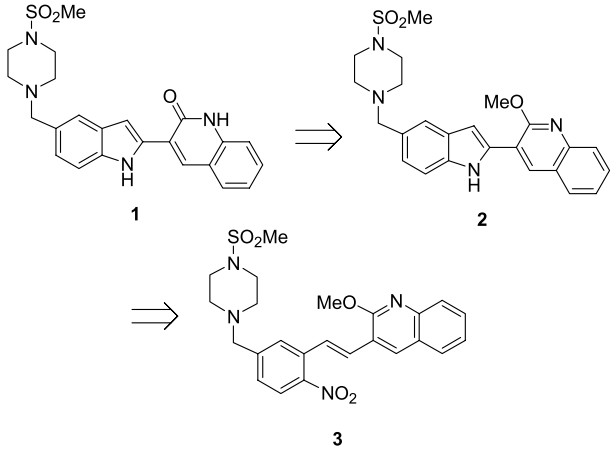
Dedicated to the memory of Jackie Smitrovich – a dear friend and a talented colleague

Abstract—A mild and efficient method for the palladium-catalyzed reductive cyclization of *ortho*-nitrostyrenes to afford indoles is reported. Treatment of *ortho*-nitrostyrenes with 0.1 mol% palladium (II) trifluoroacetate [$Pd(TFA)_2$] and 0.7 mol% 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) in DMF at 15 psig CO and 80 °C afforded indoles in good to excellent yields. When the reaction was conducted in toluene, the corresponding *N*-hydroxyindole was isolated. A mechanism that accounts for the formation of *N*-hydroxyindole is proposed.

1. Introduction

Substituted indoles are privileged structures[1] that are present in a wide range of pharmacophores.[2] As such, the synthesis of indoles represents a long and rich area of synthetic organic chemistry.[3] KDR kinase inhibitor **1** was identified as part of Merck's efforts[4] for blocking tumor-induced angiogenesis.[5] Due to the low solubility of **1** imparted by the quinilone ring, we proposed unmasking the quinolone in the final step, making methoxy-protected **2** our synthetic target (Scheme 1). Of the synthetic approaches investigated,[6] construction of the indol-2-yl methoxy-quinoline core of **2** by reductive cyclization of *ortho*-nitrostyrene **3** was appealing in that this substrate could be convergently assembled in a short number of steps.[7] This strategy would require a mild method for the reductive cyclization.



Scheme 1.

The Cadogan deoxygenation of nitroaromatics using boiling triethyl phosphite is now a classic synthetic method for the construction of a wide range of nitrogen-containing aromatic heterocycles and remains the most common method to affect deoxygenative cyclization.[8,9] While broad in scope, the generation of a large amount of phosphorous waste detracts from this approach. Transition metal promoted deoxygenation of nitroaromatics to give heterocycles was first realized by Waterman and Vivian in 1940 using stoichiometric iron oxalate at 200 °C.[10] In recent years, transition metal catalyzed variants of this reaction using CO as the stoichiometric reductant have been developed,[11] however, the moderate yields and extreme conditions (1175 psi CO and 220 °C) significantly limit the synthetic utility of this system. Palladium-based systems have subsequently been identified as more efficient catalysts for this transformation. The palladium-catalyzed reductive cyclization of *ortho*-nitrostyrenes in the presence of stoichiometric $SnCl_2$ at 100 °C and 275 psi CO was developed by Watanabe.[12] Söderberg reported a Pd/triphenylphoshphine system effective at

Keywords: Nitrostyrene; Reductive cyclization; Palladium.
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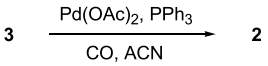
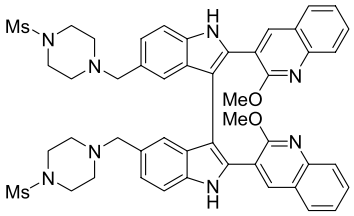
Table 1. Reductive cyclization of **3** using $Pd(OAc)_2$/triphenylphosphine



Entry	$Pd(OAc)_2$ (mol%)	PPh_3 (mol%)	CO (psig)	Temp (°C)	2 (% yield)[a]
1	6	24	60	70	95 (45)[b]
2	6	24	60	40	32
3	6	24	30	70	90
4	6	24	15	70	50
5	2	4	60	70	71
6	1	2	60	70	63

[a] HPLC assay yield.
[b] Yield reported for material isolated by crystallization.



4

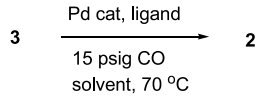
Figure 1.

lower temperatures and pressures (70 °C and 60 psi) at 6 mol% palladium loading.[13] Catalysts derived from palladium(II) salts and bidentate nitrogen ligands effect cyclization of *ortho*-nitrostyrenes at low catalyst loading, however, these reactions require harsh conditions (300 psi CO and 120 °C).[14] Catalytic alternatives effective at mild temperatures and pressures would enhance widespread uptake of this technology. Our approach to developing a highly efficient catalytic system relied upon systematic screening using a 6×8 parallel Parallel Pressure Reactor (PPR®). Results of these studies and investigations into the reaction mechanism are presented herein.

2. Results and discussion

The relatively mild pressure and temperature required for Pd/phosphine catalytic systems motivated us to apply this system towards the reductive cyclization of **3**. Using the conditions reported by Söderberg [6 mol% $Pd(OAc)_2$, 24 mol% PPh_3, CO (60 psig), 70 °C in ACN],[13] indole **2** was produced in high assay yield (95%, Table 1, entry 1). The only by-product was dimer **4** (3%, Fig. 1). Crystallization from the reaction stream resulted in a disappointing isolated yield (45%) due to the presence of triphenylphosphine and triphenylphosphine oxide. Reducing the ligand and catalyst loading resulted in decreased yields due

Table 2. Reductive cyclization using palladium/phenanthroline catalysts[a]



Entry	Catalyst (mol%)	Ligand (mol%)	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$ (1.0)	phen (2.0)	ACN	56
2	$Pd(OAc)_2$ (1.0)	phen (2.0)	THF	37
3	$Pd(OAc)_2$ (1.0)	phen (2.0)	Toluene	40
4	$Pd(OAc)_2$ (1.0)	phen (2.0)	ODCB[c]	58
5	$Pd(OAc)_2$ (1.0)	phen (2.0)	DMF	98 (94)[d]
6	$Pd(OAc)_2$ (0.5)	phen (1.0)	DMF	93
7	$Pd(OAc)_2$ (0.25)	phen (0.5)	DMF	24
8	$Pd(OAc)_2$ (0.10)	phen (0.2)	DMF	0
9	$Pd(OAc)_2$ (0.10)	phen (0.5)	DMF	6
10	$Pd(OAc)_2$ (0.10)	phen (1.0)	DMF	25
11	$Pd(OAc)_2$ (0.10)	tm-phen (0.2)	DMF	25
12	$Pd(OAc)_2$ (0.10)	tm-phen (0.5)	DMF	79
13	$Pd(OAc)_2$ (0.10)	tm-phen (1.0)	DMF	92
14	$phen_2Pd(BF_4)_2$[e] (1.0)	—	DMF	99
15	$phen_2Pd(BF_4)_2$ (0.5)	—	DMF	89
16	$phen_2Pd(BF_4)_2$ (0.25)	—	DMF	74
17	$Pd(TFA)_2$ (0.1)	phen (0.5)	DMF	32
18	$Pd(TFA)_2$ (0.1)	phen (1.0)	DMF	33
19	$Pd(TFA)_2$ (0.1)	tm-phen (0.2)	DMF	68
20	$Pd(TFA)_2$ (0.1)	tm-phen (0.5)	DMF	78
21	$Pd(TFA)_2$ (0.1)	tm-phen (1.0)	DMF	100

[a] Reactions performed at 70 °C and 15 psig CO.
[b] HPLC assay yield.
[c] *ortho*-Dichlorobenzene.
[d] Number in parentheses is yield reported for material isolated by crystallization.
[e] Pre-formed catalyst.

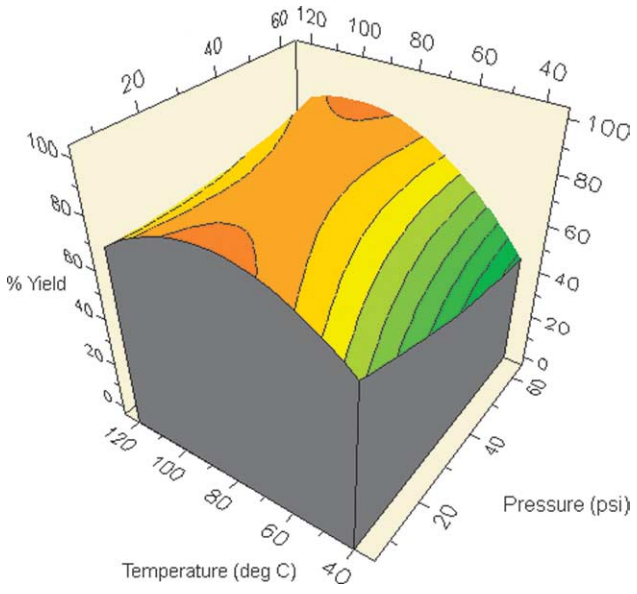
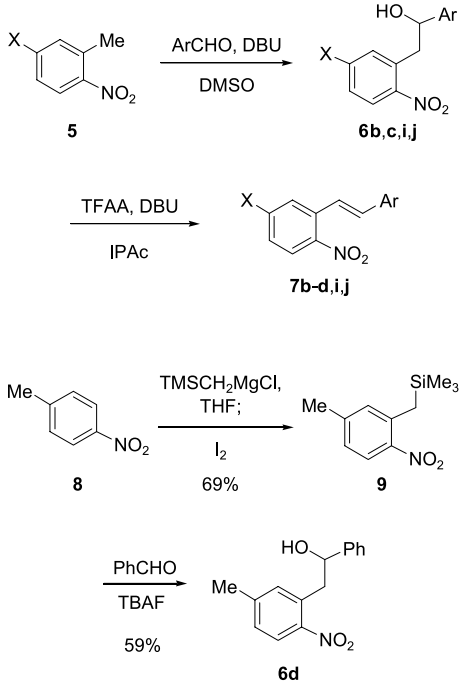


Figure 2. Temperature and pressure response surface for the cyclization of **3**.



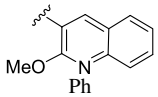
Scheme 2.

to lower conversion (entries 5 and 6). The CO pressure could be reduced to 30 psig without adversely affecting yield, but at 15 psig yield decreased due to lower conversion (entries 3 and 4). Due to the necessity for high catalyst and ligand loading, a more efficient catalytic system was sought.

Catalysts derived from palladium(II) salts and bidentate nitrogen ligands are highly reactive systems for the reduction of nitroarenes to isocyanates and carbamates[15] and have been applied to the reductive cyclization of *ortho*-nitrostyrenes at high temperatures and pressures.[13a,14] The efficiency of these systems, we proposed, may allow the reductive cyclization of **3** to occur at low catalyst and ligand loading and hence simplify isolation of indole **2**. Initial results were encouraging, with the reaction occurring at mild temperature and pressure: treatment of **3** with 1 mol% $Pd(OAc)_2$ and 2 mol% 1,10-phenanthroline (phen) in ACN at 15 psig CO and 70 °C afforded **2** in 56% yield (Table 2, entry 1). A screen of solvents identified DMF as optimal, and under identical conditions **2** was produced in 98% assay yield and 94% isolated yield (entry 5).[16] Other solvents resulted in lower conversion.

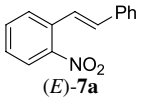
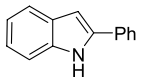
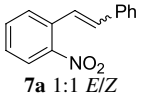
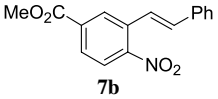
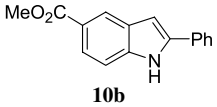
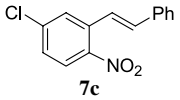
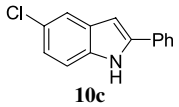
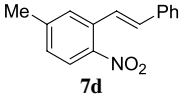
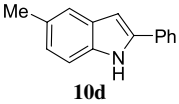
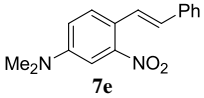
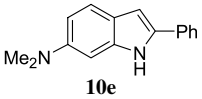
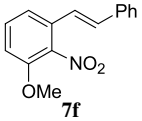
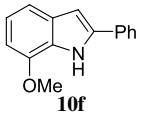
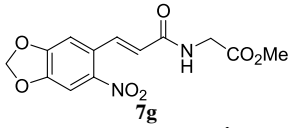
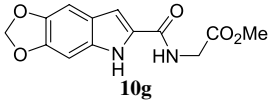
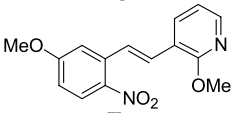
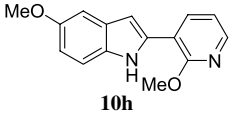
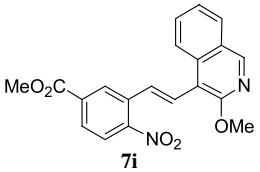
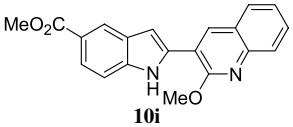
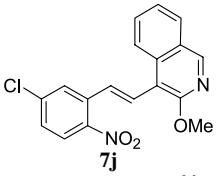
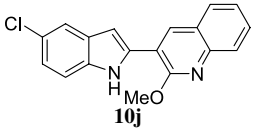
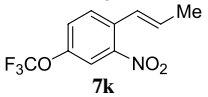
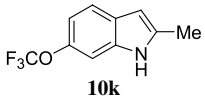
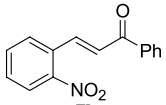
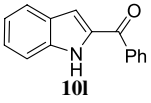
Optimization of reaction parameters was accomplished using a 6×8 module Parallel Pressure Reactor (PPR®) from Symyx Technologies, Inc. With a 1:2 $Pd(OAc)_2$/phen ratio, high yield is maintained at 0.5 mol% palladium (93%, Table 2, entry 6), but at lower palladium loading the yield dropped drastically due to decreased conversion (entry 7) and no reaction occurred at 0.1 mol% catalyst loading (entry 8). The catalyst loading could be reduced to 0.1 mol% by increasing the ligand/palladium ratio,[17] but conversion was low (entries 9 and 10). For the reductive carbonylation of nitro-arenes to afford isocyanates, increased catalytic activity is obtained with palladium (II) salts with non-coordinating counter ions and electron rich phenanthrolines.[15d,e,18] The pre-formed catalyst $phen_2Pd(BF_4)_2$[19] performed similarly to the catalyst generated in situ from 0.5 mol% $Pd(OAc)_2$ and 0.5 mol% phen (compare entries 5 and 14) and conversion dropped with decreased catalyst loading (entries 15 and 16). Due to ease of operation, the in situ catalyst system was chosen for further optimization. Palladium trifluoroacetate [$Pd(TFA)_2$] gave similar results at 0.1 mol% loading with excess phen (entries 17 and 18). Use of the more electron donating ligand and 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) gave higher conversion at a 10:1 ratio with $Pd(OAc)_2$ (92% assay yield, entry 13). Best results were obtained with 0.1 mol% $Pd(TFA)_2$ and 1 mol% tm-phen, affording indole **2** in 100% assay yield (entry 21).

Table 3. Preparation of substituted *ortho*-nitrostyrenes **7b–d,i,j**

Entry	X	Ar	Alcohol	Yield (%)[a]	Styrene	Yield (%)[a]
1	CO_2Me	Ph	**6b**	—	**7b**	75
2	Cl	Ph	**6c**	61	**7c**	64
3	Me	Ph	**6d**	59	**7d**	70
4	CO_2Me		**6i**	80	**7i**	87
5	Cl	Ph	**6j**	84	**7j**	93

[a] Isolated yield.

Table 4. Reductive cyclization of substituted *ortho*-nitrostyrenes[a]

Entry	Substrate	Product	Yield (%)[b]
1[c]	 (*E*)-**7a**	 **10a**	87
2[c]	 **7a** 1:1 *E*/*Z*	**10a**	86
3[d]	 **7b**	 **10b**	98
4	 **7c**	 **10c**	96
5	 **7d**	 **10d**	89
6[e]	 **7e**	 **10e**	61
7[e]	 **7f**	 **10f**	18
8[e]	 **7g**	 **10g**	72
9[f]	 **7h**	 **10h**	72
10[d]	 **7i**	 **10i**	78
11	 **7j**	 **10j**	91
12	 **7k**	 **10k**	84[g]
13	 **7l**	 **10l**	84

[a] Reaction conditions: 1 mol% $Pd(OAc)_2$, 2 mol% phen, 15 psig CO, 80 °C for 16 h in DMF, unless otherwise noted.
[b] Isolated yield.
[c] 1.5 mol% $Pd(OAc)_2$, 3 mol% phen employed.
[d] 0.1 mol% $Pd(TFA)_2$, 0.7 mol% tm-phen employed.
[e] 1.0 mol% $Pd(TFA)_2$, 2.0 mol% tm-phen employed.
[f] 1.5 mol% $Pd(OAc)_2$, 3 mol% phen, 30 psig CO. 70 °C for 16 h in DMF.
[g] HPLC assay yield.

With this catalyst system, the optimal temperature and pressure were identified by DOE (design of experiments, Fig. 2). The ranges investigated spanned 40–120 °C and 5–65 psig CO. Temperature had the greater effect of the two variables. The effect of pressure was minimal, with high yields occurring at both low and high pressure at the optimal temperatures. At 5–15 psig CO, the optimal temperature was 80 °C, with decreased conversion at temperatures <80 °C. At 65 psig, highest yields were obtained at 100 °C. Due to ease of operation, the milder reaction conditions were selected for further optimization.

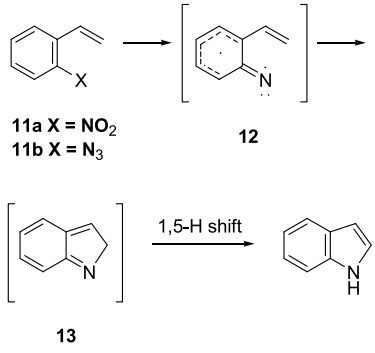
At 15 psig CO and 80 °C the ligand/palladium can be reduced to 7:1 without adversely effecting conversion. At low catalyst loadings, (0.1 mol%) rigorous air free conditions are necessary for reproducibility. Optimized conditions (0.1 mol% $Pd(TFA)_2$, 0.7 mol% tm-phen, 15 psig CO, 80 °C in DMF) afforded **2** in 94% isolated yield.

The scope was investigated using a panel of substituted *ortho*-nitrostyrenes. Substrates were commercially available, previously reported, or readily available in a few steps from commercially available starting materials. Substituted styrenes **7b–d,i,j** were prepared from the corresponding alcohols in a one pot acylation/elimination sequence with TFAA and DBU (Scheme 2, Table 3). Alcohol **6b** was prepared following the literature procedure.[20] Alcohols **6c,d,i,j** were prepared by DBU-mediated addition of the requisite *ortho*-nitrotoluene to either benzaldehyde or 2-methoxyquinoline-3-carboxaldehyde. Alcohol **6d** was prepared using the sequence optimized for **2** (Scheme 2).[6b] Addition of trimethylsilylmethylmagnesium bromide to 4-nitrotoluene followed by oxidation of the resulting nitronate intermediate with iodine afforded **9**. Treatment of **9** with catalytic tetrabutylammonium fluoride (TBAF, 0.20 mol%) in the presence of benzaldehyde afforded **6d** in 59% isolated yield. Styrenes **7e** and **7l** were prepared from the commercially available nitrobenzaldehydes by reaction with diethyl benzylphosphonate.

ortho-Nitrostyrenes **7b–l** were submitted to the reductive cyclization (Table 4). With 1 mol % $Pd(OAc)_2$ and 2 mol% phen, the catalyst and ligand can be weighed in air and added to the reaction as solids. For small scale reactions, solutions of $Pd(OAc)_2$ and phen in DMF were added to a solution of the substrate on the bench top. At 0.1 mol% catalyst loading, solutions of $Pd(TFA)_2$ and tm-phen were prepared on the bench top and then added to a solution of substrate in a nitrogen atmosphere glove box. The reductive conditions tolerate a wide range of functional groups, for example esters, aromatic chlorides, anilines and amides (entries 3, 4, 6 and 8). α,β-Unsaturated amides and ketones undergo the reaction (entries 8 and 13). Methoxy-substituted quinolines and pyridines are compatible with the conditions (entries 9–11). The olefin geometry does not effect the reaction, as demonstrated by reaction of a 1:1 mixture of (*E*)/(*Z*) isomers of **7a**,[21] which gave a comparable yield to reaction of isomerically pure (*E*)-**7a** (compare entries 1 and 2). The alkene is not required to be cross-conjugated as exemplified by entry 12, where the alkene has a methyl substituent. Electron rich substrates gave low yields under standard conditions due to poor conversion. High conversion of **7h** was obtained using 1.5 mol% $Pd(OAc)_2$ and 3 mol% phen at 30 psig CO pressure and 70 °C. Use of 1 mol% of the more reactive catalyst $Pd(TFA)_2$ with 2 mol% tm-phen was required to obtain good conversion with **7e** and **7g** and afforded indoles **10e** and **10g** in 61 and 72% isolated yields, respectively. Even under these conditions, **7f** afforded only an 18% yield due to poor conversion (entry 7).

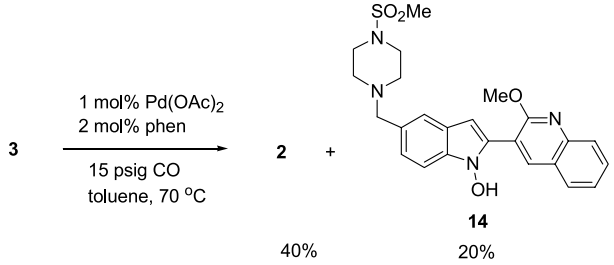
The widely accepted mechanism for the formation of heterocyclic products from nitro aromatics involves exhaustive deoxygenation to a singlet nitrene **12** which undergoes a downstream insertion into the adjacent π-bond to form **13** followed by a hydrogen migration to afford the indole (Scheme 3). This rationalization is primarily supported by the product distribution from reactions of aromatic nitro compounds and their analogous azides.[22] A significant study of the chemistry of biphenylnitrenes by laser flash photolysis and time-resolved IR experiments and by theoretical calculations has recently been published.[23] These data indicate that cyclization proceeds via a singlet nitrene with an open-shell electronic structure to form isocarbazole and a 1,5-hydrogen shift to form carbazole.

N-Hydroxy- and *N*-ethoxyindoles have been observed by Sundberg in the reduction of **11a** with triethylphosphite,

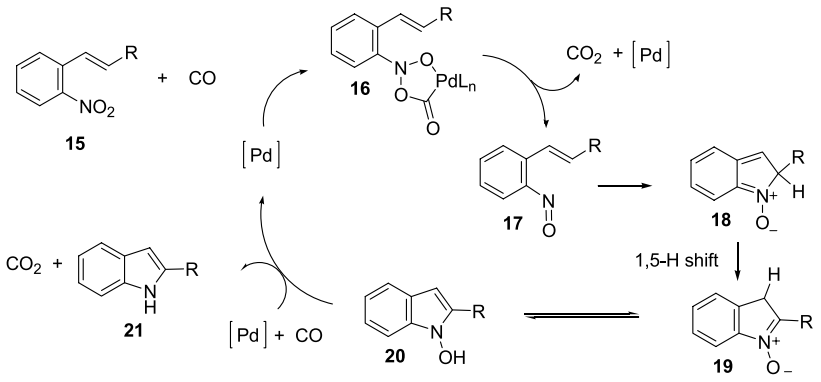


Scheme 3.

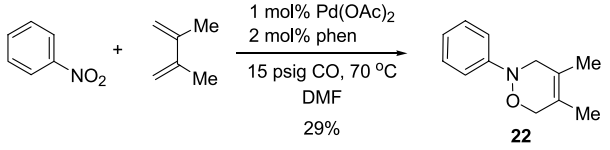
which suggests a competitive pathway might be available involving partially deoxygenated intermediates.[8c] *N*-Hydroxyindoles have been identified in the palladium-catalyzed reductive cyclization of *ortho*-nitrostyrenes in THF at 170 °C and 440 psi CO.[14a] We have observed analogous products under our milder reductive cyclization conditions. When the cyclization of styrene **3** was performed in toluene, two products were formed (Scheme 4). Expected indole **2** was isolated in 40% yield and *N*-hydroxyindole **14** was isolated in 20% yield. When **14**



Scheme 4.



Scheme 5.



Scheme 6.

was resubjected to the standard reductive cylization conditions in DMF, indole **2** was formed quantitatively.

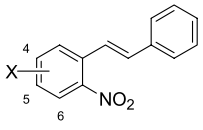
The formation of hydroxyindole **14** and its conversion to indole **2** gives some insight into the reaction mechanism. Reduction of the nitro to the nitrene does not account for the formation of **14**. We propose the following mechanism (Scheme 5). Reaction of the nitrostyrene with the catalyst and carbon monoxide gives palladacycle **16**,[24] which undergoes extrusion of CO_2 to give nitrosostyrene **17**. For the reduction of nitroaromatics to isocyanates, the nitroso species undergoes further reduction and incorporation of CO.[25] We propose that in the presence of the pendant olefin, intramolecular 6π-electron 5-atom electrocyclic reaction occurs faster than reduction, giving nitronate **18**.[26] Subsequent 1,5-hydrogen shift and isomerization affords *N*-hydroxyindole **20**, which is subsequently reduced by a second equivalent of CO to give indole **21**. The viability of the 1,5-electrocylization pathway under experimental reaction conditions has been demonstrated computationally.[27,28]

Attempts to trap nitrosostyrene **17** by conducting the cyclization reaction of *ortho*-nitrostyrene **7a** in the presence of 2,3-dimethylbutadiene were unsuccessful. Oxazine **22**[17] was produced in 29% yield from the reaction of *ortho*-nitrobenzene and 2,3-dimethylbutadiene with 1 mol% $Pd(OAc)_2$ and 2 mol% phen at 15 psig CO and 70 °C (Scheme 6). The remainder of the reaction mixture was starting material. This result indicates that aromatic nitro groups are reduced to the nitroso species under the reaction conditions. For the reaction of **7a**, intramolecular cyclization onto the pendant alkene may be faster than intermolecular cycloaddition with the diene.

In order to explore the electronic effect on the rate of reaction, competition experiments of substituted *ortho*-nitrostyrenes **7b–f** with unsubstituted **7a** (X=H) were conducted (Table 5). A 1:1 molar ratio of the substituted styrene and **7a** was submitted to the following cyclization conditions: 0.1 mol% $Pd(TFA)_2$, 0.7 mol% tm-phen, 15 psi CO, 80 °C, DMF. Relative rates were determined by HPLC assay yield of the amount of starting material remaining in the reaction mixture and are reported as an average of three experiments.

A ρ value of +1.77 was obtained by plotting log k_{rel} versus σ parameter[29] (Fig. 3), indicative of a build-up of negative charge on the nitroarene in the rate determining step of the reaction. This finding is also supported by an increase in reaction rate with the reduction potential of the nitrostyrene[30] (Fig. 4). The rate of reaction **7f**, bearing a methoxy substituent ortho to the nitro group, correlated well with the

Table 5. Substituent effects on the reductive cyclization of substituted *ortho*-nitrostyrenes



Entry	X	Substrate	E^{oa}	k_{rel}	σ_p [b]
1	4-CO_2Me	**7b**	−0.95	6.8	0.50
2	4-Cl	**7c**	−1.09	3.5	0.23
3	H	**7a**	−1.13	—	0
4	4-Me	**7d**	−1.20	0.57	−0.17
5	5-NMe_2	**7e**	−1.23	0.51	−0.15[c]
6	6-OMe	**7f**	−1.40	0.15	—

[a] $E^{o}=(E_{pc}+E_{pa})/2$.
[b] Values from Ref 30.
[c] Value reported is σ_m.

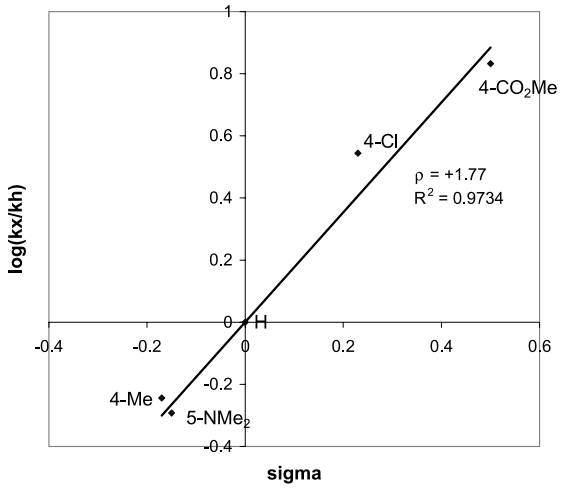


Figure 3. Hammett plot for the reaction of substituted *ortho*-nitrostyrenes **7a–e**.

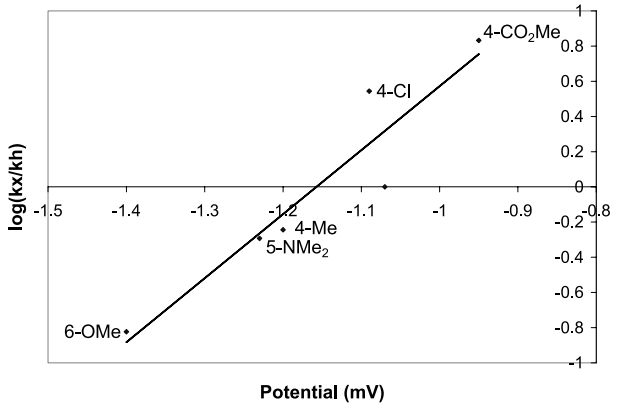


Figure 4. Plot of log k_{rel} versus reduction potential for the reductive cyclization of *ortho*-nitrostyrenes **7a–f**.

reduction potential. Severe drops in the rate of reduction of *ortho*-substituted nitroarenes by Ru(dppe)$(CO)_3$ complexes were found in arenes bearing three or more substituents.[25] Presumably, in these sterically encumbered systems, the nitro group rotates out of plane with the aromatic ring.

The electrocyclization of **17** to give **18** (Scheme 5) would not be expected to be accelerated by electron withdrawing groups.[31] A competition experiment between nitrostyrene **7b** and *N*-hydroxyindole **20a** (Scheme 5, R=Ph) indicated that the reduction of **20a** is faster than the reduction of **7b**. We propose that rate determining reduction of nitroarene **15** to nitroso intermediate **17** is followed by a faster cyclization to *N*-hydroxyindole **20**, which is then reduced to indole **21**.

3. Conclusion

We have developed a palladium-catalyzed reduction of *ortho*-nitrostyrenes to afford indoles in good to excellent yields. A range of functionality is tolerated. The cyclization occurs under much milder conditions and at lower catalyst loadings than previously reported, giving excellent yields at just 15 psig CO. Using CO as the stoichiometric reductant and 0.1 mol% palladium trifluoroacetate, CO_2 is the only stoichiometric by-product, which offers significant economic and environmental advantages over the standard triethylphosphite deoxygenation procedure.

4. Experimental

4.1. General methods

^{1}H NMR and ^{13}C NMR were recorded at ambient temperature at a frequency of 400.13 and 100.61 MHz, respectively. The chemical shifts are reported in ppm relative to residual $CHCl_3$ for proton (δ=7.27) and $CDCl_3$ for carbon (δ=77.0). The data are reported as follows: proton multiplicities (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad), coupling constants, and integration. Microanalyses were performed by Quantitative Technologies, Inc. Melting points are reported uncorrected. Flash chromatography was performed using the indicated solvent system on EM Reagents silica gel (SiO_2) 60 (230–400 mesh). All reactions were carried out under an atmosphere of nitrogen, except where indicated. All reagents used were commercially available from Aldrich Chemical Co., except the following: 2-methoxyquinoline-3-carboxaldehyde[6b] was purchased from Daito Chemix Corporation, **7g** was purchased from Menai Organics, Ltd and **7l** was purchased from Acros. DMF, DMSO, toluene and DBU were dried over 4 Å molecular sieves. Solutions of $Pd(OAc)_2$, $Pd(TFA)_2$, 1,10-phenanthroline (phen) and 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) in DMF were prepared in air.

4.1.1. Reductive cyclization of 3 with $Pd(OAc)_2$ and PPh_3: 2-methoxy-3-(5-{[4-(methylsulfonyl)-1-piperazinyl]-methyl}-1*H*-indol-2-yl)-quinoline (2). An autoclave was charged with **3**[6b] (4.0 g, 8.3 mmol), $Pd(OAc)_2$ (0.112 g, 0.50 mmol), PPh_3 (0.520 g, 2.00 mmol) and acetonitrile (40 mL). The vessel was purged three times successively with N_2 and CO. The reactor was pressurized to 30 psig with CO heated to 70 °C. After 15 h, the reaction mixture was filtered washing with hot acetonitrile, affording dimer **4** as a pale green solid (0.224 g, 0.25 mmol, 3%) in >95% purity as determined by ^{1}H NMR spectroscopic analysis. HPLC analysis of the filtrate indicated a 95% assay yield of **2**. The filtrate was concentrated in vacuo. Crystallization from 2:1 EtOAc/hexanes provided **2** as a pale yellow solid (1.79 g, 45%): mp 197–198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.68 (br s, 1H), 8.48 (s, 1H), 7.88 (d, J=8.4 Hz, 1H), 7.81 (d, J=8.1 Hz, 1H), 7.64 (t, J=8.4 Hz, 1H), 7.57 (s, 1H), 7.44 (m, 2H), 7.18 (dd, J=8.3, 1.4 Hz, 1H), 7.07 (s, 1H), 4.31 (s, 3H), 3.66 (s, 2H), 3.27 (m, 4H), 2.78 (s, 3H), 2.61 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 145.3, 136.0, 135.2, 134.0, 129.6, 129.0, 128.3, 127.6, 127.0, 125.5, 124.8, 124.2, 121.1, 116.8, 111.3, 101.5, 63.3, 54.1, 52.3, 46.0, 34.0; Anal. Calcd for $C_{24}H_{26}N_4O_3S$: C, 63.98; H, 5.82; N, 12.44. Found: C, 64.28; H, 5.68; N, 12.05.

4.1.2. 2,2′-Bis(2-methoxyquinolin-3-yl)-5,5′-bis{[4-(methylsulfonyl)piperazin-1-yl]methyl}-1*H*,1′*H*-3-3′-biindole (4). Mp 324–326 °C (dec); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.3 (br s, 2H), 7.96 (s, 2H), 7.67 (d, J=8.3 Hz,

2H), 7.57 (dt, $J=7.0$, 1.2 Hz, 2H), 7.50 (d, $J=7.9$ Hz, 2H), 7.37 (d, $J=8.3$ Hz, 2H), 7.29 (dt, $J=7.9$, 0.8 Hz, 2H), 7.01 (m, 4H), 3.67 (s, 6H), 3.44 (d, $J=12.4$ Hz, 2H), 3.22 (d, $J=12.4$ Hz, 2H), 2.92 (m, 8H), 2.82 (s, 6H), 2.22 (m, 4H), 2.15 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.0, 144.8, 138.4, 135.6, 130.2, 129.3, 127.3, 126.9, 126.1, 124.3, 123.9, 123.1, 120.2, 118.2, 110.9, 108.2, 62.4, 52.8, 51.3, 45.1, 35.6, 33.8; HRMS calcd for $C_{48}H_{51}N_8O_6S_2$: 899.3373 (M+H). Found: 899.3372 (M+H).

4.1.3. Reductive cyclization of 3 with $Pd(OAc)_2$ and phen: (2). An autoclave was charged with was charged with **3** (45.02 g, 93.3 mmol), $Pd(OAc)_2$ (0.210 g, 0.935 mmol), 1,10-phenathroline (0.336 g, 1.87 mmol) and DMF (1.3 L). The vessel was purged three times successively with N_2 and CO. The reactor was pressurized to 15 psig with CO and the mixture heated to 70 °C. After 14 h, the vessel was allowed to cool to rt. The reaction mixture was filtered through solka flok. The filtrate was concentrated to 150 mL and heated to 50 °C. MeOH (50 mL) was added and the mixture was allowed to cool to rt. Filtration afforded **2** as a pale yellow solid (39.39 g, 94%). Spectral data was identical to that prepared by Method A.

4.1.4. Reductive cyclization of 3 with $Pd(TFA)_2$ and tmphen: (2). An Endeavor™ glass liner was charged with **3** (100 mg, 0.207 mmol) and the liner was inserted into an Endeavor™ pressure reactor. To the liner was charged $Pd(TFA)_2$ (6.02×10^{-3} M solution in DMF, 34 μL, 2.05×10^{-4} mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (1.20×10^{-2} M solution in DMF, 121 μL, 1.45×10^{-3} mmol) and DMF (2.85 mL). The reactor system was sealed and purged three times with N_2 followed by CO. The system was pressurized with CO (15 psig) and heated at 80 °C for 16 h. The mixture was cooled to rt and concentrated in vacuo. Purification by flash chromatography (2:1 EtOAc/hexanes to 4:1 EtOAc/hexanes) afforded **2** as a pale yellow solid (87 mg, 94%). Spectral data was identical to that prepared by Method A.

4.1.5. Methyl 4-nitro-3-[(*E*)-2-phenylvinyl]benzoate (7b). To a solution of **6b**[20] (1.50 g, 4.98 mmol) in isopropyl acetate (IPAc, 20 mL) was added trifluoroacetic anhydride (2.07 mL, 14.9 mmol). After 1 h, DBU (3.72 mL, 24.9 mmol) was added. After 1 h, the reaction was diluted with IPAc (20 mL) and washed with 2 N HCl (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to a yellow solid. Crystallization from 1:5 EtOAc/hexanes afforded **7b** as yellow needles (1.06 g, 75%): mp 122–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (d, $J=1.6$ Hz, 1H), 8.03 (dd, $J=8.5$, 1.7 Hz, 1H), 7.96 (d, $J=8.5$ Hz, 1H), 7.58–7.55 (m, 2H), 7.51 (s, 1H), 7.43–7.34 (m, 3H), 7.22 (d, $J=16.1$ Hz, 1H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 150.3, 136.1, 135.1, 133.9, 132.9, 129.4, 128.9, 128.8, 128.6, 127.2, 124.8, 122.0, 52.8; Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.62; H, 4.53; N, 4.94.

4.1.6. 2-(5-Chloro-2-nitrophenyl)-1-phenylethanol (6c).[20] To a solution of 5-chloro-2-nitrotoluene (9.68 g, 56.0 mmol) and benzaldehyde (4.80 mL, 47.0 mmol) in DMSO (60 mL) was added DBU (8.40 mL, 56.0 mmol). After a 36 h age, the reaction mixture was diluted with IPAc (60 mL) and washed with brine (60 mL). The layers were separated. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography (1:15 to 1:8 EtOAc/hexanes) afforded **6c** as a green tacky oil (7.03 g, 61%) in >95% purity as determined by ^{1}H NMR spectroscopic analysis: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94–7.91 (m, 1H), 7.44–7.32 (m, 7H), 5.04–5.02 (m, 1H), 3.37 (dd, $J=13.6$, 3.7 Hz, 1H), 3.21 (dd, $J=13.6$, 9.0 Hz, 1H), 2.09 (d, $J=3.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.8, 143.6, 138.7, 135.7, 133.4, 128.5, 127.7, 127.5, 126.1, 125.6, 73.6, 42.4.

4.1.7. 4-Chloro-1-nitro-2[(*E*)-2-phenylvinyl]benzene (7c).[32] To a solution of **6c** (2.01 g, 7.24 mmol) in toluene (25 mL) was added PTSA (0.275 g, 1.45 mmol). The reaction vessel was equipped with a Dean Stark apparatus and heated at 110 °C for 1 h. The mixture was cooled to rt and washed with $NaHCO_3$ (saturated aq, 2×10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to a yellow solid. Crystallization from 1:2 toluene/hexanes afforded **7c** as a yellow solid (0.950 g, 51%). A second crop was obtained by crystallization from 1:5 EtOAc/hexanes (0.247 g, 13%): mp 94.2–95.3 °C (lit.[30] mp 91–93 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, $J=8.8$ Hz, 1H), 7.75 (d, $J=2.2$ Hz, 1H), 7.62–7.55 (m, 3H), 7.43–7.35 (m, 4H); 7.10 (d, $J=16.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.0, 139.4, 136.0, 135.0, 134.9, 128.9, 128.8, 127.9, 127.8, 127.2, 126.3, 122.4.

4.1.8. Trimethyl(5-methyl-2-nitrobenzyl)silane (9). To a cooled (−40 °C) solution of 4-nitrotoluene (13.7 g, 99.9 mmol) in THF (200 mL) was added $TMSCH_2MgCl$ (1.0 M in THF, 130 mL, 130 mmol) at such a rate to maintain the reaction temperature < −30 °C. After 1 h, the reaction was warmed to −10 °C. Iodine (1 M aq, 130 mL, 130 mmol) was added and the mixture was allowed to warm to rt. After 15 min, Na_2SO_3 (saturated aq, 75 mL) was charged. The mixture was extracted with MTBE (100 mL). The layers were separated and the organic layer was washed with Na_2SO_3 (saturated aq, 50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to an orange liquid. Purification by flash chromatography (1:20 EtOAc/hexanes) afforded **9** as a pale yellow liquid (15.44 g, 69%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, $J=8.4$ Hz, 1H), 7.00 (dd, $J=8.4$, 1.0 Hz, 1H), 6.94 (s, 1H), 2.58 (s, 2H), 2.37 (s, 3H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.6, 143.7, 137.7, 131.9, 125.7, 125.4, 24.9, 21.3, −1.5; Anal. Calcd for $C_{11}H_{17}NO_2Si$: C, 59.15; H, 7.67; N, 6.27. Found: C, 59.21; H, 7.74; N, 6.16.

4.1.9. 2-(5-Methyl-2-nitrophenyl)-1-phenylethanol (6d). To a solution of **9** (14.21 g, 63.6 mmol) in IPAc (250 mL) was added benzaldehyde (6.75 mL, 66.8 mmol) followed by TBAF (1 M solution in THF, 12.7 mL, 12.7 mmol). After 2 h, NH_4Cl (saturated aq, 100 mL) was added to the reaction mixture. The layers were separated. The organic layer was washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to an orange oil. Purification by flash chromatography (1:7 to 1:3 EtOAc/hexanes) afforded **6d** as an off-white solid (9.59 g, 59%): mp 77.8–78.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, $J=8.3$ Hz, 1H), 7.44–7.36 (m,

4H), 7.32–7.31 (m, 1H), 7.20–7.18 (m, 1H), 7.14 (br s, 1H), 5.07–5.03 (m, 1H), 3.40 (dd, $J=13.5$, 3.7 Hz, 1H), 3.19 (dd, $J=13.5$, 9.1 Hz, 1H), 2.40 (s, 3H), 2.15 (d, $J=3.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.5, 144.0, 143.9, 134.1, 133.6, 128.5, 128.3, 127.8, 125.6, 125.1, 74.3, 43.1, 21.3; Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.95; H, 5.84; N, 5.43.

4.1.10. 4-Methyl-1-nitro-2-[(*E*)-2-phenylvinyl]benzene (7d). To a solution of **6d** (8.56 g, 33.3 mmol) in IPAc (150 mL) was added trifluoroacetic anhydride (14.1 mL, 99.9 mmol). After 1 h, DBU (24.9 mL, 167 mmol) was added. The mixture was heated at reflux for 14 h. Upon cooling to rt, a white solid precipitated. The mixture was filtered, washing with EtOAc. The filtrate was washed with 2 N HCl (75 mL), water (75 mL), brine (75 mL) and concentrated in vacuo to a brown oil. Purification by flash chromatography (1:10 to 1:5 toluene/hexanes) afforded **7d** as a yellow oil (5.6 g, 70%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, $J=8.4$ Hz, 1H), 7.65 (d, $J=16.1$ Hz, 1H), 7.57–7.55 (m, 3H), 7.42–7.38 (m, 2H), 7.35–7.33 (m, 1H), 7.20 (d, $J=8.3$ Hz, 1H), 7.07 (d, $J=16.1$ Hz, 1H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.7, 144.2, 136.6, 133.4, 133.2, 128.7, 128.6, 128.4, 127.0, 125.0, 124.0, 21.5; ^{13}C NMR (CD_3CN, 100 MHz) δ 147.0, 145.8, 137.9, 134.1, 133.7, 130.0, 129.9, 129.7, 129.5, 128.0, 125.9, 124.9, 21.6; Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.59; H, 5.28; N, 5.78.

4.1.11. *N*,*N*-Dimethylamino-3-nitro-4-[(*E*)-2-phenylvinyl]-aniline (7e). To a solution of diethyl benzylphosphonate (0.800 mL, 3.84 mmol) and 4-dimethylamino-2-nitrobenzaldehyde (500 mg, 2.57 mmol) in DMF (20 mL) was added KO*t*-Bu (288 mg, 2.57 mmol). After 14 h, the mixture was diluted with MTBE (20 mL) and washed with water (2×5 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to a red oil. Purification by flash chromatography (1:4 EtOAc/hexanes) afforded **7e** as a red solid (363 mg, 53%): mp 105.8–106.4 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, $J=8.8$ Hz, 1H), 7.52–7.48 (m, 3H), 7.38–7.36 (m, 2H), 7.28–7.25 (m, 1H), 7.17 (d, $J=2.8$ Hz, 1H), 6.95 (d, $J=16.2$ Hz, 1H), 6.93–6.90 (m, 1H), 3.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.6, 149.0, 137.2, 129.6, 128.6, 128.4, 127.6, 126.5, 123.4, 119.7, 116.4, 106.6, 40.1; Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.52; H, 5.96; N, 10.25.

4.1.12. 4-Methoxy-2-nitro-1-[(*E*)-2-phenylvinyl]benzene (7f). To a solution of diethyl benzylphosphonate (0.860 mL, 4.14 mmol) and 3-methoxy-2-nitrobenzaldehyde (500 mg, 2.76 mmol) in DMF (10 mL) was added NaOMe (194 mg, 3.6 mmol). After 14 h, the mixture was partitioned between water (5 mL) and MTBE (10 mL). The layers were separated. The organic layer was washed with water (2× 5 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to an oil that solidified upon standing. Crystallization from 1:9 EtOAc/hexanes afforded **7f** as a pale orange solid (435 mg, 62%): mp 112.0–113.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50–7.48 (m, 2H), 7.43–7.31 (m, 5H), 7.17 (d, $J=16.1$ Hz, 1H); 6.96–6.92 (m, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8, 140.5, 136.0, 134.1, 130.7, 130.6, 128.74, 128.71, 127.0, 120.1, 117.6, 111.0, 56.3; Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.40; H, 4.92; N, 5.36.

4.1.13. Methyl 3-[2-hydroxy-2-(2-methoxyquinolin-3-yl)ethyl]-4-nitrobenzoate (6i). To a solution of methyl 3-methyl-4-nitrobenzoate (1.19 g, 6.41 mmol) and 2-methoxyquinoline-3-carboxaldehyde (1.00 g, 5.34 mmol) in DMSO (20 mL) was added DBU (0.96 mL, 6.4 mmol). After 3 h the mixture was diluted with IPAc (100 mL) and washed with brine (100 mL). The organic layer was concentrated and purified by chromatography (4:1 EtOAc/hexanes) to afford **6i** as a pale yellow solid (1.60 g, 80%): mp 130.0–131.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (s, 1H), 8.05–8.03 (m, 2H), 7.92–7.86 (m, 2H), 7.73 (d, $J=8.8$ Hz, 1H), 7.65–7.61 (m, 1H), 7.42–7.38 (m, 1H), 5.19 (br s, 1H), 4.17 (s, 3H), 3.94 (s, 3H), 3.55–3.45 (m, 2H), 2.90–2.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 159.1, 152.7, 145.6, 135.4, 134.7, 134.3, 133.2, 133.1, 129.3, 128.5, 127.4, 127.1, 126.7, 125.0, 124.2, 70.0, 53.4, 52.6, 39.4; Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.82; H, 4.62; N, 7.30.

4.1.14. Methyl 3-[(*E*)-2-(2-methoxyquinolin-3-yl)vinyl]-4-nitrobenzoate (7i). To a solution of **6i** (1.60 g, 4.18 mmol) in IPAc (60 mL) was added trifluoroacetic anhydride (1.75 mL, 12.6 mmol). After the reaction was aged for 1 h, DBU (1.88 mL, 12.6 mmol) was added. After 14 h, the reaction mixture was washed with brine (20 mL) and concentrated in vacuo. Purification by flash chromatography (1:4 EtOAc/hexanes) afforded **7i** as a white solid (1.32 g, 87%): mp 186–187 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (s, 1H), 8.23 (s, 1H), 8.01 (d, $J=8.4$ Hz, 1H), 8.00 (d, $J=8.4$ Hz, 1H), 7.85 (d, $J=8.1$ Hz, 1H), 7.77 (m, 2H), 7.64 (t, $J=7.6$ Hz, 1H), 7.52 (d, $J=16.8$ Hz, 1H), 7.41 (t, $J=8.4$ Hz, 1H), 4.18 (s, 3H), 4.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 159.7, 150.3, 146.2, 135.4, 133.9, 132.9, 129.9, 129.5, 129.1, 128.8, 127.7, 126.9, 125.1, 124.8, 124.7, 124.4, 121.3, 53.7, 52.8; Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.73; H, 4.35; N, 7.63.

4.1.15. 2-(5-Chloro-2-nitrophenyl)-1-(2-methoxyquinolin-3-yl)ethanol (6j). To a solution of 5-chloro-2-nitrotoluene (1.65 g, 9.62 mmol), 2-methoxy-3-quinoline carboxaldehyde (1.64 g, 8.74 mmol) in DMSO (40 mL) was added DBU (1.57 mL, 10.5 mmol). After 3 h, the mixture was diluted with IPAc (100 mL), washed with brine (100 mL) and concentrated in vacuo. Purification by flash chromatography (4:1 EtOAc/hexanes) afforded **6j** as a white solid (2.65 g, 84%): mp 127.1–128.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (s, 1H), 7.98–7.84 (m, 2H), 7.72 (d, $J=$ 7.6 Hz, 1H), 7.64–7.61 (m, 1H), 7.44–7.34 (m, 3H), 5.18 (br s, 1H), 4.15 (s, 3H), 3.47–3.35 (m, 2H), 3.01–2.97 (m, 1H); ^{13}C NMR (CD_3CN, 100 MHz) δ 159.1, 148.3, 145.6, 138.6, 135.4, 134.8, 132.9, 129.3, 127.5, 127.4, 127.1, 126.7, 125.9, 125.0, 124.2, 69.9, 53.4, 39.6. Anal. Calcd for $C_{18}H_{15}ClN_2O_4$: C, 60.26; H, 4.41; N, 7.81. Found: C, 60.13; H, 4.13; N, 7.73.

4.1.16. 3-[(*E*)-2-(5-Chloro-2-nitropheyl)vinyl]-2-methoxyquinoline (7j). To a solution of **6j** (1.00 g, 2.79 mmol) in IPAc (20 mL) was added trifluoroacetic anhydride (1.24 mL, 14.0 mmol). After 1 h, DBU (3.34 mL,

22.3 mmol) was added. After 14 h, the reaction mixture was washed with brine (20 mL) and concentrated in vacuo. Purification by flash chromatography (1:5 EtOAc/hexanes) afforded **7j** as a pale yellow solid (0.88 g, 93%): mp 189.0–189.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (s, 1H), 7.98 (d, J=9.2 Hz, 1H), 7.90–7.74 (m, 4H), 7.63 (t, J=8.4 Hz, 1H), 7.43 (s, 1H), 7.39 (d, J=7.6 Hz, 2H), 4.17 (s, 3H); ^{13}C NMR (CD_3CN, 100 MHz) δ 159.6, 146.3, 140.5, 139.5, 135.3, 134.9, 129.9, 129.0, 128.1, 128.0, 127.7, 126.9, 126.3, 125.1, 125.1, 124.4, 121.2, 53.7; Anal. Calcd for $C_{18}H_{13}ClN_2O_3$: C, 63.44; H, 3.85; Cl, 10.40; N, 8.22. Found: C, 63.22; H, 3.68; Cl, 10.33; N, 8.10.

4.1.17. Reductive cyclization, method A: 2-phenyl-1*H*-indole (10a).[33] On the bench top, an Endeavor™ glass liner was charged with (*E*)-**7a**,[8c] (169 mg, 0.750 mmol) and the liner was inserted into an Endeavor™ pressure reactor. To the liner was charged $phen_2Pd(OAc)_2$ {3.28×10^{-3} M solution in DMF [prepared by dissolving $Pd(OAc)_2$ (36.9 mg, 0.164 mmol) and 1,10-phenanthroline (62.0 mg, 0.328 mmol) in DMF (50 mL)], 3.43 mL, 0.011 mmol}, and DMF (2.6 mL). The reactor system was sealed and purged three times with N_2 followed by CO. The system was pressurized with CO (15 psig) and heated at 80 °C for 16 h. The mixture was cooled to rt and filtered through solka flok. The filtrate was concentrated in vacuo. Purification by flash chromatography (1:9 to 1:5 EtOAc/hexanes) afforded **10a** as a white solid (128 mg, 87%): mp 193.4–193.9 °C (lit.[31c] mp 191–192 °C).

4.1.18. Reaction of mixture of isomeric olefins, (10a). Using Method A with 1:1 (*E*/*Z*)-**4a**,[21] (169 mg, 0.750 mmol), $phen_2Pd(OAc)_2$ (3.28×10^{-3} M solution in DMF, 3.43 mL, 0.011 mmol) and DMF (2.6 mL) afforded **10a**, after purification by flash chromatography (1:9 to 1:4 EtOAc/hexanes) as a white solid (126 mg, 86%).

4.1.19. Reductive cyclization, method B: methyl 2-phenyl-1*H*-indole-5-carboxylate (10b).[34] In a nitrogen atmosphere glove box, a PPR® glass liner was charged with **7b** (141 mg, 0.500 mmol) and the liner was inserted into the Parallel Pressure Reactor system. To the liner was charged $Pd(TFA)_2$ (6.02×10^{-3} M solution in DMF, 83 μL, 5.0×10^{-4} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (1.20×10^{-2} M solution in DMF, 292 μL, 3.5×10^{-3} mmol) and DMF (2.65 mL). The reactor system was sealed and purged three times with N_2 followed by CO. The system was pressurized with CO (15 psig) and heated at 80 °C for 16 h. The mixture was cooled to rt and filtered through solka flok. The filtrate was concentrated in vacuo. Purification by flash chromatography afforded **10b** as a white solid (123 mg, 98%): mp 191.0–191.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.57 (br s, 1H), 8.41 (s, 1H), 7.92 (dd, J=8.6, 1.5 Hz, 1H), 7.69 (dd, J=8.5, 1.1 Hz, 2H), 7.50–7.35 (m, 4H), 6.91 (d, J=1.6 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 167.2, 139.7, 139.5, 131.6, 129.0, 128.2, 127.9, 125.2, 122.54. 122.51, 120.9, 111.2, 99.9, 51.6; Anal. Calcd for $C_{16}H_{13}NO_4$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.14; N, 5.47.

4.1.20. 5-Chloro-2-phenyl-1*H*-indole (10c).[31c] Using Method A with **7c**, (130 mg, 0.500 mmol), $phen_2Pd(OAc)_2$ (7.3×10^{-3} M solution in DMF, 0.70 mL, 5.1×10^{-3} mmol) and DMF (2.3 mL) afforded **10c**, after purification by flash chromatography (1:1 toluene/hexanes) as a white solid (109 mg, 96%): mp 202.9–203.7 °C (lit.[31c] mp 197–198 °C); ^{1}H NMR (d_6-DMSO, 400 MHz) δ 11.27 (br s, 1H), 7.86–7.84 (m, 2H); 7.56 (d, J=2.0 Hz, 1H), 7.49–7.45 (m, 2H), 7.39 (d, J=8.6 Hz, 1H), 7.35–7.31 (m, 1H), 7.08 (dd, J=8.6, 2.1 Hz, 1H), 6.88 (d, J=1.7 Hz, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 139.3, 135.6, 131.7, 129.8, 129.0, 127.8, 125.2, 123.9, 121.4, 119.1, 112.7, 98.4.

4.1.21. 5-Methyl-2-phenyl-1*H*-indole (10d).[35] Using Method B with **7d**, (110 mg, 0.462 mmol), $phen_2Pd(OAc)_2$ (3.6×10^{-3} M solution in DMF, 1.30 mL, 4.7×10^{-3} mmol) and DMF (2.4 mL) afforded **10d**, after purification by flash chromatography (1:3 to 1:1 toluene/hexanes) as an off-white solid (85 mg, 89%): mp 221.8–223.0 °C (lit.[33b] mp 218–219 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (br s, 1H), 7.68–7.66 (m, 2H), 7.47–7.43 (m, 3H), 7.35–7.29 (m, 2H), 7.03 (dd, J=8.2, 1.2 Hz, 1H), 6.77 (d, J=1.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9, 135.2, 132.5, 129.5, 129.5, 129.0, 127.6, 125.0, 124.0, 120.3, 110.5, 99.6, 21.5.

4.1.22. *N*,*N*-Dimethyl-2-phenyl-1*H*-indole-6-amine (10e). Using Method A with **7e** (56 mg, 0.21 mmol), $Pd(TFA)_2$ (3.0×10^{-3} M solution in DMF, 0.690 mL, 2.07×10^{-3} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (7.1×10^{-3} M solution in DMF, 0.58 mL, 4.1×10^{-3} mmol) and DMF (2.4 mL) afforded **10e**, after purification by flash chromatography (1:4 EtOAc/hexanes) as an off-white solid (30 mg, 61%): mp 190.4–190.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (br s, 1H), 7.63–7.61 (m, 2H), 7.48 (d, J=8.6 Hz, 1H), 7.44–7.40 (m, 2H), 7.29–7.25 (m, 1H), 6.79–6.73 (m, 3H), 2.99 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.4, 138.8, 135.2, 132.7, 128.8, 126.4, 124.2, 120.8, 120.3, 109.1, 98.5, 94.3, 41.2; Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.58; H, 6.85; N, 11.70.

4.1.23. 7-Methoxy-2-phenyl-1*H*-indole (10f). Using Method B with **7f** (100 mg, 0.391 mmol), $Pd(TFA)_2$ (6.0×10^{-3} M solution in DMF, 1.30 mL, 3.91×10^{-3} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (1.2×10^{-2} M solution in DMF, 0.650 mL, 7.8×10^{-2} mmol), and DMF (1.05 mL) afforded **10f**, after purification by flash chromatography as an off-white solid (16 mg, 18%). Spectral data matched that reported in the literature.[36]

4.1.24. Methyl *N*-(5*H*-[1,3]dioxolo[4,5-*f*]indol-6-ylcarbonyl)glycinate (10g). Using Method A with **7g** (231 mg, 0.750 mmol), $Pd(TFA)_2$ (3.56×10^{-3} M solution in DMF, 2.1 mL, 7.5×10^{-3} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (7.1×10^{-3} M solution in DMF, 2.1 mL, 1.5×10^{-2} mmol) and DMF (1.8 mL) afforded **10g**, after purification by flash chromatography (1:4 EtOAc/hexanes) as an off-white solid (149 mg, 72%): mp 259.2–261.4 °C; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 11.39 (s, 1H), 8.73 (t, J=5.9 Hz, 1H), 7.06–7.01 (m, 2H), 6.86 (s, 1H), 5.95 (s, 2H), 4.00 (d, J=10.7 Hz, 2H), 3.65 (s, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 170.9, 161.7, 146.4, 143.4, 132.4, 130.0, 121.3, 104.0, 100.8, 99.6, 92.5, 52.1, 41.1; Anal.

Calcd for $C_{13}H_{12}N_2O_5 \cdot \frac{1}{3}H_2O$: C, 55.32; H, 4.52; N, 9.93. Found: C, 55.69; H, 4.38; N, 9.67.

4.1.25. 5-Methoxy-2-(2-methoxypyridin-3-yl)-1*H*-indole (10h). Using Method A with **7h**[37] (215 mg, 0.750 mmol), $phen_2Pd(OAc)_2$ (3.28×10^{-3} M solution in DMF, 3.43 mL, 0.015 mmol) and 2.6 mL DMF at 30 psig CO and 70 °C afforded **10h**, after purification by flash chromatography (1:4 to 1:2 EtOAc/hexanes) as an off-white solid (138 mg, 72%): mp 120.7–121.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.59 (br s, 1H), 8.12 (dd, J=5.8, 1.8 Hz, 1H), 8.09 (dd, J=7.6, 1.9 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H), 7.09 (d, J=2.4 Hz, 1H), 7.02 (dd, J=7.6, 4.8 Hz, 1H), 6.90–6.87 (m, 2H), 4.18 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 154.3, 145.1, 135.6, 134.0, 131.4, 128.4, 117.6, 115.3, 112.9, 111.8, 101.5, 100.0, 55.7, 53.8; Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.68; H, 5.53; N, 10.90.

4.1.26. Methyl 2-(2-methoxyquinolin-3-yl)-1*H*-indole-5-carboxylate (10i). Using Method B with **7i** (182 mg, 0.50 mmol), $Pd(TFA)_2$ (6.02×10^{-3} M solution in DMF, 83 μL, 5.00×10^{-4} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (1.20×10^{-2} M solution in DMF, 292 μL, 3.5×10^{-3} mmol) and DMF (2.65 mL) afforded **10i**, after purification by flash chromatography (1:2 EtOAc/hexanes) as an off-white solid (130 mg, 78%): mp 206.2–206.8 °C; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 11.89 (br s, 1H), 8.73 (s, 1H), 8.31 (s, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.84–7.78 (m, 2H), 7.72–7.68 (m, 1H), 7.56 (d, J=8.6 Hz, 1H), 7.52–7.48 (m, 1H), 7.32 (d, J=1.8 Hz, 1H), 4.18 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 167.1, 158.3, 144.7, 139.4, 135.4, 134.2, 129.9, 127.8, 127.7, 126.4, 124.85, 124.83, 123.0, 122.9, 120.9, 116.5, 111.3, 104.7, 53.8, 51.7; Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.28; H, 4.80; N, 8.36.

4.1.27. 3-(5-Chloro-1*H*-indol-2-yl)-2-methoxyquinoline (10j). Using Method A with **7j** (71 mg, 0.21 mmol), $phen_2Pd(OAc)_2$ (3.56×10^{-3} M solution in DMF, 0.58 mL, 2.1×10^{-3} mmol) and 2.4 mL DMF afforded **10j**, after purification by flash chromatography (1:8 EtOAc/hexanes) as an off-white solid (58 mg, 91%): mp 172–174 °C; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 9.71 (br s, 1H), 8.46 (s, 1H), 7.87 (d, J=7.8 Hz, 1H), 7.79 (d, J=7.9 Hz, 1H), 7.67–7.63 (m, 2H), 7.46–7.42 (m, 1H), 7.38 (d, J=8.5 Hz, 1H), 7.17 (d, J=8.2 Hz, 1H), 7.01 (s, 1H), 4.30 (s, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 158.0, 145.3, 135.4, 134.9, 134.6, 129.7, 129.1, 127.4, 126.9, 125.7, 125.3, 124.8, 122.7, 119.6, 116.0, 112.1, 100.5, 54.0. Anal. Calcd for $C_{18}H_{13}ClN_2O \cdot 0.25H_2O$: C, 69.01; H, 4.34; N, 8.94. Found: C, 69.85; H, 4.27; N, 9.11.

4.1.28. 2-Methyl-6-(trifluoromethoxy)-1*H*-indole (5k).[6a] Using Method A with **4k**[6a] (124 mg, 0.500 mmol), $tm\text{-}phen_2Pd(TFA)_2$ (6.0×10^{-3} M solution in DMF, 0.833 mL, 5.0×10^{-3} mmol), and DMF (2.2 mL) afforded **5k** in 84% assay yield.

4.1.29. 1*H*-Indol-2-yl(phenyl)methanone (10l).[8c,38] Using Method A with **7l**, (253 mg, 1.0 mmol), $phen_2Pd(OAc)_2$ (7.3×10^{-3} M solution in DMF, 1.37 mL, 0.01 mmol) and DMF (3.6 mL) afforded **10l**, after purification by flash chromatography (1:6 EtOAc/hexanes) as a white solid (187 mg, 84%): mp 151.0–151.6 °C (lit.[8c] mp 151–152 °C).

4.1.30. 2-(2-Methoxyquinolin-3-yl)-5-{[4-(methylsulfonyl)piperazine-1-yl]methyl}-1*H*-indol-1-ol (14).[6a] Using Method B with **3** (100 mg, 0.207 mmol), $phen_2Pd(OAc)_2$ (1.55×10^{-3} M solution in toluene, 1.33 mL, 2.07×10^{-3} mmol) and toluene (1.7 mL) afforded **14**, after purification by flash chromatography (1:1 toluene/hexanes) as an off-white solid (20 mg, 20%). Spectral data matched that reported in the literature.[6a]

4.1.31. 4,5-Dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (22).[17] Using Method B with nitrobenzene (43 μL, 0.41 mmol), $phen_2Pd(OAc)_2$ (3.56×10^{-3} M solution in DMF, 1.16 mL, 4.13×10^{-3} mmol), 2,3-dimethylbutadiene (0.5 mL, 4.4 mmol) and DMF (4.3 mL) at 15 psig CO and 70 °C afforded **22** in 29% assay yield.

4.2. Electrochemical measurements

All electrochemical measurements were performed with a Bioanalytical Systems (BAS) Model C-3 electrochemical analyzer and were conducted at room temperature. Experiments were carried out with tetra-*n*-butylammonium hexafluorophosphate (0.45 M solution in DMF) electrolyte which was degassed with nitrogen while in the electrochemical cell. A polished working Pt electrode, a Pt auxiliary electrode, and a Ag/AgCl pseudoreference electrode were used. Potentials were referenced to Fc^+/Fc couple versus Ag/AgCl pseudoreference electrode, which was observed at 0.41 V. Reversible reduction was observed for **7a–f** at a scan rate of 100 mV/s.

4.3. Competition experiments, sample experimental

A PPR® glass liner was charged with **7a** (37.0 mg, 0.164 mmol) and **7e** (44.0 mg, 0.164 mmol). The liner was taken into a nitrogen atmosphere glove box and inserted into the Parallel Pressure Reactor system. To the liner was charged $Pd(TFA)_2$ (6.02×10^{-3} M solution in DMF, 27 μL, 1.6×10^{-4} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (1.20×10^{-2} M solution in DMF, 96 μL, 1.1×10^{-3} mmol) and DMF (2.9 mL). The reactor system was sealed and purged three times with N_2 followed by CO. The system was pressurized with CO (15 psig) and heated at 80 °C for 1 h. The mixture was cooled to rt and diluted with acetonitrile. HPLC analysis of the amounts of **7a** and **7e** remaining in the reaction were as follows: **7a** (7.9 mg, 0.035 mmol), **7e** (19.9 mg, 0.074 mmol).

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References and notes

1. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Verber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. H.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235–2246.
2. (a) Sundberg, R. J. The chemistry of indoles; Academic Press: New York, 1970. (b) Sundberg, R. J. In *Pyrroles and Their Benzoderivatives: Synthesis and Applications*; Katritzky, A. R., Rees, C. W., Eds.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1984; Vol. 4, Category 2, Chapter 10.13, pp 313–376. (c) Sundberg, R. J. Best Synthetic Methods, Indoles; Academic Press: San Diego, 1996. (d) Joule, J. A. In *Indole and its Derivatives*; Thomas, E. J., Ed.; Science of Synthesis: Houben-Weyl Methods of Molecular Transformations; George Thieme: Stuttgart, 2000; Vol. 10. (e) Brown, R. K. In *Indoles*; Houlihan, W. J., Ed.; Wiley: New York, 1972.
3. For reviews on indole ring syntheses, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075 and Ref. 2c.
4. (a) Fraley, M. E.; Hoffman, W. F.; Arrington, K. L.; Hungate, R. W.; Hartman, G. D.; McFall, R. C.; Coll, K. E.; Rickert, K.; Thomas, K. A.; McGaughey, G. B. *Curr. Med. Chem.* **2004**, *11*, 709–719. (b) Fraley, M. E.; Arrington, K. L.; Buser, C. A.; Ciecko, P. A.; Coll, K. E.; Fernandes, C.; Hartman, G. D.; Hoffman, W. F.; Lynch, J. J.; McFall, R. C.; Rickert, K.; Singh, R.; Smith, S.; Thomas, K. A.; Wong, B. K. *Biorg. Med. Chem. Lett.* **2004**, *14*, 351–355. (c) Fraley, M. E.; Arrington, K. L.; Bilodeau, M. T.; Hartman, G. A.; Hoffman, W. F.; Kim, Y.; Hungate, R. W. U.S. Patent 6,306,874,B1, **2001**.
5. (a) Bilodeau, M. T.; Fraley, M. E.; Hartman, G. D. *Expert Opin. Investig. Drugs* **2002**, *11*, 737–745. (b) Veikkola, T.; Karkkainen, M.; Claesson-Welsh, L.; Alitalo, K. *Cancer Res.* **2000**, *60*, 203–212. (c) Thomas, K. A. *J. Bio. Chem.* **1996**, *271*, 603–606.
6. (a) Wong, A.; Kuethe, J. T.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 7761–7764. (b) Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J. H.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2005**, *70*, 2555. (c) Payack, J.; Vazquez, E.; Matty, L.; Kress, M. H.; Huffman, M.; Guo, J.; McNamara, J. *J. Org. Chem.* **2005**, *70*, 175.
7. Ortho-nitrostyrene **3** was synthesized in five steps from readily available starting materials. See Ref. 6b for details.
8. (a) Cadogan, J. I. G. *Synthesis* **1969**, *1*, 11–17. (b) Cadogan, J. I. G. *Organo-phosphorus Reagents Org. Synth.* **1979**, 269–294. (c) Cadogan, J. I. G. *Lectures in Heterocyclic Chemistry* **1978**, *4*, 17–23. (d) Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604–3610.
9. For applications in the syntheses of carbazole alkaloids, see: (a) Lowinger, T. B.; Chu, J.; Spence, P. L. *Tetrahedron Lett.* **1995**, *36*, 8383–8386. (b) Moody, C. J. *Synlett* **1994**, 681–688. (c) Hughes, I.; Nolan, W. P.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2475–2477.
10. (a) Waterman, H. C.; Vivian, D. L. U.S. 2,292,808, **1942**.(b) Waterman, H. C.; Vivian, D. L. *J. Org. Chem.* **1949**, *14*, 289–297.
11. For ruthenium-catalyzed reductive cyclization to indoles and carbazoles, see: (a) Pizzotti, M.; Cenini, S.; Quici, S.; Tollari, S. *J. Chem. Soc., Perkin Trans. 2* **1994**, 913–917. (b) Crotti, C.; Cenini, S.; Bassoli, A.; Rindone, B.; Demartin, F. *J. Mol. Catal.* **1991**, *70*, 175–187. (c) Crotti, C.; Cenini, S.; Todeschini, R.; Tollari, S. *J. Chem. Soc. Faraday Trans.* **1991**, *87*, 2811–2820.
12. Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375–3380.
13. (a) Scott, T. L.; Söderberg, B. C. G. *Tetrahedron Lett.* **2002**, *43*, 1621–1624. (b) Söderberg, B. C.; Rector, S. R.; O'Neil, S. N. *Tetrahedron Lett.* **1999**, *40*, 3657–3660. (c) Söderberg, B. C.; Chisnell, A. C.; O'Neil, S. N.; Shriver, J. A. *J. Org. Chem.* **1999**, *64*, 9731–9734. (d) Söderberg, B. C.; Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838–5845.
14. (a) Tollari, S.; Penoni, A.; Cenini, S. *J. Mol. Catal. A* **2000**, *152*, 47–54. (b) Ragaini, F.; Sportiello, P.; Cenini, S. *J. Organomet. Chem.* **1999**, *577*, 283–291. (c) Tollari, S.; Cenini, S.; Crotti, C.; Gianella, E. *J. Mol. Catal.* **1994**, *87*, 203–214.
15. (a) Paul, F.; Fischer, J.; Ochsenbein, P.; Osborn, J. A. *C. R. Chimie* **2002**, *5*, 267–287. (b) Paul, F.; Fischer, J.; Ochsenbein, P.; Osborn, J. A. *Organometallics* **1998**, *17*, 2199–2206. (c) Santi, R.; Romano, A. M.; Panella, F.; Santini, C. *J. Mol. Catal. A* **1997**, *127*, 95–99. (d) Wehman, P.; Kaasjager, V. E.; de Lange, W. G. J.; Hartl, F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3751–3761. (e) Wehman, P.; Dol, G. C.; Moorman, E. R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1994**, *13*, 4856–4869.
16. We recently reported the palladium-catalyzed cyclization of *ortho*-nitrobiphenyl substrates to afford carbazoles using palladium (II) acetate and 1,10-phenanthroline in DMF at 140 °C and 70 psig CO: Smitrovich, J. H.; Davies, I. W. *Org. Lett.* **2004**, *6*, 533–535.
17. In the synthesis of oxazines from nitroarenes using a similar catalyst system, a 16:1 ligand/palladium ratio is optimal: Ragaini, F.; Cenini, S.; Brignoli, D.; Gasperini, M.; Gallo, E. *J. Org. Chem.* **2003**, *68*, 460–466.
18. For a review of counterion effects in transition metal catalysis, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26–47.
19. Milani, B.; Anzilutti, A.; Vicentini, L.; Santi, A. S. O.; Zangrando, E.; Geremia, S.; Mestroni, G. *Organometallics* **1997**, *16*, 5064–5075.
20. Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P. E. *J. Org. Chem.* **1986**, *51*, 3694–3696.
21. Génisson, V. B.; Bouniol, A.-V.; Nepveu, F. *Synlett* **2001**, 700–702.
22. Söderberg, B. C. G. *Curr. Org. Chem.* **2000**, *4*, 727–764.
23. Tsao, M.-L.; Gritsan, N.; James, T. R.; Platz, M. S.; Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2003**, *125*, 9343–9358.
24. Osborn et al. have proposed the formation of an analogous palladacycle as the first step in the catalytic cycle for the palladium-catalyzed reduction of nitroaromatics to isocyanates. See Refs. 15a and b.
25. Nitrosoarene-metal complexes have been identified as intermediates in the ruthenium-catalyzed reductive deoxygenation of nitroarenes: Skoog, S. J.; Gladfelter, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 11049–11060.
26. *ortho*-Nitroarylethanes have also been shown to react under basic conditions to give *N*-hydroxyindoles at 20 °C. The reaction was rationalized to proceed through an *ortho*-nitrosostyrene species that undergoes a 6π-electron 5-atom electrocyclic reaction: Wróbel, Z.; Mękosza, M. *Tetrahedron* **1997**, *53*, 5501–5514.
27. Davies, I. W.; Guner, V. A.; Houk, K. N. *Org. Lett.* **2004**, *6*, 743–746.

28. While palladium may be involved in the cyclization of **17**, calculations reveal that the presence of palladium is not required: Ref. 27.
29. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; p 144.
30. Ragaini et al. reported reduced yields and conversions for the palladium-catalyzed formation of oxazines from electron rich nitroarenes and 2,3-dimethylbutadiene in the presence of CO: Ref. 17.
31. Donor substituents accelerate the rate of the Cope rearrangement: Dollinger, M.; Henning, W.; Kirmse, W. *Chem. Ber.* **1982**, *115*, 2309.
32. Lawrence, N. J.; Liddle, J.; Jackson, D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2260–2267.
33. (a) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, 89–92 and references cited therein. (b) Kato, N.; Miyaura, N. *Tetrahedron* **1996**, *52*, 13347–13354. (c) Hudkins, R. L.; Diebold, J. L.; Marsh, F. D. *J. Org. Chem.* **1995**, *60*, 6218–6220.
34. Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307–2310.
35. (a) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136. (b) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957–2969.
36. Macleod, C.; Hartley, R. C.; Hamprecht, D. W. *Org. Lett.* **2002**, *4*, 75–78.
37. Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3975–3978.
38. Gharpure, M.; Stoller, A.; Bellamy, F.; Firnau, G.; Snieckus, V. *Synthesis* **1991**, 1079–1082.

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Palladium-catalyzed carbene insertion into benzyl bromides

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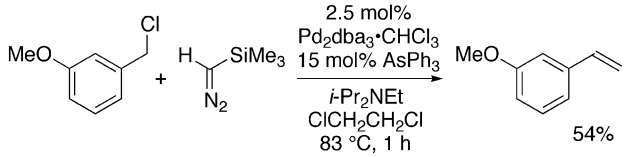
Abstract—Palladium can catalyze the insertion of ethyl diazoacetate into benzyl bromides. The key step in the catalytic cycle is the migratory insertion of a carbene, derived from ethyl diazoacetate, into a Pd–C bond.

1. Introduction

Palladium-catalyzed CO insertion offers a precise and powerful method for introduction of one carbon units. In contrast, the analogous palladium-catalyzed insertion of carbenes has received little attention. In published crystal structures of alkylpalladium–carbene complexes, the Pd-alkyl bond is generally aligned with the empty p-orbital of the carbene ligand,[1] suggesting that migratory insertion of the carbene ligand could be facile when the carbene is not stabilized by donor groups. The first reported examples of palladium-catalyzed carbene insertion using trimethylsilyldiazomethane[2] (TMSD) suffered from low turnover and palladium-catalyzed protodesilylation[3] (Scheme 1). Since that time, Ihara and co-workers showed that Pd(II) can catalyze the polymerization of ethyl diazoacetate in the presence of amines.[4] In addition, several elegant examples of non-catalytic carbene insertion have been documented for palladium carbene complexes. Albéniz and co-workers showed that a Fischer carbene ligand could insert into a Pd–C_6F_5 bond, although the reaction was not catalytic.[5] Two more recent examples of stoichiometric insertion of Fischer carbenes into Pd–C bonds have been reported.[6,7] Solé and co-workers showed that dichlorocarbene, ethyl diazoacetate, and TMSD can insert into the Pd–C bond of a 4-membered palladacycle, again a non-catalytic reaction.[8] In a recent advance, Montgomery and Ni demonstrated that TMSD can participate in a nickel-catalyzed [4+2+1] reaction.[9]

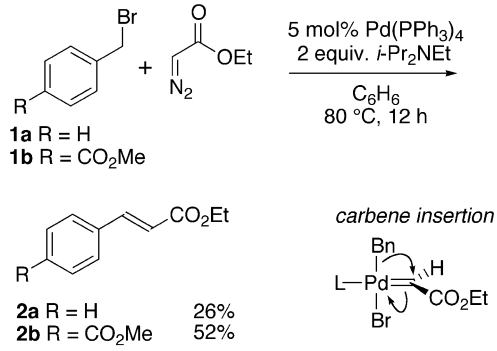


Scheme 1. Precedented insertion of TMSD.

This communication describes the first example of palladium-catalyzed carbene insertion leading to homologation without loss of the carbene functional group. The deceptively simple one-step transformation of benzyl bromides to cinnamates has previously been achieved using a tandem alkylation/sulfenate elimination reaction under phase transfer conditions.[10] This work reveals the broader potential for migratory insertion of carbenes in metal-catalyzed synthetic transformations.

2. Results and discussion

In theory, α-diazoesters could react with benzyl halides without the aid of a catalyst. However, when 1.5 equiv ethyl diazoacetate was added slowly to benzyl bromide at 83 °C over 12 h with Hünig's base in the absence of a palladium catalyst, no reaction was observed. In contrast, when



Scheme 2. Initial homologation experiments.

Keywords: Palladium; Carbene; Stoichiometric insertion.
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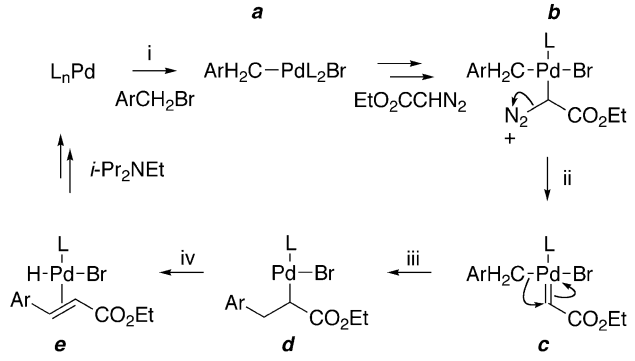
5 mol% $(Ph_3P)_4Pd$ was included the corresponding α,β-unsaturated ester was isolated in 26% yield (Scheme 2). At the end of the reaction, the ethyl diazoacetate was depleted, but unreacted benzyl bromide was still present. Using excess ethyl diazoacetate did not improve the yield, implying that the yield was limited by catalyst turnover.

When the reaction was carried out on bromide **1b** a more gratifying 52% yield of the homologation product was obtained. A series of experiments was carried out with $Pd_2dba_3 \cdot CHCl_3$ in order to identify the best ligand and the best ratio of ligand to palladium (Table 1). With triphenylphosphine, the best results were obtained with a 2:1 ratio of phosphine to palladium. A hindered, strongly donating ligand did not improve the results with a ligand to palladium ratio of 1:1. Since phosphines are known to react with ethyl diazoacetate[11] and benzyl bromide,[12] triphenylarsine was tested as a ligand. At a ligand to palladium ratio of 4:1 triphenylarsine gave much better results than triphenylphosphine. A control reaction with triphenylarsine alone generated no homologation product. Using 2.5 mol% $Pd_2dba_3 \cdot CHCl_3$ and 20 mol% Ph_3As, benzene proved to be the best solvent for the reaction. Other typical solvents such as MeCN, DME, THF, and 1,2-dichloroethane gave yields between 50 and 60%.

Table 1. Ligand effect on insertion of ethyl diazoacetate into bromide **1b** using 2.5 mol% $Pd_2dba_3 \cdot CHCl_3$

Ligand	Yield
20 mol% Ph_3P	28%
10 mol% Ph_3P	55%
5 mol% Ph_3P	32%
5 mol% Cy_2P(*o*-biphenyl)	25%
20 mol% Ph_3As	74%
10 mol% Ph_3As	28%
5 mol% Ph_3As	27%

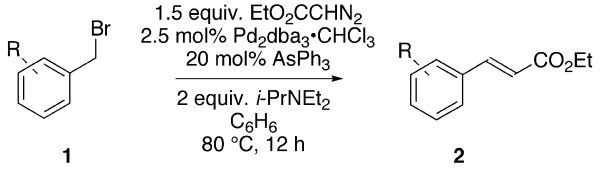
Since the migratory insertion of carbene ligands into palladium–carbon bonds is now well precedented, it is reasonable to propose a mechanism involving the steps shown in Scheme 3: (i) oxidative addition to benzyl bromide,[13] (ii) carbene formation,[14] (iii) migratory carbene insertion,[8] and (iv) beta-hydride elimination. There is literature precedent for each of these processes at or below room temperature; however, no product was formed unless the reaction was heated. The slow steps may involve isomerization between *trans*-L_2BnPdX to *cis*-L_2BnPdX.



Scheme 3. Proposed catalytic cycle.

A series of substituted benzylic bromide starting materials was examined in order to better understand the scope and limitations of the reaction (Table 2). When the reaction was applied to 3-methoxybenzyl bromide **1c** the starting materials remained virtually un-reacted, suggesting that there was no catalyst turnover. In general, electron-rich benzyl bromides gave low yields and low conversion. For substrates **1a**, **1d**, **1e**, and **1f** the mass balance was poor, even when starting material was observed in the final reaction mixture (Table 2). The best yields were obtained when the benzyl bromide was substituted by carboethoxy groups (substrates **1b** and **1h**). No starting material remained at the end of these reactions.

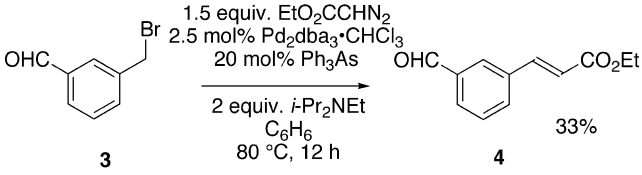
Table 2. Arene substituent effects



	R	Yield	S.M.?
1a	H	25%	Yes
1b	4-MeO_2C	74%	No
1c	3-MeO	0%	Yes
1d	2,4,6-Me_3	27%	Yes
1e	3,5-F_2	51%	Yes
1f	3-Cl	50%	Yes
1 g	3-O_2N	52%	No
1 h	3-MeO_2C	68%	No

When ethyl cinnamate **2a** was added to the reaction of substrate **1b**, 93% of the ethyl cinnamate was recovered at the end of the reaction. Thus, product decomposition does not account for low yields. Since the starting material **1b** and ethyl diazoacetate were shown to be stable to the reaction conditions in the absence of catalyst, the mass deficit is probably due to a competitive catalytic process. The only additional products visible by TLC appeared at the baseline. When eluted from silica gel, these low-mobility by-products gave a ^1H NMR spectrum that did not integrate to enough protons in the aromatic region to account for the fate of the benzyl bromide that was not converted to ethyl cinnamate.

As a test of functional group compatibility, the homologation reaction was carried out on 3-formylbenzyl bromide **3**. Even though the yield for this homologation reaction was lower than that for the analogous ester substrate **1h**, the selectivity was extraordinary for a one step transformation (Scheme 4).



Scheme 4. Selectivity of Pd-catalyzed insertion in the presence of an aldehyde.

3. Conclusion

In summary, we have shown that palladium can catalyze the homologation of alkyl halides to α,β-unsaturated carbonyls. This report describes the first practical application of palladium-catalyzed reaction involving insertion of a carbene ligand into a Pd–C bond. The reaction works best with electron deficient benzyl halide substrates, apparently because they resist decomposition under the reaction conditions. Ultimately, related migratory palladium-catalyzed insertion of carbene ligands could be used to install chiral centers in a manner analogous to CO insertion.

4. Experimental

4.1. General procedure

A flame dried round bottom flask, equipped with a reflux condenser and a magnetic stir bar, was charged with $Pd_2(dba)_3 \cdot CHCl_3$ (13 mg, 0.013 mmol) and triphenylarsine (32 mg, 0.104 mmol). The flask was evacuated and backfilled with an atmosphere of argon three times. Anhydrous benzene (5.0 mL) was added, and the solution was heated to reflux. After 5 min, the resulting clear yellow solution was cooled to room temperature. *N*,*N*-diisopropylethylamine (175 μL, 1.00 mmol) and a solution of the appropriate benzylic bromide (0.5 mmol) in anhydrous benzene (5.0 mL) were added. The solution was returned to reflux. Ethyl diazoacetate (0.11 mL, 0.76 mmol) in anhydrous benzene (1.0 mL) was added via syringe pump over 12 h, after which time the mixture was cooled to room temperature. EtOAc (50 mL) was added, and the organic phase was washed with water (3×10 mL) and dried (Na_2SO_4). Concentration in vacuo afforded a brown residue, which was purified by flash chromatography

4.1.1. (*E*)-Ethyl cinnamate (2a). Following the general procedure, purification by flash chromatography (95:5 hexanes/EtOAc) afforded the previously described[15] **2a** in 25% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J=16.0 Hz, 1H), 7.51–7.53 (m, 2H), 7.37–7.39 (m, 3H), 6.44 (d, J=16.0 Hz, 1H), 4.25 (q, J=7.1 Hz, 2H), 1.34 (t, J=7.1 Hz, 3H).

4.1.2. Methyl 4-((*E*)-2-(ethoxycarbonyl)vinyl)benzoate (2b). Following the general procedure, purification by flash chromatography (93:7 hexanes/EtOAc) afforded the previously described[16] **2b** in 74% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J=8.3 Hz, 2H), 7.70 (d, J=16.0 Hz, 1H), 7.59 (d, J=8.3 Hz, 2H), 6.52 (d, J=16.0 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 3.93 (s, 3H), 1.35 (t, J=7.1 Hz, 3H).

4.1.3. (*E*)-Ethyl 3-mesitylacrylate (2d). Following the general procedure, purification by flash chromatography (95:5 hexanes/EtOAc) afforded the previously described[17] **2d** in 27% yield: ^{1}H NMR δ 7.84 (d, J=16.4 Hz, 1H), 6.89 (s, 2H), 6.05 (d, J=16.4 Hz, 1H), 4.27 (q, J=7.1 Hz, 2H), 2.32 (s, 6H), 2,28 (s, 3H), 1.34 (t, J=7.1 Hz, 3H).

4.1.4. (*E*)-Ethyl 3-(3,5-difluorophenyl)acrylate (2e). Following the general procedure, purification by flash chromatography (95:5 hexanes/EtOAc) afforded the previously described[18] **2e** in 51% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J=16.1 Hz, 1H), 7.01-7.05 (m, 2H), 6.83 (tt, J=8.7, 2.3 Hz, 1H), 6.42 (d, J=16.1 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 1.34 (t, J=7.1 Hz, 3H).

4.1.5. (*E*)-Ethyl 3-(3-chlorophenyl)acrylate (2f). Following the general procedure, purification by flash chromatography (95:5 hexanes/EtOAc) afforded the previously described[19] **2f** in 50% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J=16.0 Hz, 1H), 7.51 (t, J=1.6 Hz, 1H), 7.30-7.40 (m, 3H), 6.44 (d, J=16.0 Hz, 1H), 4.27 (q, J=7.1 Hz, 2H), 1.34 (t, J=7.1 Hz, 3H).

4.1.6. (*E*)-Ethyl 3-(3-nitrophenyl)acrylate (2g). Following the general procedure, purification by flash chromatography (90:10 hexanes/EtOAc) afforded the previously described[20] **2g** in 52% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (t, J=1.8 Hz, 1H), 8.24 (dd, J=8.1, 2.1 Hz, 1H), 7.81-7.85 (m, 1H), 7.72 (d, J=16.0 Hz, 1H), 7.59 (t, J=8.1 Hz, 1H), 6.57 (d, J=16.0 Hz, 1H), 4.30 (q, J=7.1 Hz, 2H), 1.36 (t, J=7.1 Hz, 3H).

4.1.7. Methyl 3-((*E*)-2-(ethoxycarbonyl)vinyl)benzoate (2h). Following the general procedure, purification by flash chromatography (93:7 hexanes/EtOAc) afforded the previously described[21] **2h** in 68% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (t, J=1.5 Hz, 1H), 8.05 (dt, J=7.8, 1.5 Hz, 1H), 7.69-7.71 (m, 1H and d, J=16.0 Hz, 1H), 7.47 (t, J=7.8 Hz, 1H), 6.52 (d, J=16.0 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 3.94 (s, 3H), 1.35 (t, J=7.1 Hz, 3H).

4.1.8. (*E*)-Ethyl-3-(3-formylphenyl)acrylate (4). Following the general procedure, purification by flash chromatography (93:7 hexanes/EtOAc) afforded **4** in 33% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.03 (t, J=1.7 Hz, 1H), 7.90 (dt, J=7.5, 1.4 Hz, 1H), 7.77-7.79 (m, 1H), 7.74 (d, J=16.0 Hz, 1H), 6.54 (d, J=16.0 Hz, 1H), 4.29 (q, J=7.1 Hz, 2H), 1.35 (t, J=7.1 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 191.7, 166.6, 142.9, 137.0, 135.6, 133.6, 131.1, 129.8, 128.9, 120.3, 60.8, 14.4; FT-IR (thin-film) 2980, 2925, 2846, 1705, 1640 cm^{-1}; GC-MS (EI) *m*/*z* 204(17), 175(20), 159(41), 131(52), 103(86), 77(100).

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References and notes

1. Tulloch, A. A. D.; Danopoulos, A. A.; Tooze, R. P.; Cafferkey, S. M.; Kleinheinz, S.; Hursthouse, M. B. *Chem. Commun.* **2000**, 1247–1248.
2. Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219–5225.
3. Hallberg, A.; Westerlund, C. *Chem. Lett.* **1982**, 1993–1994.
4. Ihara, E.; Haida, N.; Iio, M.; Inoue, K. *Macromolecules* **2003**, *36*, 36–41.

5. (a) Albéniz, A. C.; Espinet, P.; Manrique, R.; Pérez-Mateo, A. *Angew. Chem.* **2002**, *114*, 2469–2472. (b) *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2363–2366.
6. Marshall, W. J.; Grushin, V. V. *Organometallics* **2003**, *22*, 1591–1593.
7. Danopoulos, A. A.; Tsoureas, N.; Green, J. C.; Hursthouse, M. B. *Chem. Commun.* **2003**, 756–757.
8. Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *Organometallics* **2004**, *23*, 1438–1447.
9. Ni, Y.; Montgomery *J. Am. Chem. Soc.* **2004**, *126*, 11162–11163.
10. Xu, C. Y.; Liu, G. J.; Zhang, Z. *Synth. Commun.* **1987**, *17*, 1839–1843.
11. Wittig, G.; Schlosser, M. *Tetrahedron* **1962**, *18*, 1023–1028.
12. Cevasco, G.; Thea, S. J. *Org. Chem.* **1999**, *64*, 5422–5426.
13. Lau, K. S. Y.; Wong, P. K.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5832–5840.
14. Bröring, M.; Brandt, C. D.; Stellwag, S. *Chem. Commun.* **2003**, 2344–2345.
15. Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; de Vicente *J. Am. Chem. Soc.* **2003**, *125*, 6034–6035.
16. Chen, Y.; Huang, L.; Ranade, M. A.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 3714–3717.
17. Medina, E.; Moyano, A.; Pericas, M. A.; Riera, A. *Helv. Chim. Acta* **2000**, *83*, 972–988.
18. Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587–3606.
19. Huang, Z.-Z.; Tang, Y. J. *Org. Chem.* **2002**, *67*, 5320–5326.
20. Qian, C.; Wang, L. *Tetrahedron* **2000**, *56*, 7193–7198.
21. Reich, S. H.; Johnson, T.; Wallace, M. B.; Kephart, S. E.; Fuhrman, S. A.; Worland, S. T.; Matthews, D. A.; Hendrickson, T. F.; Chan, F.; Meador, J.; Ferre, R. A.; Brown, E. L.; DeLisle, D. M.; Patrick, A. K.; Binford, S. L.; Ford, C. E. *J. Med. Chem.* **2000**, *43*, 1670–1683.

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Dramatic catalyst evolution in the asymmetric addition of diethylzinc to benzaldehyde

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Abstract—We have observed product ee's that begin at 20% at low reaction conversion and rise to 79% ee at the completion of the reaction in the asymmetric addition of alkyl groups to benzaldehyde. This rare behavior is attributed to autoinduction, in which the catalyst evolves by incorporation of the product. Based on this, we have been able to optimize the catalyst by variation of achiral, rather than enantiopure ligands.

1. Introduction

Asymmetric catalysts can evolve over the course of reactions to generate new catalysts that exhibit different properties. This behavior can manifest itself in enantioselectivities that change as reactions progress. One cause of catalyst evolution is the incorporation of the product of the asymmetric reaction into the catalyst. This process is known as autoinduction and was first described by Alberts and Wynberg.[1,2] Since then, other researchers have reported this behavior.[3–16]

The observation of autoinduction can provide insight into the mechanisms of asymmetric reactions and, in some cases, expedite the catalyst optimization process. Herein, we report dramatic increases in the product ee's as a function of reaction conversion in the asymmetric addition of ethyl groups to aldehydes. The increase in ee's is attributed to an autoinduction process in which catalyst evolution provides a system that exhibits greatly improved enantioselectivity. Based on a study of this process, we were able to develop a catalyst that exhibited excellent enantioselectivity. The catalyst optimization was performed by variation of achiral ligands[17–21] rather than enantiopure ligands.

Keywords: Diethylzinc; Titanium tetraisopropoxide; Autoinduction; Bis(sulfonamides).
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2. Results and discussion

Several titanium catalysts have been found to be highly enantioselective in the addition of Et_2Zn to aldehydes. Catalysts derived from TADDOL[22] (**1**), BINOL[23–25] (**2**), and bis(sulfonamide) ligands[26–33] (**3a**, **3b**, **4**) are widely employed in this reaction (Fig. 1). Studies have demonstrated that most of these catalytic systems generate product of constant ee over the course of the reaction. We recently reported, however, that certain bis(sulfonamide)-based catalysts derived from ligands **3c**–**3d** do show changes in

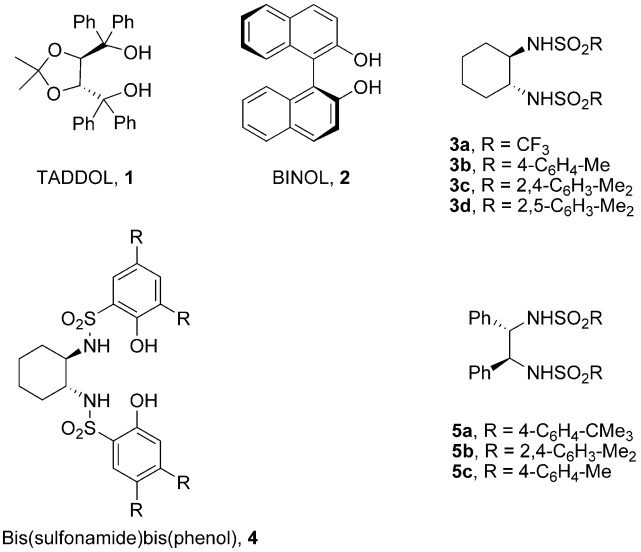
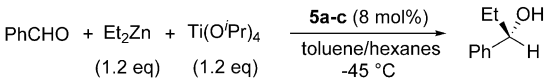


Figure 1. Ligands employed in the asymmetric addition of alkyl groups to aldehydes.



Scheme 1. Diethylzinc addition to benzaldehyde in the presence of bis(sulfonamide) ligands derived from stilbene diamine.

enantioselectivity of 8% over the course of the reaction (Scheme 1). We postulated that this behavior was due to autoinduction, which was supported by mechanistic studies and the observation of nonlinear behavior.[34]

During our studies of the mechanism of the asymmetric addition of alkyl groups to aldehydes promoted by bis(sulfonamide)-based catalysts (Scheme 1) we found that catalysts prepared from stilbene diamine (**5a–c**, Fig. 1) exhibited large changes in product ee with conversion. Employing 8 mol% of **5a** in Scheme 1 and following the reaction by removal of aliquots and analysis we observed that the ee was 20% at around 10% conversion. As the reaction proceeded, however, the ee rose rapidly to a maximum 79% at 100% conversion. These results are illustrated in Figure 2, curve A. In this reaction, the enantioselectivities of the catalysts generated at higher conversion must be greater than the final ee of 79%. The use of catalyst **5c** led to a similar, but smaller, increase in the ee of the product over time. Interestingly, catalyst **5b** initially gave the (*R*)-enantiomer of the product with an enantioselectivity of 18%. As the reaction progressed, however, the sense of the enantioselectivity switched and the (*S*)-enantiomer predominated with an ee of 27% (Fig. 2, curve B).

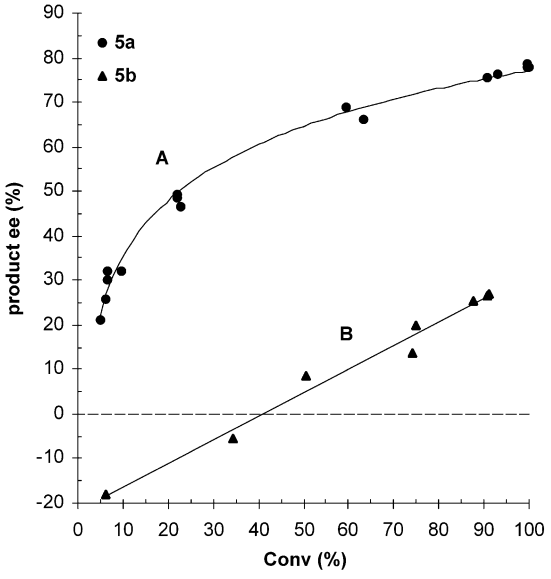
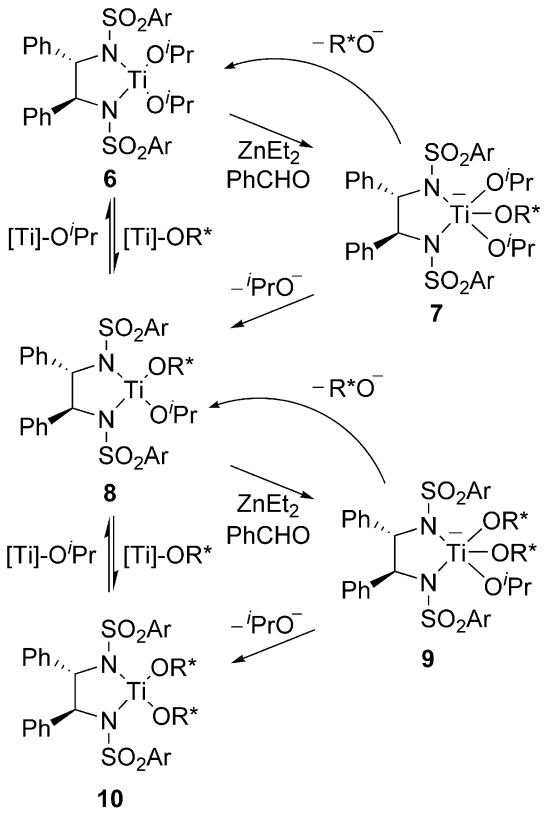


Figure 2. Plot of ee (%) vs conversion (%) with ligands **5a–b** (Scheme 1).

To explain the results in Figure 2, we propose a mechanism involving catalyst evolution (Scheme 2). The initial catalyst for this reaction is proposed to be L*Ti(O^iPr)$_2$, **6**, [L*= bis(sulfonamido)].[26–29] We envision that the aldehyde is first activated by coordination to the titanium center and the ethyl group is delivered. It is not known which metal is responsible for delivery of the ethyl group in this system, the zinc or the titanium. In related systems, the organozinc has

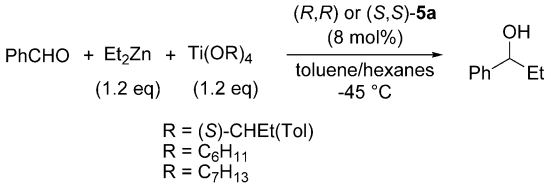


Scheme 2. Proposed mechanism of catalyst evolution.

been found to undergo transmetallation with titanium to give MeTi(O^iPr)$_3$ and it is titanium that is responsible for delivery of the methyl to the aldehyde carbonyl.[35,36] Addition of the ethyl group to the aldehyde is proposed to give an intermediate complex (**7**) containing three alkoxides bonded to titanium. To regenerate the proposed catalyst, one of the alkoxide groups must be removed from **7**, where OR* is the alkoxide formed by ethyl addition to benzaldehyde. Removal of the chiral alkoxide (R*O$^-$) regenerates the initial catalyst, **6**, while loss of (^{i}PrO$^-$) affords two new diastereomeric catalysts (**8**) where R*O$^-$ has the (*S*)-configuration (major) or the (*R*)-configuration. Likewise, addition promoted by L*Ti(O^iPr)(OR*), **8**, can generate three diastereomeric L*Ti(OR*)$_2$ catalysts (**10**). These new catalysts will likely have different activities and enantioselectivities from the initial catalyst **6**.

The issue of alkoxide exchange is of fundamental importance in a number of enantioselective processes.[37–39] The proposed mechanism in Scheme 2 requires that alkoxide exchange between Ti(O^iPr)$_4$ and catalysts bearing chiral alkoxide groups be slow relative to the asymmetric addition. If this exchange process were fast, the distribution of alkoxide ligands would be under equilibrium control. The concentrations of L*Ti(OR*)$_2$ and L*Ti(OR*)(O^iPr) would, therefore, be low due to the high ratio of isopropoxide ligands to chiral alkoxide ligands (4.8:1 at the end of the addition reaction). In the fast alkoxide exchange scenario, it would be unlikely to observe the high degree of autoinduction necessary for the changes in product ee outlined in Figure 2.

The second tenant of the mechanistic proposal in Scheme 2 is that L*Ti(OR*)$_2$ and/or L*Ti(OR*)(O^{i}Pr) are considerably more enantioselective than L*Ti(O^{i}Pr)$_2$. The results of the autoinduction study suggest that bulkier alkoxide ligands, such as OR*, result in more enantioselective catalysts. This proposal was examined by employing the enantioenriched alkoxide complexes Ti(OR*)$_4$ (R* = CH(Et)Tol). The impact of the configuration of the chiral alkoxide ligands in Ti(OR*)$_4$ on the product ee was found to be significant. The (*R*,*R*)-bis(sulfonamide) ligand **5a** and Ti(O^{i}Pr)$_4$ form a catalyst that generates the (*S*)-alkoxide product in 79% ee at 100% conversion. When titanium alkoxide (*S*)-Ti(OR*)$_4$ was substituted for Ti(O^{i}Pr)$_4$ and used with (*R*,*R*)-**5a** (Scheme 3), the (*S*)-alcohol was generated with an initial ee of 84%, and a 5% drop in ee over the course of the reaction. Use of mismatched alkoxide complex (*S*)-Ti(OR*)$_4$ with (*S*,*S*)-**5a** resulted in product ee of 72%.

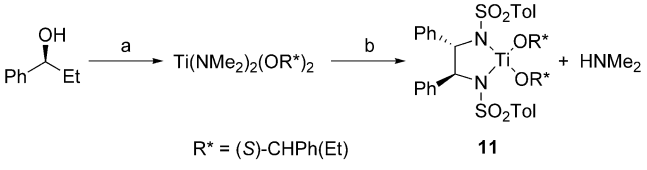


Scheme 3. Diethylzinc addition to benzaldehyde in the presence of bis(sulfonamide) ligand **5a** and various titanium alkoxides.

These experiments indicate that bulkier alkoxides on titanium generate more enantioselective catalysts and that L*Ti(OR*)$_2$ is significantly more enantioselective than L*Ti(O^{i}Pr)$_2$.

We then examined the influence of achiral titanium alkoxides, Ti(OR)$_4$, on the enantioselectivity of the catalysts (Scheme 3). Based on the results outlined above, we anticipated that the use of a bulkier alkoxide would generate a more enantioselective catalyst. We therefore began with the cyclohexyl and the cycloheptyl derivatives [Ti(OR)$_4$, R = C$_6$H$_{11}$ and R = C$_7$H$_{13}$]. With these titanium alkoxides, a significant improvement in ee was observed: from the final ee of 79% using Ti(O^{i}Pr)$_4$ to 90.9 and 92.7% ee with Ti(OR)$_4$ where R = C$_6$H$_{11}$ and R = C$_7$H$_{13}$, respectively. Catalysts formed with titanium(IV) *tert*-butoxide, however, were very slow. Presumably, the *tert*-butoxide groups are too bulky and prevent the catalyst from forming or turning over.

We were also interested in examining the structure of the L*Ti(OR*)$_2$ species. Therefore, we prepared the titanium complex **11** as shown in Scheme 4. A single crystal was obtained by crystallization of compound **11** from dichloromethane/hexanes and an X-ray structure determination was



Scheme 4. Reagents and conditions: (a) (i) BuLi, Et$_2$O, rt; (ii) Ti(NMe$_2$)$_2$Cl$_2$, rt, 3 h, 99%. (b) **5c**, pentane, rt, 36 h, 85%.

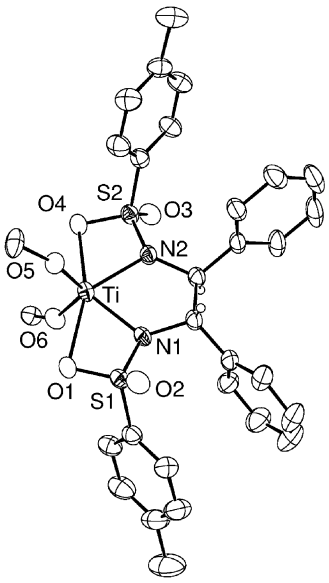


Figure 3. ORTEP drawing of **11** (the chiral CH(Et)Ph groups of the alkoxide have been removed for clarity).

performed.[40] An ORTEP drawing of **11** is illustrated in Figure 3. In this structure the chiral CH(Et)Ph groups of the alkoxides have been removed for clarity. The structure of **11** is reminiscent of related bis(sulfonamido)Ti-based complexes reported by us[29,41,42] and Gagné.[43] Like the bis(sulfonamido)Ti(O^{i}Pr)$_2$ complexes based on *trans*-1,2-diaminocyclohexane,[29] compound **11** exhibits close contacts between titanium and one of the diastereotopic sulfonyl oxygens of each sulfonamido group. These distances range from 2.235 to 2.408 Å. The long Ti–O(sulfonyl) distances can be compared to the Ti–O distances of the isopropoxide ligands (1.758 and 1.765 Å). The Ti–N distances are also longer than titanium amides of the type Ti–NMe$_2$, which generally have Ti–N distances of 1.88 Å. The Ti–N distances in **11** of 2.039 and 2.042 Å reflect the electron withdrawing nature of the sulfonyl group. These distances are similar to those observed with other bis(sulfonamido)Ti-complexes.[29,41–43]

3. Conclusions

In conclusion, we have found that use of bis(sulfonamide) ligands derived from stilbene diamine in the asymmetric addition of diethylzinc to benzaldehyde (Scheme 1) resulted in large changes in product ee over the course of the reaction. With ligand **5a** we observed a change in the ee of the product by nearly 60%. This represents one of the largest increases in ee attributed to autoinduction. During the reaction the catalyst evolves by incorporation the product of the asymmetric addition reaction. The resulting catalysts exhibit enhanced enantioselectivity. Based on our study of the autoinduction process, we were able to streamline the catalyst optimization process. Rather than optimizing the catalyst using traditional methods, which involve modification and screening of enantioenriched chiral ligands, in this system we have found that the catalyst enantioselectivity could be increased by screening achiral ligands.[17,18] This is a powerful approach to asymmetric catalysis,

because it does not revolve around the synthesis and screening of chiral ligands, which is often an arduous task.

4. Experimental

4.1. General procedures

All manipulations involving titanium alkoxides and diethylzinc were carried out under an inert atmosphere in a Vacuum Atmospheres dry box with attached MO-40 Dritrain, or by using standard Schlenk or vacuum line techniques. Solutions were degassed as follows: they were cooled to −196 °C, evacuated under high vacuum, and thawed. This sequence was repeated three times in each case. ^{1}H NMR spectra were obtained on a Bruker 360-MHz Fourier transform NMR spectrometer at the University of Pennsylvania NMR facility. ^{1}H NMR spectra were recorded relative to residual protiated solvent. Chemical shifts are reported in units of parts per million relative to tetramethylsilane and all coupling constants are reported in Hz. Unless otherwise specified, all reagents were purchased from Aldrich Chemical Co. and used without further purification. Titanium tetraisopropoxide, benzaldehyde, 4-methylbenzaldehyde, (*S*)-1-phenyl-1-propanol and (*S*)-1-tolyl-1-propanol were distilled under vacuum and stored in glass vessels sealed with Teflon stoppers. Et_2Zn (1.0 M in toluene) and titanium alkoxides (in hexanes) solutions were prepared in the dry box and stored in Schlenk storage tubes under nitrogen. The following compounds were prepared by literature procedures: (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine,[44] 2,4-dimethylbenzenesulfonyl chloride,[20] bis(sulfonamide) ligands **5a–c**,[44,45] Ti[(*S*)-OCH(Tol)Et]$_4$,[20] and $Ti(NMe_2)_2Cl_2$.[46] Tetrakis(cyclohexyloxy)titanium and tetrakis(cycloheptyloxy)titanium were prepared by mixing of titanium tetraisopropoxide and 4 equiv of cyclohexanol or cycloheptanol, respectively, in toluene, and subsequent azeotropic removal of ^{i}PrOH with toluene. Hexanes (UV grade, alkene free) was distilled from sodium benzophenone ketyl/tetraglyme under nitrogen. Toluene, pentane and diethylether were distilled from sodium benzophenone ketyl under nitrogen. Deuterated solvents (purchased from Cambridge Isotopes) for use in NMR experiments were dried in the same manner as their protiated analogs, but were vacuum transferred from the drying agent. $CDCl_3$ was dried over calcium hydride and vacuum transferred.

Enantiomeric excesses were determined using GC methods. GC-analyses were carried on a Hewlett–Packard gas chromatograph with a 30-m Supelco β-DEX^{TM} column.

4.2. General procedure for the asymmetric alkylation of benzaldehyde using chiral bis(sulfonamide) ligands and titanium tetraisopropoxide

The chiral bis(sulfonamide) **5** (0.11 mmol, 8 mol%) was introduced in a dry Schlenk flask, and the system was purged with nitrogen. Diethylzinc (1.7 mL, 1.0 M in toluene, 1.2 equiv) was added and the mixture cooled to −45 °C. After 10 min, titanium tetraisopropoxide (1.2 mL, 1.4 M in hexanes, 1.2 equiv) was slowly added to the mixture. Stirring was continued for 10 min and benzaldehyde (0.14 mL, 1.38 mmol, 1.0 equiv) was added. The reaction was sampled at different times by carefully removing aliquots and quenching them with 2 N HCl. The aqueous layer was extracted with pentane and the resulting solutions were analyzed by GC (Supelco SPB-5, 30 m× 0.25 mm. 115 °C, 1.3 mL/min. (*S*)-1-phenylpropanol: 16.0 min; (*R*)-1-phenylpropanol: 16.9 min).

The asymmetric alkylations of benzaldehyde mediated by other titanium alkoxides were performed analogously. In the case of tetrakis(cyclohexyloxy)titanium and tetrakis(cycloheptyloxy)titanium the concentrations of the titanium alkoxide solutions used were 0.7 and 1.0 M, respectively.

4.2.1. Preparation of $Ti(NMe_2)_2[O\text{-}((S)\text{-}CHPh(Et))]_2$. (*S*)-1-phenylpropanol (203 mg, 1.49 mmol) was dissolved in Et_2O (5 mL) in the dry box and BuLi (0.6 mL, 2.49 M in hexanes, 1.49 mmol) was added. After 10 min at rt, a solution of $Ti(NMe_2)_2Cl_2$ (155 mg, 0.75 mmol) in Et_2O (1 mL) was added and the reaction mixture was stirred for 3 h. $Ti(NMe_2)_2[O\text{-}((S)\text{-}CHPh(Et))]_2$ (302 mg, 99%) was obtained as a light brown oil and used without further purification. The ^{1}H NMR spectrum (C_6D_6) of this compound showed it to be a mixture of different compounds of formula $Ti(NMe_2)_n(OR^*)_{4-n}$.

4.2.2. Preparation of 11. $Ti(NMe_2)_2(O\text{-}((S)\text{-}CHPh(Et)))_2$ (81 mg, 0.20 mmol) and bis(sulfonamide) ligand **5c** (101 mg, 0.19 mmol) were combined in pentane (3 mL), resulting in an orange suspension. After stirring for 36 h at rt, the undissolved ligand was filtered and the filtrate was concentrated under vacuum to yield a white solid (138 mg, 85%). X-ray crystals were grown over several days by slow diffusion of hexanes into a CH_2Cl_2 solution of crude **11**. ^{1}H NMR (360 MHz, C_6D_6): δ 1.19 (t, J=7.3 Hz, 6H), 1.87 (s, 6H), 2.06 (m, 2H), 2.16 (m, 2H), 5.16 (s, 2H), 6.01 (t, J=6.4 Hz, 2H), 6.50 (d, J=7.4 Hz, 4H), 6.57 (t, J=8.3 Hz, 4H), 6.69 (t, J=7.1 Hz, 2H), 6.85 (d, J=7.8 Hz, 4H), 7.14 (t, J=6.9 Hz, 2H), 7.23 (t, J=7.2 Hz, 4H), 7.63 (d, J=7.8 Hz, 4H), 7.71 (d, J=7.5 Hz, 4H).

Acknowledgements

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References and notes

1. Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265–7266.
2. Alberts, A. H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1990**, 453–454.
3. Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740–6741.
4. Kogut, E. F.; Thoen, J. C.; Lipton, M. A. *J. Org. Chem.* **1998**, *63*, 4604–4610.
5. Sheng, L.; Yaozhong, J.; Aiqiao, M.; Guishu, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 885–886.
6. Rebiere, F.; Riant, O.; Kagan, H. B. *Tetrahedron: Asymmetry* **1990**, *1*, 199–214.

7. Heller, D. P.; Goldberg, D. R.; Wulff, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 10551–10552.
8. Szlosek, M.; Figadère, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1799–1801.
9. De Rosa, M.; Acocella, M. R.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1529–1531.
10. Villano, R.; De Rosa, M.; Salerno, C.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1949–1952.
11. Imma, H.; Mori, M.; Nakai, T. *Synlett* **1996**, 1229–1230.
12. Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317–3321.
13. Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770–11771.
14. Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660–2661.
15. Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 1657–1659.
16. Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767–768.
17. Walsh, P. J.; Lurain, A. E.; Balsells, J. *Chem. Rev.* **2003**, *103*, 3297–3344.
18. For a review of achiral additives in asymmetric catalysis see: Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570–1577.
19. Miura, K.; Katsuki, T. *Synlett* **1999**, 783–785.
20. Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1802–1803.
21. Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 2161–2164.
22. Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92–138.
23. Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585–589.
24. Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236.
25. Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494.
26. Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095–7098.
27. Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691–5700.
28. Knochel, P.; Vettel, S.; Eisenberg, C. *Applied Organomet. Chem.* **1995**, *9*, 175–188.
29. Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423–6424.
30. Luukas, T. O.; Fenwick, D. R.; Kagan, H. B. *C. R. Chimie* **2002**, *5*, 487–491.
31. Guo, C.; Qiu, J.; Zhang, X.; Verdugo, D.; Larter, M. L.; Christie, R.; Kenney, P.; Walsh, P. J. *Tetrahedron* **1997**, *53*, 4145–4158.
32. Qiu, J.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 2665–2668.
33. Lurain, A. E.; Maestri, A.; Rowley Kelly, A.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13608–13609.
34. Balsells, J.; Costa, A. M.; Walsh, P. J. *Isr. J. Chem.* **2001**, *41*, 251–261.
35. Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336–10348.
36. Wu, K.-H.; Gau, H.-M. *Organometallics* **2004**, *23*, 580–588.
37. Bradley, D. C.; Mehrotra, R. C.; Gaur, D. P. *Metal Alkoxides*; Academic: London, 1978.
38. Bradley, D. C. *Adv. Inorg. Chem. Radiochem.* **1972**, *15*, 259–322.
39. Mehrotra, R. C.; Singh, A. In Karlin, K. D., Ed.; Recent Trends in Metal Alkoxide Chemistry; Wiley: New York, 1997; Vol. 46, pp 239–454.
40. Crystallographic data (excluding structure factors) for **11** have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC255161.
41. Pritchett, S.; Gantzel, P.; Walsh, P. J. *Organometallics* **1997**, *16*, 5130–5132.
42. Pritchett, S.; Gantzel, P.; Walsh, P. J. *Organometallics* **1999**, *18*, 823–831.
43. Armistead, L. T.; White, P. S.; Gagné, M. R. *Organometallics* **1998**, *17*, 216–220.
44. Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495.
45. Bis(sulfonamide) ligands **5a–c** were prepared according to the literature procedures and were further purified by recrystallization from CH_2Cl_2/hexanes.
46. Benzing, E.; Kornicker, W. *Chem. Ber.* **1961**, *94*, 2263–2267.

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Stereoselective synthesis of *N*-protected pyrrolidines via Pd-catalyzed reactions of γ-(*N*-acylamino) alkenes and γ-(*N*-Boc-amino) alkenes with aryl bromides

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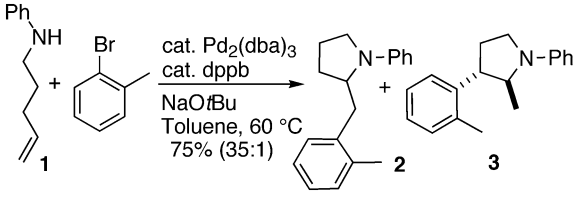
Abstract—The stereoselective synthesis of *N*-acyl- and *N*-Boc-protected pyrrolidines via Pd-catalyzed reactions of γ-(*N*-acylamino) alkenes and γ-(*N*-Boc-amino) alkenes with aryl bromides is described. These reactions effect formation of two bonds in a single operation and proceed with generally high levels of diastereoselectivity. In contrast to previously described reactions of γ-(*N*-arylamino) alkenes, these transformations proceed in high yield and high regioselectivity with both electron-rich and electron-deficient aryl bromides as well as vinyl bromide substrates.

1. Introduction

A diverse array of biologically active molecules contain substituted pyrrolidine cores.[1] Many strategies for the synthesis of substituted pyrrolidines employ intramolecular C–N bond-forming reactions for the construction of the heterocyclic ring.[2] However, very few methods allow for simultaneous intramolecular C–N bond formation and intermolecular formation of a C1′ carbon–carbon bond;[3] existing methods are limited in scope and/or require harsh reaction conditions or toxic reagents.

We recently described a new method for the stereoselective synthesis of *N*-aryl pyrrolidines via Pd-catalyzed reactions of γ-(*N*-arylamino) alkenes with aryl bromides (Eq. 1).[4,5] This transformation effects the formation of two bonds (one C–C bond and one C–N bond) along with upto two stereocenters in a single step. This method is effective for the preparation of a number of *N*-aryl pyrrolidine derivatives (e.g., **2**), and substrates bearing substituents at C-1 or C-3 are converted to the corresponding *cis*-2,5-disubstituted- or *trans*-2,3-disubstituted pyrrolidines in good yield with excellent (>20:1) diastereoselectivity. In most reactions small amounts of regioisomeric products **3** are formed in addition to the desired product **2**, although ratios of **2**:**3** are typically ≥10:1.



(1)

Despite the utility of this transformation for the synthesis of *N*-aryl pyrrolidines, these products cannot be easily transformed into other *N*-substituted (or unsubstituted) pyrrolidine derivatives, as cleavage of the aryl C–N bond is not readily accomplished.[6] In addition, reactions of **1** or related γ-*N*-(*p*-methoxyphenyl) aminoalkenes provide only moderate yields of the desired product when vinyl bromides or electron-deficient aryl bromides are used as coupling partners due to competing *N*-arylation or *N*-vinylation of the relatively electron-rich nitrogen.

To address the limitations described above, we have developed conditions to effect the conversion of *N*-acyl and *N*-Boc protected γ-aminoalkenes into the corresponding pyrrolidines. The Boc and acyl protecting groups can be readily cleaved under relatively mild conditions,[7] and also serve to minimize competing *N*-arylation side reactions by decreasing the nucleophilicity of the nitrogen atom. Our preliminary studies on the scope and limitations of these transformations are described herein.

Keywords: Stereoselective synthesis; Pyrrolidines; Diastereoselectivity; Palladium; Arylhalide.
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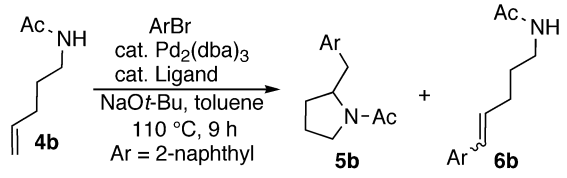
2. Results and discussion

2.1. Optimization studies

In order to develop a new route to *N*-protected pyrrolidines, we initially examined Pd-catalyzed reactions of 2-bromonaphthalene with *N*-4-pentenylacetamide (**4b**). Our previous studies on Pd/phosphine-catalyzed reactions of γ-(*N*-arylamino) alkenes with aryl bromides showed that the nature of the phosphine ligand had a pronounced effect on the yield of the desired pyrrolidine product.[4] Thus, **4b** was treated with 2-bromonaphthalene and NaO*t*Bu in the presence of a catalytic amount of $Pd_2(dba)_3$ and various phosphine ligands. The reactions were heated at 110 °C for 9 h, quenched, and assayed by GC. As shown in Table 1, dpe-phos[8] gave the highest yield in the conversion of **4b** to **5b**. The use of rigid bidentate phosphine ligands generally provides higher yields than monodentate ligands. However, subsequent studies on the scope of these reactions revealed that the optimal bidentate ligand for a given transformation is somewhat dependent on substrate structure. The use of dppe,[8] dppb,[8] or nixantphos[8] provides the highest yields in some reactions (see below), and in some cases $Pd(OAc)_2$ was found to provide slightly better results than $Pd_2(dba)_3$.

Table 1. Ligand effects



Ligand	% Conversion	GC ratio		
		5b	**6b**	Other[a]
PPh_3	59	34	6	19
P(*o*-tol)$_3$[b]	35		23	3
Dppb	61	53	8	—
Dppf	91	76	10	5
Xantphos	95	84	7	4
Dpe-phos	96	85	5	6

[a] Small amounts of other side products including regioisomers of **6b** and *N*-arylated compounds were also formed.
[b] The reaction was conducted for 20 h.

The effect of *N*-protecting groups on the efficiency of these transformations was probed by conducting reactions of 2-bromonaphthalene with various *N*-protected 5-amino-1-pentene derivatives in the presence of NaO*t*Bu and a catalytic amount of $Pd_2(dba)_3$/dpe-phos (Table 2). These transformations afford the desired pyrrolidine **5** along with Heck-type[9] side product **6** and/or *N*-arylated[10] side product **7**. As expected, the nature of the *N*-protecting group has a large impact on the ratio of **5**:**6**:**7**. In most cases, as the electron-withdrawing ability of the protecting group increased, the amount of *N*-arylation decreased but the amount of Heck olefination increased. For example, the reaction of a substrate bearing an *N*-phenyl substituent (**1**) afforded a 75:25 ratio of **5**:**7**, whereas the analogous transformation of a *N*-benzoyl substituted amine (**4e**) provided a 58:42 ratio of **5**:**6**; the formation of **7** was not observed. The best results were obtained in reactions of *N*-acyl and *N*-Boc substituted substrates **4b** and **4c**, which were converted to the desired pyrrolidines in good yield with high regioselectivity. In contrast, the Pd-catalyzed reactions of 2-bromonaphthalene with *N*-benzyl substituted substrate **4a** and *N*-(*p*-trifluoromethylbenzoyl) substituted derivative **4f** failed to provide detectable amounts of pyrrolidine products.[11]

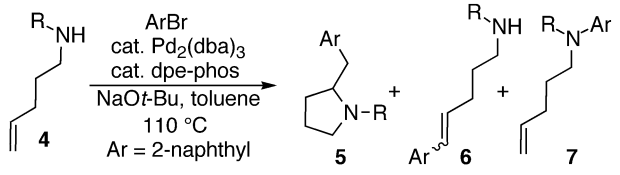
The effect of other parameters such as solvent and base was also examined in several different reactions. In general, weak bases such as K_2CO_3 or Cs_2CO_3 were less effective than NaO*t*Bu; their use resulted in the formation of large amounts of Heck-type products. Toluene was found to be the optimal solvent although ethereal solvents such as DME and dioxane provided satisfactory results in many instances. Use of THF as solvent in reactions of Boc-protected substrates led to diminished product yields due to base-induced cleavage of the boc-group from the substrate.[12,13]

2.2. Scope and limitations

Following our initial optimization studies we examined reactions of *N*-acyl-protected substrate **4b** and *N*-Boc-protected substrate **4c** with a variety of different aryl and vinyl bromides. As shown in Table 3, the transformations proceed in good yield with electron-neutral (entries 1, 2, and 5) and electron-poor (entries 3 and 6) aryl bromides. Use of an electron-rich aryl bromide afforded a moderate yield of the desired product, although partial oxidation of the *N*-acyl pyrrolidine product to the corresponding 2,3-dihydropyrrole occurred under the reaction conditions (entry 7).[14] In all cases examined a single product regioisomer was formed. The major side products observed in reactions of **4b** and **4c** derive from competing Heck arylation or *N*-arylation of the substrate. The competing Heck arylation is more problematic in reactions of acetate protected substrate **4b**.

Most transformations are efficiently catalyzed by mixtures of $Pd_2(dba)_3$ and dpe-phos. However, use of dppe as ligand provided higher yields for some substrate combinations

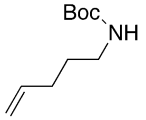
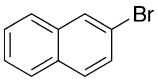
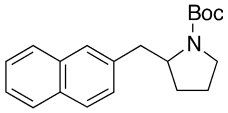
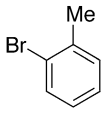
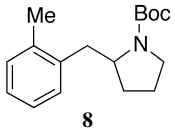
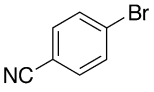
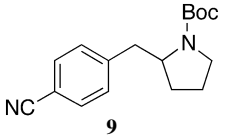
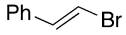
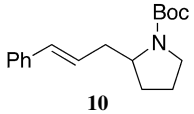
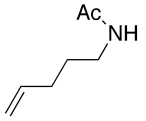
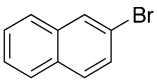
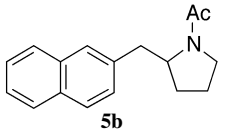
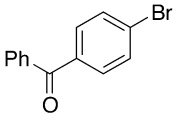
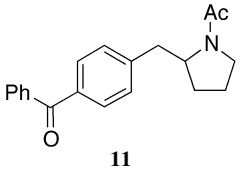
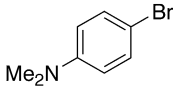
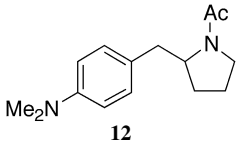
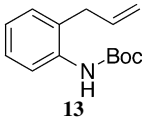
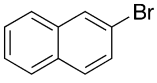
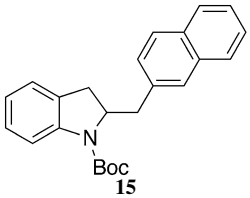
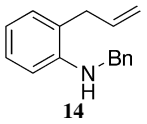
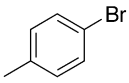
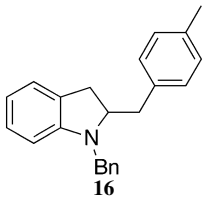
Table 2. *N*-Substitutent effects



N-Substituent	GC ratio (isolated yield)		
	5	**6**	**7**
R=Bn[a] (**4a**)	—	40[b]	34
R=Ph (**1**)	75 (63%)[c–e]	—	25
R=Ac[a] (**4b**)	88 (72%)	12	—
R=Boc[a] (**4c**)	82 (77%)	4[b]	—
R=4-MeO-Bz (**4d**)	77 (63%)	23	—
R=Bz (**4e**)	58 (48%)	42	—
R=4-F_3C-Bz[a] (**4f**)	—	89[b]	—

[a] Other minor, unidentified side products were also observed.
[b] Mixtures of alkene regioisomers were obtained.
[c] GC yield.
[d] This product was obtained as a 15:1 mixture of regioisomers.
[e] Use of 1,4-bis(diphenylphosphino) butane (dppb) as ligand provided a 94% isolated yield of **5** as a 25:1 mixture of regioisomers. See Ref. 4.

Table 3. Synthesis of *N*-protected pyrrolidines and indolines[a]

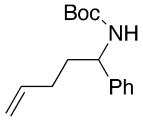
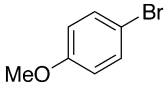
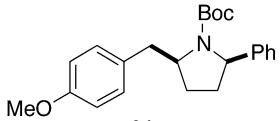
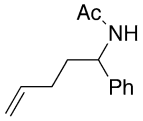
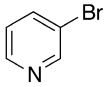
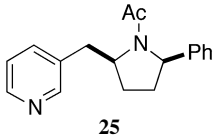
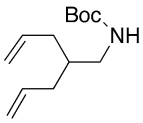
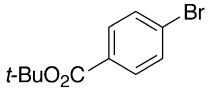
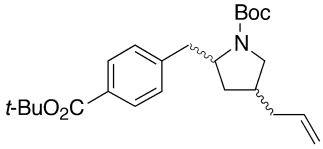
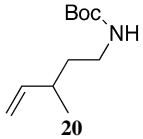
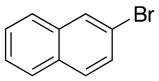
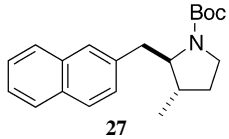
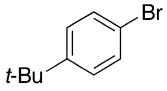
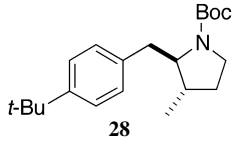
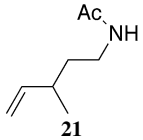
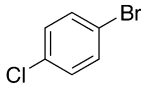
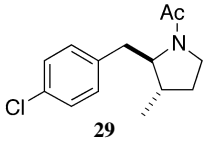
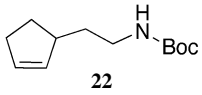
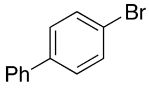
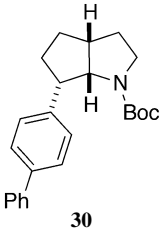
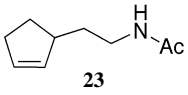
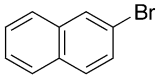
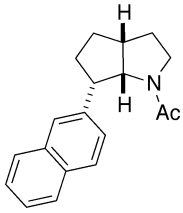
Entry	Amine	Aryl bromide	Catalyst	Product	Yield
1	 **4c**		$Pd(OAc)_2$/dpe-phos	 **5c**	77[b]
2			$Pd_2(dba)_3$/dpe-phos	 **8**	81
3			$Pd_2(dba)_3$/dppb	 **9**	71
4			$Pd(OAc)_2$/dppe	 **10**	75[b]
5	 **4b**		$Pd_2(dba)_3$/dpe-phos	 **5b**	72
6			$Pd_2(dba)_3$/dppe	 **11**	78
7			$Pd_2(dba)_3$/xantphos	 **12**	67[c]
8	 **13**		$Pd_2(dba)_3$/dpe-phos	 **15**	50
9	 **14**		$Pd_2(dba)_3$/nixantphos	 **16**	48

[a] Conditions: 1.0 equiv substrate, 1.1–1.2 equiv ArBr, 1.2–2.0 equiv NaO*t*Bu, 2 mol% Pd (1 mol% $Pd_2(dba)_3$ or 2 mol% $Pd(OAc)_2$), 2–4 mol% ligand, toluene (0.25 M), 105 °C.
[b] The reaction was conducted at 65 °C.
[c] This material contained ca 15% of the corresponding 2,3-dihydropyrrole (1-[5-(4-dimethylaminobenzyl)-2,3-dihydropyrrol-1-yl]ethanone).

by minimizing competing *N*-arylation or *N*-vinylation processes (Table 3, entries 4 and 6).[10] The reaction of the electron-rich *N*,*N*-dimethyl-4-bromoaniline was most efficiently catalyzed by a mixture of $Pd_2(dba)_3$ and xantphos (entry 7).

The results obtained in the reactions of **4b** and **4c** described above contrast with related transformations of *N*-phenyl substituted substrate **1**. For example, the Pd-catalyzed reaction of **4b** with 4-bromobenzophenone proceeded in 78% isolated yield (entry 6), whereas the analogous reaction of **1** provided only a modest 45% yield.[4] Additionally, the reaction of **1** with β-bromostyrene proceeds in low yield due to competing *N*-vinylation,[15,16] but the reaction of **4c** with this vinyl bromide affords the desired product in 75% isolated yield (entry 4).

Table 4. Stereoselective synthesis of *N*-protected pyrrolidines[a]

Entry	Amine	Aryl bromide	Catalyst	Product	dr[b]	Yield
1	 **17**		$Pd_2(dba)_3$/dppb	 **24**	>20:1	60
2	 **18**		$Pd_2(dba)_3$/dppb	 **25**	>20:1	82
3	 **19**		$Pd_2(dba)_3$/dpe-phos	 **26**	3:1	72
4	 **20**		$Pd(OAc)_2$/dpe-phos	 **27**	>20:1	66[c,d]
5			$Pd(OAc)_2$/dpe-phos	 **28**	>20:1	59[c,d]
6	 **21**		$Pd_2(dba)_3$/dpe-phos	 **29**	>20:1	61[c]
7	 **22**		$Pd(OAc)_2$/xantphos	 **30**	>20:1	53[d]
8	 **23**		$Pd_2(dba)_3$/nixantphos	 **31**	>20:1	61[e,f]

[a] Conditions: 1.0 equiv substrate, 1.1–1.2 equiv ArBr, 1.2–2.0 equiv NaO*t*Bu, 2 mol% Pd (1 mol% $Pd_2(dba)_3$ or 2 mol% $Pd(OAc)_2$), 2–4 mol% ligand, toluene (0.25 M), 105 °C.
[b] Diastereomeric ratios described in Table 4 represent ratios of diastereomers for the isolated material upon which the yield is based. These ratios may differ from diastereomeric ratios observed in crude reaction mixtures as noted below.
[c] A 10:1 ratio of diastereomers was observed in the crude reaction mixture.
[d] The reaction was conducted at 65 °C.
[e] The reaction was conducted using 2.5 mol% $Pd_2(dba)_3$.
[f] The reaction was stopped at 77% conversion after two days at 110 °C.

The synthesis of *N*-protected indolines from *N*-allylaniline derivatives was also briefly examined (Table 3, entries 8 and 9). Treatment of *N*-Boc-2-allylaniline (**13**) with 2-bromonaphthalene under our optimized reaction conditions afforded a 50% yield of the desired indoline product **15**. The moderate yield in this transformation was mainly due to competing base-induced cleavage of the Boc-group from the substrate[12] and/or base-induced olefin isomerization of the substrate.[17] In contrast to the reactions of *N*-benzyl protected aliphatic amine substrates, *N*-benzyl-2-allylaniline (**14**) was converted to the *N*-benzyl-2-benzylindoline **16** in 48% yield. The major side product obtained

in this reaction was *N*-benzyl-2-methylindole, which presumably derives from Pd-catalyzed oxidative amination of the substrate.[18] Attempts to transform *N*-acyl-2-allylaniline to the corresponding indoline were unsuccessful; competing Heck arylation was observed.

The stereoselective synthesis of disubstituted pyrrolidines bearing *N*-Boc or *N*-acyl groups was achieved via Pd-catalyzed carboamination of substrates **17–21** bearing substituents on the tether between the alkene and the nitrogen (Table 4). Comparable diastereoselectivities were obtained with both *N*-acyl and *N*-Boc protected substrates, and the nature of the aryl bromide did not have a large effect on diastereoselectivity in the transformations examined. The synthesis of *trans*-2,3-disubstituted pyrrolidines (entries 4–6) and *cis*-2,5-disubstituted pyrrolidines (entries 1 and 2) was effected in good yield with good levels of diastereoselectivity.[19,20] In contrast, the reaction of **19** with *tert*-butyl-(4-bromo)benzoate afforded a 2,4-disubstituted pyrrolidine product in 72% yield, but with only modest (ca 3:1) diastereoselectivity (entry 3). The reactions of **17–21** proceed with similar diastereoselectivities and significantly higher regioselectivities than transformations of the analogous *N*-aryl substituted substrates.[4]

The yields obtained in reactions of substrates **17–18** bearing substituents at the 1- or 3-position were slightly lower than yields obtained in reactions of unsubstituted substrates **4b–c**. The diminished yields are due in part to competing base-induced cleavage of the Boc group from the more hindered substrates.[12] The rate of Boc cleavage is relatively rapid in THF at 65 °C and toluene at 110 °C, whereas little or no cleavage occurs in toluene at 65 °C. Competing Heck arylation also becomes more problematic as steric hindrance at C-1 or C-3 increases. The Heck side products formed in reactions of *N*-acylated substrates were more difficult to separate from the desired product than the side products obtained in analogous reactions of Boc-protected substrates, which also led to slightly diminished yields.

The transformations of substrates **22–23** bearing internal cyclic alkenes proceeded in moderate yield with excellent regioselectivity and diastereoselectivity (>20:1) to afford products **30** and **31** (entries 7 and 8).[21] In both reactions the observed diastereomer derives from *syn* addition of the nitrogen and the aryl group across the double bond.[20] The yields and regioselectivities in these transformations sharply contrast with those obtained in the reaction of the analogous *N*-(4-methoxyphenyl) substituted substrate, which afforded a mixture of two regioisomeric products along with an *N*-arylated side product and a side product derived from oxidative amination of the substrate.[4]

2.3. Proposed catalytic cycle and mechanism

A proposed catalytic cycle for this transformation is shown (Fig. 1). The catalytic cycle presumably commences with oxidative addition of the aryl bromide to the Pd(0) catalyst to afford Pd(Ar)(Br) complex **32**. Reaction of this complex with the γ-aminoalkene substrate in the presence of NaO*t*Bu likely results in the formation of palladium aryl(amido) complex **33**,[10] which undergoes insertion of the alkene into the Pd–N bond[4,22] followed by C–C bond-forming reductive elimination[23] of the resulting intermediate **34** to afford the observed pyrrolidine with concomitant regeneration of the Pd(0) catalyst.

This mechanism described above is analogous to that previously proposed for reactions of γ-(*N*-arylamino) alkene substrates.[4] The formation of products that result from *syn* addition of the aryl group and the nitrogen across the C–C double bond (Table 4, entries 7 and 8) is consistent with this mechanistic proposal.[24] This mechanism also accounts for the formation of *N*-benzyl-2-methylindole as a side product in the reaction of *N*-benzyl-2-allylaniline (Table 3, entry 9). The *N*-benzyl-2-methylindole likely derives from competing β-hydride elimination of intermediate **34** followed by double bond isomerization.[18a]

The regioisomeric products **3** observed in reactions of *N*-aryl substituted substrates[4] (e.g., **1**) are believed to derive from reversible β-hydride elimination/reinsertion processes as shown in Scheme 1. The absence of these side products in reactions of *N*-Boc and *N*-acyl protected substrates may result from a decrease in the rate of β-hydride elimination of intermediate **34**. This may be due to stabilization of **34** through chelation of the metal to the carbonyl of the amide or carbamate,[25] or due to electronic effects induced by the less electron-donating nature of the protected nitrogen.[26,27] The increased yields obtained in reactions of *N*-Boc and *N*-acyl protected amines with electron-deficient aryl bromides and vinyl bromides is likely due to the fact that C–N bond-forming reductive elimination of intermediate **33**

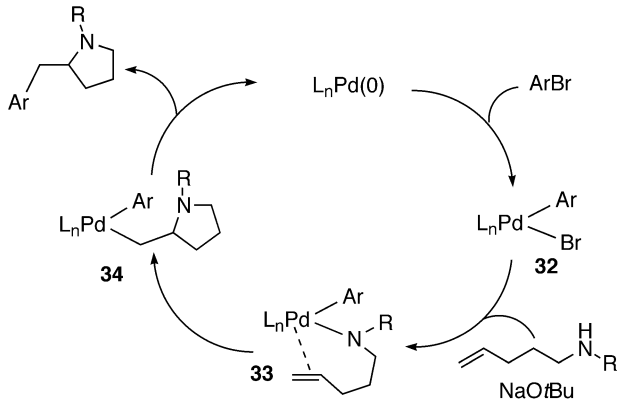
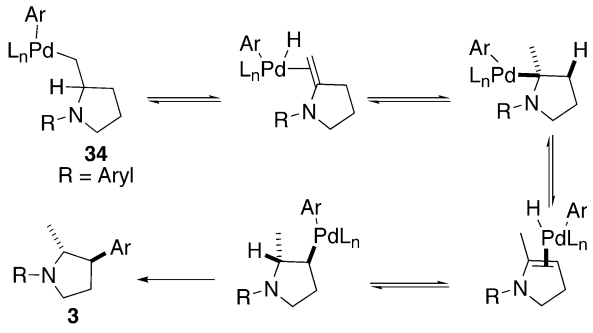


Figure 1. Proposed catalytic cycle.



Scheme 1.

slows as the nucleophilicity of the amine, amide, or carbamate decreases.[28]

3. Summary and conclusion

In conclusion, the synthesis of *N*-Boc and *N*-acyl pyrrolidine derivatives via reactions of *N*-protected γ-aminoalkenes is achieved in good yield with excellent regioselectivity and diastereoselectivities of up to >20:1. In contrast to related transformations of γ-(*N*-arylamino) alkenes, reactions of *N*-Boc or *N*-acyl protected substrates with vinyl bromides or electron-deficient aryl bromides proceed in good yield with minimal competing *N*-arylation/vinylation. The *N*-Boc and *N*-acyl substituents can be readily cleaved from the products, which allows for potential access to a broad variety of pyrrolidine derivatives.

4. Experimental

4.1. General

All reactions were carried out under an argon or nitrogen atmosphere in oven or flame dried glassware. Palladium acetate, tris(dibenzylideneacetone)dipalladium(0), and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. Acetic anhydride, di-*tert*-butyldicarbonate, cyclopent-2-enyl-acetic acid, and all aryl bromides were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were used as without purification. Pent-4-enylphenylamine (**1**),[4] *N*-benzyl-4-pentenylamine (**4a**),[29] *N*-(pent-4-enyl-benzamide) (**4e**),[30] and 2-allylaniline[31] were prepared according to published procedures. *N*-Benzyl-2-allylaniline (**14**)[32] was prepared by *N*-benzylation[33] of 2-allylaniline. Toluene and THF were purified using a GlassContour solvent purification system. Product regiochemistry was assigned on the basis of ^{1}H NMR 2-D COSY experiments; stereochemistry was assigned on the basis of ^{1}H NMR NOE experiments. Ratios of regioisomers and/or diastereomers were determined by either ^{1}H NMR or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, and either capillary GC (known compounds) or combustion analysis (new compounds). The yields reported in Section 4 describe the result of a single experiment, whereas the yields reported in Tables 2–4 are average yields of two or more experiments. Thus, the yields reported in the Section 4 may differ from those shown in Tables 2–4.

4.2. Synthesis of *N*-protected γ-aminoalkenes

4.2.1. *N*-Pent-4-enyl-acetamide (4b).[34] A flame-dried flask was cooled under a stream of nitrogen and charged with 4-pentenoic acid (5.7 mL, 49.8 mmol). The flask was purged with nitrogen, benzene (100 mL) was added and the resulting solution was cooled to ca 10 °C using an ice water bath. Oxalyl chloride (8.7 mL, 100 mmol) was added dropwise via syringe to the solution and the resulting mixture was warmed to rt, stirred for 1 h, and then concentrated in vacuo. The crude 4-pentenoyl chloride was dissolved in THF (100 mL), and slowly added to a separate flask containing aqueous ammonium hydroxide (100 mL) at 0 °C. The resulting mixture was stirred for 6 h and then concentrated in vacuo. The mixture was diluted with H_2O (50 mL) and ethyl acetate (100 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 3.86 g (77%) of 4-pentenamide[35] as a white solid; mp 104–106 °C (lit. mp 106 °C)[35] that was used without further purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with 4-pentenamide (3.30 g, 33.3 mmol). The flask was purged with nitrogen, THF (100 mL) was added via syringe and the resulting solution was cooled to 0 °C. A solution of $LiAlH_4$ in THF (100 mL, 100 mmol, 1.0 M) was added dropwise via syringe. The reaction mixture was warmed to rt, and stirred for 36 h, then was cooled to 0 °C, quenched with H_2O (16 mL), and diluted with ether (200 mL). An aqueous solution of NaOH (30 mL, 10 M) was added and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with ether (100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and filtered to afford a solution of 4-pentenylamine[36] in diethyl ether (ca 0.1 M), which was used without further purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with a solution of 4-pentenylamine in diethyl ether (165 mL, 16.5 mmol, 0.1 M). The solution was cooled to 0 °C and acetic anhydride (4.7 mL, 5.10 g, 50 mmol) was added via syringe. The resulting mixture was stirred for 5 h and then aqueous NaOH (100 mL, 1.0 M) was added. The biphasic mixture was vigorously stirred for 12 h and then the layers were separated. The aqueous layer was extracted with ethyl acetate (3×75 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel to afford 1.36 g (65%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86–5.57 (m, 2H), 5.07–4.93 (m, 2H), 3.25 (q, J=6.0 Hz, 2H), 2.12–2.02 (m, J=5.8 Hz, 2H), 1.95 (s, 3H), 1.59 (p, J=7.7 Hz, 2H).

4.2.2. Pent-4-enyl-carbamic acid *tert*-butyl ester (4c).[37] A flame-dried round bottom flask was cooled under a stream of nitrogen and charged with a solution of 4-pentenylamine (165 mL, 16.5 mmol, 0.1 M). Di-*tert*-butyl dicarbonate (5.4 g, 25 mmol) was added to the solution and the resulting mixture was stirred for 4 h and then aqueous NaOH (100 mL, 1.0 M) was added. The biphasic mixture was vigorously stirred for 12 h and then the layers were separated. The aqueous layer was extracted with ethyl acetate (3×75 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel to afford 2.05 g (67%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80–5.70 (m, 1H), 5.01–4.90 (m, 2H), 4.54 (s, br, 1H), 3.13–2.98 (m, 2H), 2.03 (q, J=6.6 Hz, 2H), 1.52 (p, J=6.6 Hz, 2H), 1.39 (s, 9H).

4.2.3. *N*-(Pent-4-enyl)-4-methoxybenzamide (4d).[30] An oven-dried round-bottom flask was charged with 1,1′-carbonyldiimidazole (486 mg, 3.0 mmol) and then purged with argon. THF (15 mL) and 4-methoxybenzoic acid (456 mg, 3.0 mmol) were added to the flask, and the resulting mixture was stirred at rt for 1 h. A solution of 4-pentenylamine in ether (30 mL, 3.0 mmol, 0.1 M) was then added via syringe and the mixture was stirred at rt for 4 h. The reaction mixture was then diluted with ethyl acetate (15 mL) and H_2O (15 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3× 40 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 438 mg (67%) of the title compound as a white solid; mp 42–44 °C (lit. mp not reported). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 6.10 (br s, 1H), 5.85–5.75 (m, 1H), 5.05–4.95 (m, 2H), 3.80 (s, 3H), 3.41 (q, J=7.0 Hz, 2H), 2.11 (q, J=7.0 Hz, 2H), 1.68 (p, J=7.7 Hz, 2H).

4.2.4. *N*-Pent-4-enyl-4-trifluoromethyl benzamide (4f). Treatment of 570 mg (3.0 mmol) of 4-(trifluoromethyl) benzoic acid with a solution of 4-pentenylamine in ether (30 mL, 3.0 mmol) using a procedure analogous to that described above in the synthesis of **4d** afforded 475 mg (63%) of the title compound as a white solid; mp 69–71 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=8.1 Hz, 2H), 7.60 (d, J=8.1 Hz, 2H), 6.60 (s, br, 1H), 5.83–5.70 (m, 1H), 5.05–4.90 (m, 2H), 3.45–3.36 (m, 2H), 2.15–2.05 (m, 2H), 1.73–1.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 138.2, 137.8, 133.2 (q, J=41 Hz), 127.5, 125.7, 123.8 (q, J=340 Hz), 115.6, 40.0, 31.4, 28.8; IR (film) 3309, 2930, 1638, 1550 cm^{-1}. Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 60.70; H, 5.49; N, 5.44. Found: C, 60.97; H, 5.46; N, 5.40.

4.2.5. (2-Allylphenyl) carbamic acid *tert*-butyl ester (13).[38] Treatment of 904 mg (6.8 mmol) of 2-allylaniline[31] with 2.2 g (10.2 mmol) of di-*tert*-butyldicarbonate using a procedure analogous to that described above in the synthesis of **4c** (with THF used in place of diethyl ether as solvent) afforded 1.11 g (70%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=7.7 Hz, 1H), 7.20 (t, J=8.4 Hz, 1H), 7.11 (d, J=7.7 Hz, 1H), 7.02 (t, J=7.3 Hz, 1H), 6.41 (s, br, 1H), 5.97–5.88 (m, 1H), 5.14–5.00 (m, 2H), 3.33 (d, J=6.2 Hz, 2H), 1.47 (s, 9H).

4.2.6. (1-Phenylpent-4-enyl) carbamic acid *tert*-butyl ester (17). A flame-dried round bottom flask was cooled under a stream of argon and charged with 1-phenylpent-4-en-1-one[39] (11.0 g, 69.0 mmol), activated 3 Å molecular sieves (10.0 g), and methanol (200 mL). The mixture was stirred at rt for 5 min and then ammonium acetate (53 g, 690 mmol) and sodium cyanoborohydride (4.3 g, 69 mmol) were added. The flask was purged with argon and then stirred at rt for 19 h. Ether (500 mL) was added, the mixture was decanted, and the organic phase was washed with 200 mL of aqueous $NaHCO_3$. The layers were separated, the aqueous phase was extracted with ether (1×100 mL), and the combined organic layers were extracted with 1 M HCl (3×100 mL). The organic phase was discarded and the combined acidic aqueous extracts were basicified to pH 10 with 10 M NaOH and extracted with ether (3×100 mL). The combined organic extracts were diluted with hexanes (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 2.1 g (19%) of 1-phenyl-pent-4-enylamine[40] as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.36–7.29 (m, 4H), 7.27–7.21 (m, 1H), 5.87–5.76 (m, 1H), 5.05–4.94 (m, 2H), 3.92–3.87 (m, 1H), 2.14–1.96 (m, 2H), 1.84–1.70 (m, 2H), 1.52 (s, 2H).

Treatment of 1.51 g (9.4 mmol) of 1-phenylpent-4-enylamine with 2.62 g (12.0 mmol) of di-*tert*-butyl dicarbonate using a procedure analogous to that described above in the synthesis of **4c** provided 2.26 g (92%) of the title compound as a white solid; mp 76–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.16 (m, 5H), 5.83–5.70 (m, 1H), 5.02–4.91 (m, 2H), 4.88–4.74 (s, br, 1H), 4.67–4.52 (s, br, 1H), 2.10–1.92 (m, 2H), 1.90–1.71 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 143.0, 137.8, 128.8, 127.4, 126.6, 115.4, 79.6, 54.7, 36.2, 30.6, 28.6; IR (film) 3370, 2978, 1687, 1519 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.41; H, 8.78; N, 5.32.

4.2.7. *N*-(1-Phenylpent-4-enyl)-acetamide (18). Treatment of 517 mg (3.21 mmol) of 4-pentenylamine with 0.8 mL (8.03 mmol) of acetic anhydride using a procedure analogous to that described above in the synthesis of **4b** provided 530 mg (81%) of the title compound as a white solid; mp 44–46 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5H), 6.25 (d, J=8.1 Hz, 1H), 5.80–5.70 (m, 1H), 4.97–4.90 (m, 3H), 2.09–1.92 (m, 2H), 1.90 (s, 3H), 1.88–1.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 142.4, 137.8, 128.8, 127.5, 126.8, 115.4, 53.3, 35.5, 30.6, 23.5; IR (film) 3279, 2934, 1646, 1549 cm^{-1}. MS (ESI) 226.1206 (226.1208 calcd for $C_{13}H_{17}NO$, M+Na$^+$).

4.2.8. 1-Allylbut-3-enyl-carbamic acid *tert*-butyl ester (19). A flame-dried round bottom flask was cooled under a stream of nitrogen and charged with diisopropylamine (8.4 mL, 60 mmol) and THF (100 mL). The flask was cooled to −78 °C and a solution of *n*-butyllithium in hexanes (22 mL, 55 mmol, 2.5 M) was added dropwise. The mixture was stirred at −78 °C for 1 h and then acetonitrile (2.6 mL, 50 mmol) was added dropwise. The mixture was warmed to rt and stirred for 3 h, then allyl bromide (4.8 mL, 55 mmol) was added dropwise. The mixture was stirred for 1 h, then a solution of saturated aqueous ammonium chloride (50 mL) was added. The mixture was extracted with ether (3×150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a mixture of 4-cyano-1-butene, 4-cyano-4-allyl-1-butene, and 4-cyano-4,4-diallyl-1-butene (ca 50 mmol) that was used without further purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with a mixture of 4-cyano-1-butene, 4-cyano-4-allyl-1-butene, and 4-cyano-4,4-diallyl-1-butene (ca 50 mmol). The flask was purged with nitrogen, ether (200 mL) was added via syringe and the resulting solution was cooled to 0 °C. A solution of $LiAlH_4$ in ether (150 mL, 150 mmol, 1.0 M) was added dropwise via syringe. The reaction mixture was warmed to rt and stirred for 12 h, then was cooled to 0 °C, quenched with H_2O (30 mL), and diluted with ether (150 mL). An aqueous

solution of NaOH (80 mL, 10 M) was added and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the solution was dried over anhydrous sodium sulfate and filtered to afford a mixture of 4-pentenylamine, 3-allyl-4-pentenylamine, and 3,3-diallyl-4-pentenylamine as a solution in diethyl ether (550 mL, ca 0.1 M). This mixture was used without further purification.

A solution containing a mixture of 4-pentenylamine, 3-allyl-4-pentenylamine, and 3,3-diallyl-4-pentenylamine in ether (100 mL, 10 mmol, 0.1 M) was treated with 2.62 g (12 mmol) of di-*tert*-butyl dicarbonate using a procedure analogous to that described above in the synthesis of **4c**. The three products were separated by flash chromatography on silica gel to afford 675 mg (30%) of **19** as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80–5.67 (m, 2H), 5.04–4.96 (m, 4H), 4.52 (s, br, 1H), 3.03 (t, $J=6.2$ Hz, 2H), 2.08–1.94 (m, 4H), 1.72–1.57 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 136.5, 116.8, 79.9, 43.7, 38.3, 36.2, 28.6; IR (film) 3351; 2978, 1694, 1515 cm^{-1}. Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.27; H, 10.26; N, 6.22.

4.2.9. (3-Methylpent-4-enyl)-carbamic acid *tert*-butyl ester (20). 3-Methyl-pent-4-enoic acid[41] (3.33 g, 29.2 mmol) was converted to 3.0 g (52%) of the title compound using a four-step procedure analogous to that described above for the conversion of 4-pentenoic acid to **4c**. The product was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62–5.53 (m, 1H), 4.90–4.82 (m, 2H), 4.59 (s, br, 1H), 3.09–2.91 (m, 2H), 2.15–2.02 (m, 1H), 1.44–1.27 (m, 11H), 0.91 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 143.9, 113.4, 79.0, 38.9, 36.7, 35.8, 28.5, 20.3; IR (film) 3351, 2977, 1694, 1526 cm^{-1}. Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.04; H, 10.60; N, 6.97.

4.2.10. *N*-(3-Methylpent-4-enyl) acetamide (21). Treatment of a solution of 3-methyl-4-pentenylamine in ether (100 mL, 10 mmol, 0.1 M) with 3 mL (30 mmol) of acetic anhydride using a procedure analogous to that described above in the synthesis of **4b** provided 720 mg (51%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (s, br, 1H), 5.61–5.52 (m, 1H), 4.90–4.82 (m, 2H), 3.15–3.07 (m, 2H), 2.13–2.03 (m, 1H), 1.85 (s, 3H), 1.46–1.32 (m, 2H); 0.90 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 143.8, 113.5, 38.0, 36.2, 35.9, 23.3, 20.4; IR (film) 3290, 2964, 1649, 1558 cm^{-1}. MS (ESI) 142.1228 (142.1232 calcd for $C_8H_{16}NO$, $M+H^+$).

4.2.11. (2-Cyclopent-2-enylethyl) carbamic acid *tert*-butyl ester (22). Cyclopent-2-enyl-acetic acid (3.0 g, 23.8 mmol) was converted to 2.41 g (48%) of the title compound using a four-step procedure analogous to that described above the conversion of 4-pentenoic acid to **4c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69–5.65 (m, 1H), 5.62–5.57 (m, 1H), 4.52 (s, br, 1H), 3.16–2.99 (m, 2H), 2.67–2.56 (m, 1H), 2.34–2.15 (m, 2H), 2.06–1.94 (m, 1H), 1.59–1.48 (m, 1H), 1.45–1.31 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 134.5, 131.0, 79.2, 43.2, 39.5, 36.4, 32.1, 29.9, 28.6; IR (film) 3351, 2977, 1692, 1524 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 67.99; H, 10.06; N, 6.63.

4.2.12. *N*-(2-Cyclopent-2-enylethyl) acetamide (23). Cyclopent-2-enyl-acetic acid (2.0 g, 15.9 mmol) was converted to 1.27 g (52%) of the title compound using a four-step procedure analogous to that described above the conversion of 4-pentenoic acid to **4b**. The product was obtained as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (s, br, 1H), 5.68–5.63 (m, 1H), 5.59–5.55 (m, 1H), 3.18 (q, $J=7.3$ Hz, 2H), 2.65–2.55 (m, 1H), 2.33–2.14 (m, 2H), 2.03–1.93 (m, 1H), 1.89 (s, 3H), 1.59–1.49 (m, 1H), 1.45–1.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 134.3, 131.1, 43.3, 38.5, 35.8, 32.1, 29.8, 23.4; IR (film) 3289, 2932, 1653, 1559 cm^{-1}. MS (ESI) 153.1154 (153.1153 calcd for $C_9H_{15}NO$).

4.3. General procedures for the Pd-catalyzed synthesis of pyrrolidines

General procedure A: Palladium-catalyzed synthesis of pyrrolidines and indolines using Pd(OAc)$_2$. A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2 mol%) and a bidentate phosphine ligand (4 mol%). The tube was purged with nitrogen and toluene was added (2 mL/mmol amine). The mixture was stirred at rt for ~2 min then the aryl bromide (1.2 equiv) was added followed by a solution of the amine (1 equiv) in toluene (2 mL/mmol amine). The mixture was allowed to stir ~1 min before the addition of NaO*t*Bu (2.0 equiv). The tube was purged with nitrogen and the sides of the flask were rinsed with toluene (2 mL/mmol amine; final concentration = 0.17 M). The mixture was heated to 65 °C with stirring until the starting material had been consumed as judged by GC or ^{1}H NMR analysis. The reaction mixture was cooled to rt, quenched with saturated aqueous NH_4Cl and diluted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel.

General procedure B: Palladium-catalyzed synthesis of pyrrolidines and indolines using Pd$_2$(dba)$_3$. A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol% complex, 2 mol% Pd), a bidentate phosphine ligand (2 mol%), NaO*t*Bu (1.2 equiv), and the aryl bromide (1.1 equiv). The tube was purged with nitrogen and a solution of the amine substrate (1.0 equiv) in toluene (4 mL/mmol amine) was added. The mixture was heated to 105 °C with stirring until the starting material had been consumed as judged by GC or ^{1}H NMR analysis. The reaction mixture was cooled to rt, quenched with saturated aqueous NH_4Cl and diluted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel.

4.3.1. (4-Methoxyphenyl)-(2-naphthalen-2-ylmethyl-pyrrolidin-1-yl) methanone (5d). Reaction of 52 mg

(0.25 mmol) of **4d** with 2-bromonaphthalene (57 mg, 0.28 mmol), dpe-phos (2.7 mg, 0.005 mmol, 2 mol%) and NaO*t*Bu (29 mg, 0.30 mmol) following general procedure B afforded 54.3 mg (63%) of the title compound as a pale yellow oil that was contaminated with ca 5% of Heck-type side product **6d**. The title compound was found to exist as a ca 9:1 mixture of rotamers as judged by ^{1}H NMR analysis. Data are for the major rotamer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.58 (m, 4H), 7.57–7.30 (m, 5H), 6.88 (d, $J=8.8$ Hz, 2H), 4.62–4.49 (m, 1H), 3.80 (s, 3H), 3.45–3.30 (m, 2H), 3.26–3.14 (m, 1H), 3.13–3.00 (m, 1H), 2.01–1.83 (m, 1H), 1.82–1.51 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 161.2, 136.4, 133.7, 132.4, 129.6, 128.7, 128.4, 127.9, 127.8, 127.7, 126.1, 125.5, 113.7, 58.7, 55.5, 51.1, 39.0, 29.6, 25.3 (two aromatic signals are incidentally equivalent); IR (film) 2967, 1608, 1420 cm^{-1}. MS (ESI) 368.1625 (368.1626 calcd for $C_{23}H_{23}NO_2$, M+Na$^+$).

4.3.2. (2-Naphthalen-2-ylmethylpyrrolidin-1-yl) phenylmethanone (5e). Reaction of 48 mg (0.25 mmol) of **4e** with 2-bromonaphthalene (57 mg, 0.28 mmol), dpe-phos (2.7 mg, 0.005 mmol, 2 mol%) and NaO*t*Bu (29 mg, 0.30 mmol) following general procedure B afforded 38 mg (48%) of the title compound as a pale yellow oil. This compound was found to exist as a 4:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.78 (m, 3H), 7.78–7.74 (m, 0.2H), 7.72 (s, 0.8H), 7.70–7.60 (m, 0.8H), 7.56–7.42 (m, 1.4H), 7.50–7.38 (m, 5.8H), 7.19 (s, 0.2H), 6.74–6.68 (m, 0.2H), 4.62–4.52 (m, 1H), 4.20–4.11 (m, 0.2H), 3.78–3.67 (m, 0.4H), 3.43–3.29 (m, 1.6H), 3.22–3.13 (m, 0.8H), 3.12–3.03 (m, 0.8H), 2.77–2.18 (m, 0.2H), 2.61–2.50 (m, 0.2H), 2.04–1.88 (m, 1H), 1.87–1.73 (m, 1H), 1.72–1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 137.6, 136.4, 135.8, 133.7, 132.4, 130.2, 129.6, 128.7, 128.5, 128.3, 128.0, 127.8, 127.7, 127.5, 127.3, 126.7, 126.2, 126.1, 125.7, 125.5, 60.9, 58.7, 50.9, 46.0, 41.2, 39.0, 29.9, 29.5, 25.1, 22.1 (three sets of carbons are incidentally equivalent); IR (film) 2968, 1625, 1412 cm^{-1}. MS (ESI) 338.1519 (338.1521 calcd for $C_{22}H_{21}NO$, M+Na$^+$).

4.3.3. 2-Napthalen-2-ylmethylpyrrolidine-1-carboxylic acid *tert*-butyl ester (5c). Reaction of 93 mg (0.50 mmol) of **4c** with 2-bromonaphthalene (124 mg, 0.60 mmol), dpe-phos (11 mg, 0.02 mmol 4 mol%) and NaO*t*Bu (96 mg, 1.0 mmol) following general procedure A afforded 120 mg (77%) of the title compound as a pale yellow oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.74 (m, 3H), 7.78–7.58 (m, 1H), 7.51–7.30 (m, 3H), 4.21–4.02 (m, 1H), 3.46–3.18 (m, 3H), 2.78–2.63 (m, 1H), 1.73 (m, 4H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 137.0, 133.8, 132.3, 128.5, 128.2, 128.0, 127.8, 127.7, 126.2, 126.1, 125.6 125.5, 79.5, 79.3, 59.0, 47.1, 46.5, 41.0, 39.9, 29.9, 29.1, 28.8, 23.7, 22.9 (nine sets of carbons are incidentally equivalent); IR (film) 3052, 2973, 1692, 1395 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.78; H, 8.24; N, 4.57.

4.3.4. 2-(2-Methylbenzyl) pyrrolidine-1-carboxylic acid *tert*-butyl ester (8). Reaction of 93 mg (0.5 mmol) of **4c** with 2-bromotoluene (66 μL, 94 mg, 0.55 mmol), dpe-phos (5.4 mg, 0.01 mmol, 2 mol%) and NaO*t*Bu (58 mg, 0.6 mmol) following general procedure B afforded 112 mg (81%) of the title compound as a pale yellow oil. This compound was found to exist as a 2:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.08 (m, 4H), 4.02 (s, br, 1H), 3.42–3.02 (m, 3H), 2.50–2.29 (m, 4H), 1.92–1.59 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8; 154.2, 137.9, 137.2, 130.7, 130.5, 126.9, 126.6, 126.1, 79.7, 79.6, 57.5, 46.9. 46.4, 38.5, 37.7, 37.0, 29.7, 29.2, 28.8, 28.7, 23.7, 22.8, 20.0, 19.9 (three sets of signals are incidentally equivalent); IR (film) 2973, 1693, 1394 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.84; H, 9.16; N, 5.10.

4.3.5. 2-(4-Cyanobenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (9). Reaction of 185 mg (1.00 mmol) of **4c** with 4-bromobenzonitrile (200 mg, 1.10 mmol), dppb (8.8 mg, 0.02 mmol, 2 mol%) and NaO*t*Bu (116 mg, 1.20 mmol) following general procedure B afforded 203 mg (71%) of the title compound as a pale yellow oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2H), 7.26–7.22 (m, 2H), 3.80–3.97 (m, 1H), 3.35–2.95 (m, 4H), 2.62–2.55 (m, 1H), 1.81–1.52 (m, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 145.1, 132.6, 132.2, 130.4, 128.2, 119.0, 110.3, 79.5, 58.4, 46.81, 46.79, 41.0, 40.1, 30.1, 28.9, 28.7, 23.6, 22.9 (five sets of signals are incidentally equivalent); IR (film) 2974, 2228, 1690, 1395 cm^{-1}. Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.15; H, 7.82; N, 9.69.

4.3.6. 2-(3-Phenylallyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (10). Reaction of 93 mg (0.50 mmol) of **4c** with β-bromostyrene (80 μL, 110 mg, 0.60 mmol), dppe (8 mg, 0.02 mmol, 4 mol%) and NaO*t*Bu (96 mg, 1.00 mmol) following general procedure A afforded 108 mg (79%) of the title compound as a pale yellow oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.10 (m, 5H), 6.38 (d, $J=16.0$ Hz, 1H), 6.20–6.05 (m, 1H), 3.90–3.78 (m, 1H), 3.42–3.32 (m, 2H), 2.71–2.52 (m, 1H), 2.32–2.23 (m, 1H), 1.95–1.73 (m, 4H); 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 138.0, 137.7, 132.4, 128.7, 127.2, 126.2, 79.39, 79.36, 57.4, 46.9, 46.6, 38.4, 37.6, 30.5, 29.6, 28.8, 23.9, 23.2 (nine sets of signals are incidentally equivalent); IR (film) 2972, 1693, 1394 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.24; H, 8.59; N, 4.81.

4.3.7. 1-(2-Naphthalen-2-ylmethylpyrrolidin-1-yl) ethanone (5b). Reaction of 32 mg (0.25 mmol) of **4b** with 2-bromonaphthalene (57 mg, 0.28 mmol), dpe-phos (2.7 mg, 0.005 mmol, 2 mol%) and NaO*t*Bu (29 mg, 0.30 mmol) following general procedure B afforded 44 mg (70%) of the title compound as a pale yellow oil. This compound was found to exist as a 7:3 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.78 (m, 3H), 7.66 (s, 0.3H), 7.60 (s, 0.3H), 7.51–7.40 (m, 3H), 4.45–4.38 (m, 0.7H), 4.15–4.08 (m, 0.3H), 3.63–3.48 (m, 0.7H), 3.43–3.31

(m, 2H), 3.07–3.00 (m, 0.3H), 2.84–2.70 (m, 1H), 2.14–2.03 (m, 3H), 1.96–1.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 169.4, 137.0, 135.7, 135.7, 133.8, 132.5, 132.4, 128.7, 128.4, 128.15, 128.05, 128.03, 127.94, 127.87, 127.76, 127.72, 126.5, 126.2, 126.0, 125.6, 60.3, 58.6, 48.2, 45.8, 41.2, 39.1, 30.3, 28.7, 24.0, 23.4, 22.4, 22.1 (one set of carbons are incidentally equivalent); IR (film) 2968, 1637, 1417 cm^{-1}. MS (ESI) 276.1359 (276.1364 calcd for $C_{17}H_{19}NO$, M+Na$^+$).

4.3.8. 1-[2-(4-Benzoylbenzyl)pyrrolidin-1-yl]ethanone (11). Reaction of 32 mg (0.25 mmol) of **4b** with 4-bromobenzophenone (72 mg, 0.28 mmol), dppe (2.0 mg, 0.005 mmol, 2 mol%) and NaO*t*Bu (29 mg, 0.30 mmol) following the general procedure B afforded 61 mg (80%) of the title compound as a pale yellow oil. This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.64 (m, 4H), 7.58–7.51 (m, 1H), 7.47–7.40 (m, 2H), 7.32–7.22 (m, 2H), 4.34–4.26 (m, 0.75H), 4.08–4.00 (m, 0.25H), 3.60–3.32 (m, 2H), 3.24 (dd, J=3.3, 12.8 Hz, 0.75H), 2.92 (dd, J=5.1, 13.6 Hz, 0.25H), 2.72 (m, 0.25H), 2.67–2.60 (m, 0.75H), 2.20–2.05 (m, 0.75H), 2.06–1.98 (m, 3H), 1.90–1.74 (m, 3.25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 196.6, 169.6, 169.5, 144.5, 143.0, 138.3, 138.0, 136.2, 135.8, 132.7, 132.5, 130.8, 130.5, 130.2, 129.6, 129.4, 128.5, 128.4, 60.0, 58.4, 48.2, 45.7, 41.1, 39.0, 30.3, 28.7, 24.0, 23.2, 22.3, 22.0 (one set of carbons are incidentally equivalent); IR (film) 2960, 1638, 1414 cm^{-1}. MS (ESI) 330.1466 (330.1470 calcd for $C_{20}H_{21}NO_2$, M+Na$^+$).

4.3.9. 1-[2-(4-Dimethylaminobenzyl)pyrrolidin-1-yl]-ethanone (12). Reaction of 32 mg (0.25 mmol) of **4b** with *N*,*N*-dimethyl-4-bromoaniline (55 mg, 0.28 mmol), xantphos (2.9 mg, 0.005 mmol, 2 mol%) and NaO*t*Bu (29 mg, 0.30 mmol) following general procedure B afforded 42 mg (67%) of the title compound as a pale yellow oil. This compound was found to exist as a 3:2 mixture of rotamers as judged by ^{1}H NMR analysis. This material contained ca 15% of the corresponding 2,3-dihydropyrrole (1-[5-(4-dimethylaminobenzyl)-2,3-dihydropyrrol-1-yl]ethanone), which could not be separated by chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–6.95 (m, 2H), 6.72–6.57 (m, 2H), 4.32–4.20 (m, 0.6H), 4.01–3.88 (m, 0.4H), 3.57–3.39 (m, 0.8H), 3.38–3.29 (m, 1.2H), 3.06–2.98 (m, 0.6H), 2.93–2.85 (m, 6H), 2.77–2.70 (m, 0.4H), 2.57–2.43 (m, 1H), 2.07–1.95 (m, 3H), 1.89–1.67 (m, 4H); ^{13}C NMR (125 MHz, CD_3OH) δ 170.9, 170.6, 150.1, 149.8, 129.9, 129.8, 113.4 113.3, 112.6, 112.4, 60.9, 59.0, 45.3, 40.1, 40.0, 39.9, 39.8, 39.1, 38.9, 36.9, 23.1, 21.5, 21.33, 21.28, 20.6; IR (film) 2930, 1638, 1417 cm^{-1}. MS (ESI) 269.1361 (269.1630 calcd for $C_{15}H_{22}N_2O$, M+Na$^+$).

4.3.10. 2-Naphthalen-2-ylmethyl-2,3-dihydroindole-1-carboxylic acid *tert*-butyl ester (15). Reaction of 59 mg (0.25 mmol) of **13** with 2-bromonaphthalene (57 mg, 0.28 mmol), dpe-phos (2.7 mg, 0.005 mmol, 2 mol%) and NaO*t*Bu (29 mg, 0.30 mmol) following general procedure B afforded 44 mg (50%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.76 (m, 3H), 7.63 (s, 1H), 7.48–7.34 (m, 4H), 7.22–7.30 (m, 2H), 6.94 (t, J=7.3 Hz, 1H), 4.71 (s, br, 1H), 3.41 (s, br, 1H) 3.21–3.00 (m, 1H), 2.81–2.67 (m, 2H), 1.59 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 142.2, 135.7, 133.8, 132.5, 130.2, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 126.2, 125.7, 125.3, 122.7, 115.6, 81.1, 60.8, 40.6, 31.7, 28.7; IR (film) 2974, 1702, 1483, 1392 cm^{-1}. MS (ESI) 382.1787 (382.1783 calcd for $C_{24}H_{25}NO_2$, M+Na$^+$).

4.3.11. 1-Benzyl-2-(4-methylbenzyl)-2,3-dihydro-1*H*-indole (16). Reaction of 65 mg (0.29 mmol) of **14** with 4-bromotoluene (40 μL, 55 mg, 0.32 mmol), nixantphos (3.2 mg, 0.0058 mmol, 2 mol%) and NaO*t*Bu (34 mg, 0.30 mmol) following general procedure B afforded 44 mg (48%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.22 (m, 5H), 7.07–6.94 (m, 6H), 6.59 (t, J=7.0 Hz, 1H), 6.33 (d, J=7.7 Hz, 1H), 4.46 (d, J=16.1 Hz, 1H), 4.24 (d, J=16.1 Hz, 1H), 3.86–3.78 (m, 1H), 3.12 (dd, J=4.0, 13.2 Hz, 1H), 2.96–2.89 (m, 1H), 2.78–2.62 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 139.2, 136.0, 135.6, 129.33 129.29, 128.69, 128.67 127.56, 127.54, 127.2, 124.4, 117.7, 107.1, 66.7, 51.8, 40.1, 35.1, 21.2; IR (film) 2921, 2360, 1484 cm^{-1}. MS (ESI) 314.1901 (314.1909 calcd for $C_{23}H_{23}N$, M+H$^+$).

4.3.12. (±)-(2*S*,5*R*)-2-(4-Methoxybenzyl)-5-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (24). Reaction of 261 mg (1.00 mmol) of **17** with 4-bromoanisole (140 μL, 206 mg, 1.1 mmol), dppb (8.0 mg, 0.02 mmol, 2 mol%) and NaO*t*Bu (116 mg, 1.20 mmol) following general procedure B afforded 219 mg (60%) of the title compound as a pale yellow oil. This compound was found to exist as a 7:3 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.05 (m, 7H), 6.82 (d, J=8.4 Hz, 2H), 4.97–4.61 (m, 1H), 4.22–3.98 (m, 1H), 3.76 (s, 3H), 3.56–3.29 (m, 1H), 2.59 (t, J=11.4 Hz, 1H), 2.22 (sx, J=6.6 Hz, 1H), 1.97–1.81 (m, 1H), 1.82–1.66 (m, 2H), 1.62–1.04 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 155.1, 131.6, 130.5, 128.5, 128.3, 126.6, 125.8, 114.1, 79.5, 63.3, 61.3, 55.4, 40.6, 34.4, 28.5 (nine sets of carbons are incidentally equivalent); IR (film) 2974, 1686, 1454 cm^{-1}. MS (ESI) 390.2038 (390.2045 calcd for $C_{23}H_{29}NO_3$, M+Na$^+$).

4.3.13. (±)-(2*S*,5*R*)-1-(2-Phenyl-5-pyridin-3-ylmethyl-pyrrolidin-1-yl) ethanone (25). Reaction of 51 mg (0.25 mmol) of **18** with 3-bromopyridine (27 μL, 43.5 mg, 0.28 mmol), dppb (2.2 mg, 0.005 mmol, 2 mol%) and NaO*t*Bu (29 mg, 0.3 mmol) following general procedure B afforded 57.2 mg (82%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49–8.41 (m, 2H), 7.67–7.62 (m, 1H), 7.38–7.18 (m, 6H), 4.85 (t, J=7.3 Hz, 1H), 4.41–4.34 (m, 1H), 3.62 (dd, J=7.3, 12.8 Hz, 1H), 2.59 (dd, J=10.6, 12.8 Hz, 1H), 2.34 (sx, J=7.6 Hz, 1H), 2.03–1.94 (m, 1H), 1.80–1.72 (m, 4H), 1.66–1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 150.6, 148.1, 143.2, 137.0, 134.8, 129.2, 127.6, 125.7, 123.7, 64.1, 60.6, 37.6, 35.5, 28.2, 23.4; IR (film) 2968, 1643, 1404 cm^{-1}. MS (ESI) 281.1653 (281.1654 calcd for $C_{18}H_{20}N_2O$, M+H$^+$).

4.3.14. 4-Allyl-2-(4-*tert*-butoxycarbonyl-benzyl) pyrrolidine-1-carboxylic acid *tert*-butyl ester (26). Reaction of 57 mg (0.25 mmol) of **19** with 4-bromo-*tert*-butyl benzoate (71 mg, 0.28 mmol), dpe-phos (2.7 mg, 0.005 mmol, 2 mol%) and NaO*t*Bu (29 mg, 0.3 mmol) following general procedure B afforded 80 mg (70%) of the title compound as

a pale yellow oil. This product was isolated as a ca 3:1 mixture of diastereomers. Data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.79 (m, 2H), 7.17 (s, br, 2H), 5.72–5.57 (m, 1H), 4.99–4.86 (m, 2H), 4.06–2.83 (m, br, 3H), 2.76–2.48 (m, 2H), 2.07–1.88 (m, 4H), 1.57–1.40 (m, 18H), 1.27–1.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 157.5, 154.7, 149.5, 146.2, 143.8, 136.4, 130.2, 129.7, 116.3, 116.2, 81.0, 79.4, 77.6, 77.2, 76.9, 58.7, 52.7, 52.1, 51.7, 41.8, 41.0, 40.1, 37.9, 37.7, 37.3, 37.0, 36.3, 35.6, 34.9, 28.8, 28.4; IR (film) 2976, 1712, 1694, 1395 cm^{-1}. Anal. Calcd for $C_{24}H_{35}NO_4$: C, 71.79; H, 8.79; N, 3.49. Found: C, 71.60; H, 8.75; N, 3.45.

4.3.15. (±)-(2*R*,3*S*)-3-Methyl-2-naphthalen-2-ylmethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (27). The reaction of 100 mg (0.5 mmol) of **20** with 2-bromonaphthalene (124 mg, 0.60 mmol), dpe-phos (10.8 mg, 0.02 mmol, 4 mol%) and NaO*t*Bu (96 mg, 1.00 mmol) was conducted following general procedure A. ^{1}H NMR analysis of the crude product showed the formation of the desired product as a 10:1 mixture of diastereomers. The minor diastereomer was separated upon chromatographic purification to afford 106 mg (65%) of the title compound as a white solid with >20:1 dr; mp 107 °C. Data are for the major diastereomer, which was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.73 (m, 3H), 7.62 (d, J=16.3 Hz, 1H), 7.50–7.28 (m, 3H), 3.78–3.60 (m, 1H), 3.61–3.38 (m, 1H), 3.33–3.08 (m, 2H), 2.96–2.73 (m, 1H), 2.15–2.09 (m, 1H), 1.98–1.80 (m, 1H), 1.53 (s, 9H), 1.49–1.34 (m, 1H), 0.84 (s, br, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 136.8, 133.7, 132.3, 128.6, 128.2, 128.0, 127.8, 127.7, 126.2, 126.0, 125.5, 125.4, 79.6, 79.5, 66.0, 65.7, 45.7, 45.0, 40.6, 39.1, 37.0, 36.1, 31.3, 30.4, 28.8, 19.6, 19.4 (seven sets of carbons are incidentally equivalent); IR (film) 2964, 1692, 1396 cm^{-1}. MS (ESI) 348.1943 (348.1939 calcd for $C_{21}H_{27}NO_2$, M+Na^+).

4.3.16. (±)-(2*R*,3*S*)-2-(4-*tert*-Butylbenzyl)-3-methyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (28). The reaction of 100 mg (0.5 mmol) of **20** with 4-bromo-*tert*-butylbenzene (105 μL, 128 mg, 0.60 mmol), dpe-phos (10.8 mg, 0.02 mmol, 4 mol%) and NaO*t*Bu (96 mg, 1.00 mmol) was conducted following general procedure A. ^{1}H NMR analysis of the crude product showed the formation of the desired product as a 10:1 mixture of diastereomers. The minor diastereomer was separated upon chromatographic purification to afford 97.4 mg (59%) of the title compound as a pale yellow oil with >20:1 dr. Data are for the major diastereomer, which was found to exist as a 3:2 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (m, 2H), 7.16–7.06 (m, 2H), 3.69–3.37 (m, 2H), 3.31–2.92 (m, 2H), 2.76–2.56 (m, 1H), 2.05 (s, br, 1H), 1.97–1.79 (m, 1H), 1.51 (s, 9H), 1.45–1.35 (m, 1H), 1.32 (s, 9H), 0.88 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 149.2, 149.0, 136.1, 129.5, 129.3, 125.5, 125.3, 79.4, 79.1, 66.1, 65.6, 45.6, 45.0, 39.9, 38.5, 37.1, 36.0, 34.6, 31.6, 31.2, 30.4, 28.8, 19.7, 19.5 (five sets of carbons are incidentally equivalent); IR (film) 2963, 1696, 1395 cm^{-1}. MS (ESI) 354.2402 (354.2409 calcd for $C_{21}H_{33}NO_2$, M+Na^+).

4.3.17. (±)-(2*R*,3*S*)-1-[2-(4-Chlorobenzyl)-3-methyl pyrrolidin-1-yl]ethanone (29). The reaction of 72 mg (0.5 mmol) of **21** with 4-bromochlorobenzene (106 mg, 0.55 mmol), dpe-phos (10.8 mg, 0.02 mmol, 4 mol%) and NaO*t*Bu (58 mg, 1.00 mmol) was conducted following general procedure B. ^{1}H NMR analysis of the crude product showed the formation of the desired product as a 10:1 mixture of diastereomers. The minor diastereomer was separated upon chromatographic purification to afford 69.4 mg (61%) of the title compound as a pale yellow oil with >20:1 dr. Data are for the major diastereomer, which was found to exist as a 7:3 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.16 (m, 2H), 7.12–7.00 (m, 2H), 3.86–3.78 (m, 0.7H), 3.71–3.60 (m, 0.3H), 3.55–3.48 (m, 0.3H), 3.47–3.29 (m, 1H), 3.26–3.16 (m, 0.7H), 3.08–2.98 (m, 0.7H), 2.81–2.73 (m, 0.3H), 2.72–2.57 (m, 1H), 2.14–2.08 (m, 0.3H), 2.07–1.95 (m, 3.1H), 1.92–1.84 (m, 1.6H), 1.52–1.38 (m, 1H), 0.89–0.80 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.7, 137.5, 136.5, 132.8, 132.1, 131.1, 130.7, 129.1, 128.6, 67.4, 65.3, 46.9, 44.1, 40.6, 37.7, 37.2, 35.6, 31.4, 29.1, 23.2, 22.2, 19.8, 19.3; IR (film) 2961, 1641, 1417 cm^{-1}. MS (ESI) 274.0969 (274.0975 calcd for $C_{14}H_{18}ClNO$, M+Na^+).

4.3.18. (±)-(3a*R*,6*S*,6a*S*)-6-Biphenyl-4-yl-hexahydro-cyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (30). Reaction of 53 mg (0.25 mmol) of **22** with 4-bromobiphenyl (64 mg, 0.28 mmol), xantphos (5.8 mg, 0.01 mmol, 4 mol%) and NaO*t*Bu (36 mg, 0.38 mmol) following general procedure A afforded 42.8 mg (47%) of the title compound as a white solid; mp 128 °C. This compound was found to exist as a 3:2 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.34 (m, 6H), 7.32–7.16 (m, 3H), 4.54–4.30 (m, 1H), 3.83–3.71 (m, 0.6H), 3.55–3.17 (m, 1.4H), 3.10–2.78 (m, 2H), 2.12–1.98 (m, 1H), 1.97–1.60 (m, 5H), 1.21–0.89 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 141.6, 141.2, 139.4, 129.6, 128.9, 127.2, 127.1, 127.0, 126.6, 94.6, 79.0, 65.4, 52.3, 51.2, 47.8, 43.5, 42.5, 34.2, 33.7, 32.4, 32.2, 31.8, 28.4, 27.9 (thirteen sets of carbons are incidentally equivalent); IR (film) 2952, 1689, 1392 cm^{-1}. MS (ESI) 386.2105 (386.2096 calcd for $C_{24}H_{29}NO_2$, M+Na^+).

4.3.19. (±)-(3a*R*,6*S*,6a*S*)-1-(6-Naphthalen-2-yl-hexa-hydrocyclopenta[*b*]pyrrol-1-yl) ethanone (31). Reaction of 78 mg (0.25 mmol) of **23** with 2-bromonaphthalene (114 mg, 0.55 mmol), nixantphos (13.8 mg, 0.025 mmol, 5 mol%), $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol, 2.5 mol%) and NaO*t*Bu (58 mg, 0.60 mmol) following general procedure B afforded 85 mg (61%) of the title compound as a pale yellow oil. This compound was found to exist as a 7:3 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.69 (m, 3H), 7.57 (s, 1H), 7.48–7.34 (m, 2H), 7.28–7.24 (m, 1H), 4.90 (t, J=8.6 Hz, 0.3H), 4.43 (t, J=7.0 Hz, 0.7H), 4.14–4.06 (m, 0.70H), 3.54 (q, J=8.1 Hz, 0.3H), 3.48–3.20 (m, 2H), 3.13–3.04 (m, 0.7H), 2.92–2.82 (m, 0.3H), 2.17–1.92 (m, 4H), 1.85–1.72 (m, 2H), 1.64 (s, 0.6H), 1.11 (s, 2.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 168.8, 139.2, 138.2, 133.6, 133.5, 132.7, 132.4, 128.31, 128.29, 128.1, 127.91, 127.90, 129.86, 127.81, 127.2, 127.0, 126.6, 126.4, 125.9, 125.8, 125.3, 67.0, 65.2, 53.4, 49.9, 49.1, 47.4, 44.0, 42.3, 33.7, 32.6, 32.4, 32.3, 32.2, 31.4, 22.5, 21.8; IR (film) 2950, 1638,

1413 cm^{-1}. MS (ESI) 302.1523 (302.1521 calcd for $C_{19}H_{21}NO$, $M+Na^+$).

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References and notes

1. (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446. (b) Lewis, J. R. *Nat. Prod. Rep.* **2001**, *18*, 95–128.
2. (a) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862–2892 and earlier reviews in this series. (b) Pichon, M.; Figadére, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927–964.
3. For examples of pyrrolidine synthesis that involve intramolecular C–N bond formation and intermolecular C–C bond formation, see: (a) Tamaru, Y.; Kimura, M. *Synlett* **1997**, 749–757. (b) Tamaru, Y.; Hojo, M.; Yoshida, Z.-i. *J. Org. Chem.* **1988**, *53*, 5731–5741. (c) Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. B. *Chem. Soc. Jpn.* **2001**, *74*, 1963–1970. (d) Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172–4178.
4. Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605–3608.
5. For related transformations that afford indoline or tetrahydrofuran products, see: (a) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906–13907. (b) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620–1621.
6. Several examples of cleavage of *p*-methoxyphenyl groups from nitrogen have been described. However, these transformations are typically facilitated by the use of strong oxidants and exhibit relatively low functional group tolerance. See: (a) Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett.* **2000**, *2*, 1891–1894. (b) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett.* **2003**, *5*, 1809–1812. (c) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1999**, *10*, 221–223.
7. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.
8. Dpe-phos = bis(2-diphenylphosphinophenyl) ether. Dppf = 1,1′-bis(diphenylphosphinoferrocene). Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino) xanthene. Dppe = 1,2-bis(diphenylphosphino) ethane. Dppb = 1,4-bis(diphenylphosphino) butane. Nixantphos = 4,6-bis(diphenylphosphino) phenoxazine.
9. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
10. For reviews on Pd-catalyzed *N*-arylation of amines, which involve $Pd(Ar)(NR_2)$ intermediates, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209. (b) Hartwig, J. F. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinhem, Germany, 2002; pp 107–168.
11. Balme has previously described the Pd/dppp-catalyzed Heck arylation of **4a** with iodobenzene. See: Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1990**, *46*, 7763–7774.
12. Tom, N. J.; Simon, W. M.; Frost, H. N.; Ewing, M. *Tetrahedron Lett.* **2004**, *45*, 905–906.
13. Control experiments demonstrated the Boc-cleavage is base-induced (not Pd-catalyzed). See Ref. 12.
14. The product isolated from this reaction contained ca 15% of the corresponding dihydropyrrole. Similar side reactions have been previously observed in reactions of 2-allylaniline or γ-*N*-arylaminoalkenes with electron-rich aryl bromides. See Refs. 4,5a.
15. Ney, J. E.; Wolfe, J. P. Unpublished results.
16. For recent studies on Pd-catalyzed *N*-vinylation of amines, See: Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2004**, *10*, 494–507.
17. The base induced substrate olefin isomerization was only observed in reactions of 2-allylaniline derivatives.
18. For Pd-catalyzed oxidative amination reactions that afford indole products, see: (a) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807. (b) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3585.
19. Proton NMR analysis of crude reaction mixtures revealed diastereomer ratios of 10–20:1; the minor diastereomer was usually readily separated by chromatography to provide isolated products with >20:1 dr. Thus, diastereomeric ratios reported in Table 4 represent ratios of diastereomers for the isolated material upon which the yield is based. The diastereomeric ratios observed in crude reaction mixtures were >20:1 for 2,5-disubstituted pyrrolidines, >20:1 for 6-substituted hexahydrocyclopenta[*b*]pyrroles, and ca 10:1 for 2,3-disubstituted pyrrolidines.
20. The relative stereochemistry of the pyrrolidine products was assigned on the basis of ^1H NMR NOE experiments. Diastereomeric ratios were determined by GC and/or ^1H NMR analysis.
21. The Pd/dpe-phos-catalyzed reaction of a *N*-Boc protected substrate bearing an internal acyclic alkene afforded a single pyrrolidine product, albeit in low yield (ca 20%).
22. (a) Boncella, J. M.; Villanueva, L. A. *J. Organomet. Chem.* **1994**, *465*, 297–304. (b) Villanueva, L. A.; Abboud, K. A.; Boncella, J. M. *Organometallics* **1992**, *11*, 2963–2965. (c) Helaja, J.; Göttlich, R. *J. Chem. Soc., Chem. Commun.* **2002**, 720–721. (d) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **1999**, 45–46.
23. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981–4991.
24. Although we currently favor this mechanistic hypothesis, an alternate mechanism involving alkene insertion into the Pd–C bond of **33** followed by C–N bond-forming reductive elimination cannot be excluded in all transformations.
25. (a) Zhang, L.; Zetterberg, K. *Organometallics* **1991**, *10*, 3806–3813. (b) Lee, C. W.; Oh, K. S.; Kim, K. S.; Ahn, K. H. *Org. Lett.* **2000**, *2*, 1213–1216. (c) Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439–1442. (d) Clique, B.; Fabritius, C. H.; Couturier, C.; Monteiro, N.; Balme, G. *Chem. Commun.* **2003**, 272–273.
26. Electron-donating groups may facilitate β-hydride elimination by stabilizing the developing positive charge on the β-carbon in the transition state. See: Mueller, J. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 7005–7013.
27. The small size of the *N*-acyl and *N*-Boc substituents relative to *N*-aryl groups may also alter the rate of β-hydride elimination in some systems.

28. (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048. (b) Yamashita, M.; Cuevas Vicario, J. V.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 16347–16360.
29. Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056–7066.
30. Abd El Samii, Z. K. M.; Al Ashmawy, M. I.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2517–2522.
31. Organ, M. G.; Xu, J.; N'Zemba, B. *Tetrahedron Lett.* **2002**, *43*, 8177–8180.
32. Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1993**, *58*, 5095–5100.
33. Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396–1408.
34. Kuehne, M. E.; Horne, D. A. *J. Org. Chem.* **1975**, *40*, 1287–1292.
35. Paul, R.; Tchelitcheff, S. *B. Chem. Soc. Fr.* **1949**, 470–475.
36. Tebben, G. D.; Rauch, K.; Stratmann, C.; Williams, C. M.; de Meijere, A. *Org. Lett.* **2003**, *5*, 483–486.
37. Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron* **1999**, *55*, 63–88.
38. Lane, C.; Snieckus, V. *Synlett* **2000**, 1294–1296.
39. Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830–846.
40. Eddaif, A.; Laurent, A.; Mison, P.; Pellissier, N.; Carrupt, P. A.; Vogel, P. *J. Org. Chem.* **1987**, *52*, 5548–5560.
41. Couffignal, R.; Moreau, J.-L. *Tetrahedron Lett.* **1978**, *19*, 3713–3716.

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A new class of readily available and conformationally rigid phosphino-oxazoline ligands for asymmetric catalysis

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Abstract—A new class of conformationally rigid phosphino-oxazoline ligands **3** were synthesized via an efficient *ortho*-substitution of phenyl glycinol as the key step. Divergent synthetic routes for easy ligand modulation, as well as a procedure suitable for scale-up synthesis, were established. The catalytic potential of ligands **3** has been demonstrated in the highly enantioselective Ir-catalyzed hydrogenation of alkenes and Pd-catalyzed allylic substitution and intermolecular Heck reactions.

1. Introduction

Discovering metal-catalyzed asymmetric transformations is among the most attractive frontiers in modern organic chemistry.[1] Since, chiral ligand has a significant influence on the metal catalyst reactivity and enantioselectivity, searching ligands with appropriate steric and electronic natures is one of the major tasks in asymmetric catalysis. Hetero-bidentate ligands, especially those bearing a phosphorus and a nitrogen as the donor atoms (called P,N-ligands), have become a particularly interesting ligand family because of the good π-acceptor character of phosphorus atom and the good σ-donor ability of nitrogen atom, the combination of which can help to stabilize the intermediate oxidation states during the catalytic cycle.[2] In addition, independent structural alternation on each of the P and N donor site makes it convenient to build a ligand set for optimization of a given reaction (Fig. 1).

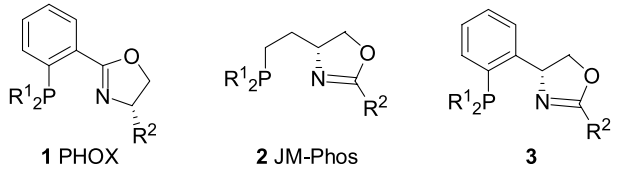

Figure 1.

Numerous chiral P,N-ligands have been reported for asymmetric catalysis by a number of groups during the past decades.[3] However, for most of these ligands, the application scope is limited regarding both the reaction type and enantioselectivity. Discovering readily available new P,N-ligands with high catalytic efficiency in various type of transformations is still needed. Ligand **1** (PHOX), invented by Pfaltz/Helmchen/Williams, has proven to be a superior ligand in a number of transition metal catalyzed reactions.[4] Burgess also obtained very good enantioselectivities in Pd-catalyzed allylic alkylation reactions and Ir-catalyzed hydrogenation of several unfunctionalized olefins with ligand **2** (JM-Phos),[5] although this ligand is fairly conformationally flexible with an ethylene linker. Recently, we have designed many conformationally rigid chiral bisphosphine ligands for achieving high enantioselectivities in asymmetric hydrogenation.[6] Bidentate ligand with a more rigid linker reduces the number of conformations in the transition state of the stereo-determining step and consequently enhances the enantioface differentiation.[7] On the basis of this consideration, we envisioned that ligands **3** might be superior to JM-Phos due to their more rigid 1,2-phenyl linker. Furthermore, ligands **3** are structurally highly resemble the PHOX, it would be of interest for a comparison with PHOX in their catalytic behavior. We have previously communicated the divergent syntheses of a series of ligands **3a–e** and their utilities in Ir-catalyzed highly enantioselective hydrogenation of unfunctionalized alkenes and α,β-unsaturated esters.[8] In this article, we want to give full details of the ligand synthesis including a new procedure suitable for scale-up ligand preparation. In addition to previously reported Ir-catalyzed hydrogenation reactions, evaluations of this new class of P,N-ligands in Pd-catalyzed asymmetric allylic substitution and intermolecular Heck reactions are also discussed.

Keywords: Ligand; Catalysis; Enantioselectivity.
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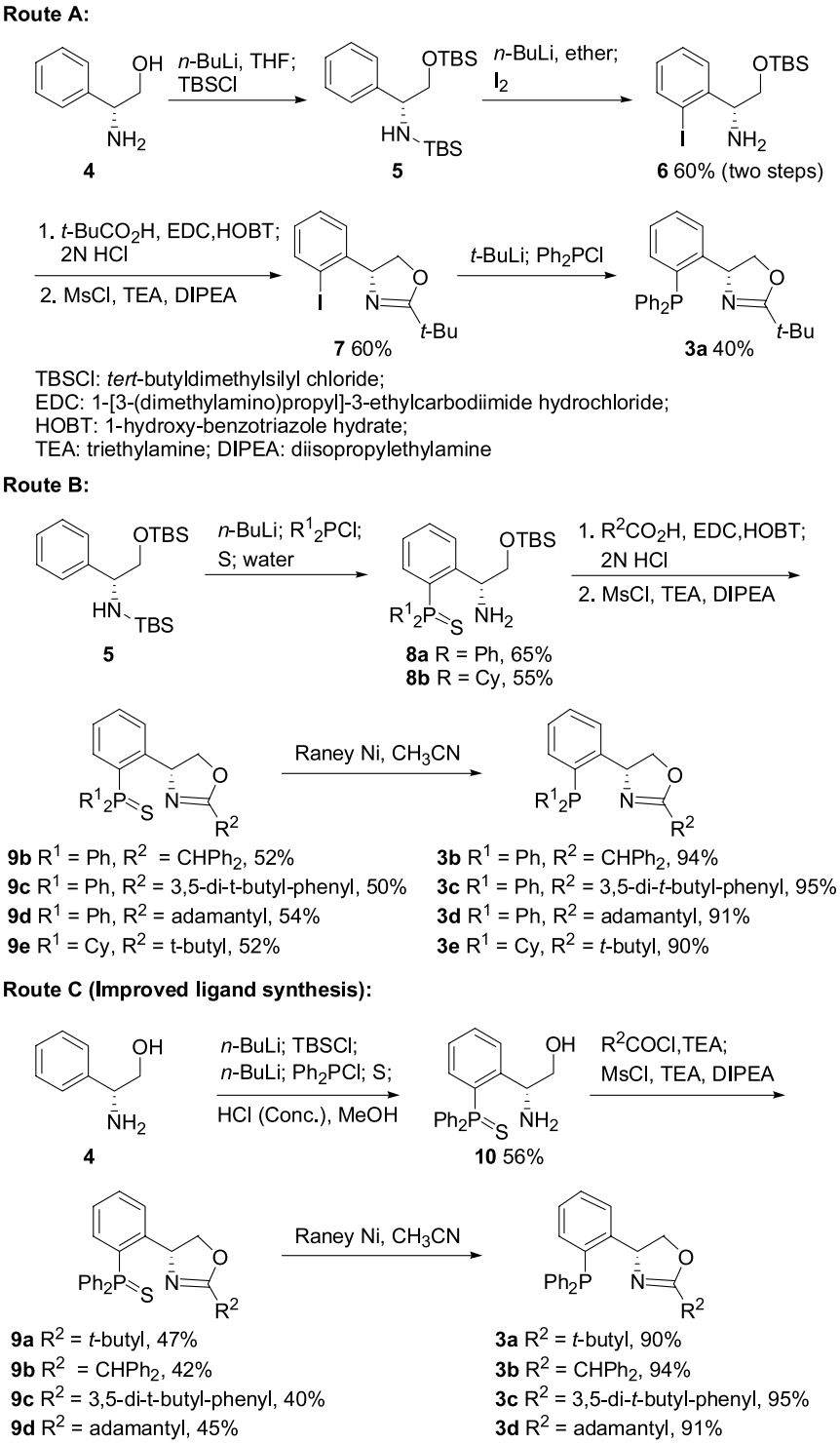
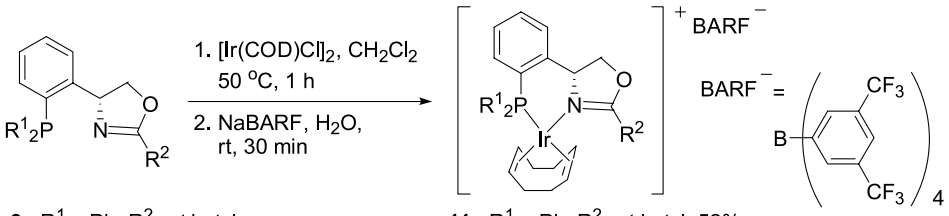


Scheme 1. Divergent synthesis of ligands **3a–e**.

2. Results and disccussion

2.1. Synthesis of phosphino-oxazoline ligands

The inexpensive enantiopure phenyl glycinol is widely used as a building block for the preparation of chiral ligands and auxilaries.[4,9] However, *ortho*-substituted phenyl glycinol derivatives are rarely used due to the lack of efficient synthesis.[10] One of the most direct ways to make ligands **3** would be based on *ortho*-substitution of phenyl glycinol. Thus, developing an efficient method of *ortho*-substitution of phenyl glycinol was desirable. Although the α-*N*,*N*-dimethyl amino group is commonly used as an *ortho*-directing group for metallation of aromatic rings,[11] direct use of primary amines for such a purpose was much less explored and was not used to construct chiral ligands.[12] Polniaszek et al. prepared (2-chloro or 2,6-dichlorophenyl) ethylamine from phenylethylamine via *ortho*-lithiation



3a R^1 = Ph, R^2 = *t*-butyl
3b R^1 = Ph, R^2 = $CHPh_2$
3c R^1 = Ph, R^2 = 3,5-di-*t*-butyl-phenyl
3d R^1 = Ph, R^2 = Adamantyl
3e R^1 = Cy, R^2 = *t*-butyl

11a R^1 = Ph, R^2 = *t*-butyl, 52%
11b R^1 = Ph, R^2 = $CHPh_2$, 50%
11c R^1 = Ph, R^2 = 3,5-di-*t*-butyl-phenyl, 63%
11d R^1 = Ph, R^2 = Adamantyl, 57%
11e R^1 = Cy, R^2 = *t*-butyl, 58%

Scheme 2. Preparation of Ir-complexes with P,N-ligands **3a–e**.

directed by the in situ generated *N*-lithiosilylamine.[13] After modification of their method, we successfully carried out, for the first time, an *ortho*-lithiation of silyl-protected phenyl glycinol. Subsequent reaction with I_2 or different phosphine chlorides efficiently gave rise to (2-iodo or 2-phosphino) phenyl glycinol derivatives, which are novel and highly modular chiral synthons for ligand synthesis. On the basis of this method, two different routes were developed for making ligands **3** (Scheme 1). In route A, (*R*)-phenyl glycinol (**4**) was protected with TBSCl to give an intermediate **5**, which was directly subjected to *ortho*-lithiation with 3 equiv of *n*-BuLi. Subsequent iodination followed by aqueous workup afforded aryl iodide **6**. Oxazoline formation using literature methods[4] gave the key intermediate **7**. Lithium–halogen exchange of **7** with *t*-BuLi followed by reaction with Ph_2PCl afforded the desired ligand **3a**. Presumably, variation of the phosphine chloride in the last step would allow a facile tuning of the phosphine site. In route B, a phosphine chloride, instead of I_2, was used as the electrophile after the *ortho*-lithiation step. Subsequent protection of the phosphine with sulfur followed by aqueous workup generated a phosphine sulfide **8**, which could be converted into a series of oxazolines **9** with various R^2 substituents by reaction with essentially unlimited carboxylic acids. Reduction of **9** with Raney-Ni[14] afforded ligands **3b–e**. The combination of both routes provides convenient ways of tuning either the phosphine site or the oxazoline site from intermediates **7** or **8**. This is useful for building a ligand set to optimize a particular reaction.

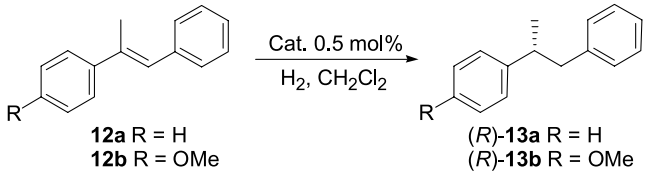
It is noteworthy that relatively expensive reagents EDC and HOBT were used in the preparation of oxazoline derivatives **7** and **9**. This renders a negative cost effect to scale-up ligand synthesis. In addition, both **6** and **8**, which are fairly polar intermediates, need to be purified by column chromatography before transformations to **7** and **9**, respectively. This adds another problem to the practicability of ligand synthesis. Solving these problems is critical for potential application of ligands **3** in catalysis. Route C in Scheme 1 outlines a slightly revised procedure for the synthesis of several ligands of **3**. After *ortho*-substitution of **4** with a diphenylphosphino group and subsequent sulfur protection, the crude product was treated with HCl (conc.) in MeOH to afford amino alcohol **10**, which can be purified by conventional washing and extraction procedures under different pH conditions. Therefore, **10** (90% pure by NMR) was obtained in 56% yield, which could be directly used for the next step. In instead of using EDC and HOBT, we attempted applying readily available and inexpensive carboxylic acid chlorides for the amide intermediates formation. We were pleased to find that this method provided comparable yields of the oxazolines **9a–c** and **9e** (42–47%) after subsequent one-pot mesylation and substitution reactions, considering that the starting material **10** of only 90% purity was used. **9a–d** were then reduced with Raney-Ni to afford **3a–d** in high yields, respectively. Thus, an overall three step synthesis of ligands **3** was established. Ligand **3a** was then prepared in 3.7 g scale through route C and this indicates that the new procedure is scalable.

2.2. Ir-Catalyzed asymmetric hydrogenations

Various P,N-ligands have exhibited superior reactivities and selectivities in Ir-catalyzed asymmetric hydrogenation of unfunctionalized alkenes.[15] To evaluate the catalytic properties of ligands **3** in asymmetric hydrogenation, their Ir-complexes **11** were prepared according to a literature procedure,[16] in which a weakly coordinating group BARF (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was used as the counter ion. These complexes are air-stable and can be stored in air for months without losing their catalytic properties (Scheme 2).

Methylstilbene (**12a**), a typical substrate for Ir-catalyzed asymmetric hydrogenation of unfunctionallized olefins, was initially tested with complexes **11a–e** under 50 bar of H_2 pressure at rt in CH_2Cl_2. As shown in Table 1, all the catalysts gave excellent enantioselectivity (97–99% ee), except for **11b** (83% ee). Although the conversions were not satisfactory with **11a**, **11b**, and **11c**, high conversions were obtained with **11d** and **11e** (entries 7 and 8). Pressure and temperature effects were examined with **11a** on the same substrate (entries 1–4). Increasing the H_2 pressure dramatically improved the conversion, while the enantioselectivity did not change significantly. Performing the reaction at an elevated temperature also resulted in a great increase in conversion. Pfaltz et al. reported that the formation of inactive hydride-bridged Ir-trimers during the catalytic cycle might be one of the major reasons for the deactivation of catalyst and isolated a trimeric Ir(PHOX)-hydride complex after treating the corresponding Ir-complex with H_2 (Fig. 2).[15a] On the basis of this hypothesis and our observations, we suppose that: (1) a relatively larger R^2 substituent on the oxazoline ring might be beneficial not only for the enantioselectivity, but also for the reactivity; (2) more electron-donating ligands might form more reactive

Table 1. Asymmetric hydrogenation of methylstilbene derivatives with **11**[a]



Entry	Substrate	Catalyst	H_2 pressure (bar)	Temperature	Conversion (%)[b]	ee (%)[c]
1	**12a**	**11a**	10	rt	31	98
2	**12a**	**11a**	50	rt	64	98
3	**12a**	**11a**	90	rt	94	97
4	**12a**	**11a**	50	50 °C	98	98
5	**12a**	**11b**	50	rt	77	83
6	**12a**	**11c**	50	rt	68	97
7	**12a**	**11d**	50	rt	98	97
8	**12a**	**11e**	50	rt	>99	99
9	**12a**	**11e**	100	rt	>99	98
10	**12b**	**11a**	100	rt	>99	97
11	**12b**	**11d**	100	rt	>99	97
12	**12b**	**11e**	100	rt	>99	90

[a] For a general procedure, see Section 4.
[b] The conversions were determined by GC.
[c] The enantiomeric excesses were determined by chiral HPLC (Chiralcel OJ-H) or chiral GC (Chiralselect 1000). The absolute configuration was assigned by comparison of the retention times of two enantiomers with reported data.[15g]

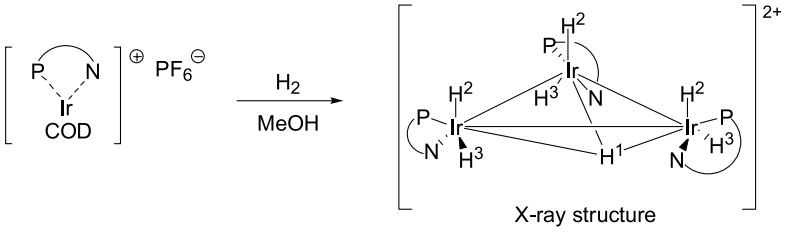
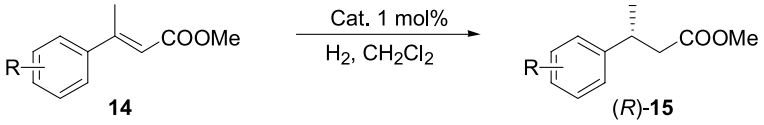


Figure 2. Formation of a hydride-bridged Ir-trimer.

catalyst or more stable catalytic species by preventing the formation of the hydride-bridged Ir-trimer, presumably through a *trans*-effect; (3) increasing the H_2 pressure might accelerate the desired catalytic cycle relative to the formation of the Ir-trimer; (4) a higher reaction temperature might either accelerate the desired catalytic cycle or possibly decelerate the formation of the Ir-trimer. These hypotheses can give us some guidance for further ligand modification and optimization of reaction conditions for a particular substrate. Another methylstilbene derivative **12b**

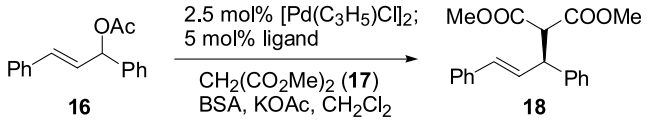
Table 2. Asymmetric hydrogenation of β-methylcinnamic esters with **11**[a]



Entry	Substrate	Catalyst	H_2 pressure (bar)	Temperature	Conversion (%)[b]	ee (%)[c]
1	**14a** R=H	**11a**	100	rt	>99	98
2	**14a** R=H	**11d**	100	rt	>99	99
3	**14a** R=H	**11e**	100	rt	>99	91
4	**14b** R=*p*-F	**11a**	100	rt	32	89
5	**14b** R=*p*-F	**11d**	100	rt	58	91
6	**14b** R=*p*-F	**11e**	100	rt	94	85
7	**14b** R=*p*-F	**11d**	100	50 °C	90	96
8	**14a** R=H	**11d**	100	50 °C	>99	99
9	**14c** R=*p*-Cl	**11d**	100	50 °C	87	98
10	**14d** R=*p*-CH_3	**11d**	100	50 °C	>99	98
11	**14e** R=*m*-CH_3	**11d**	100	50 °C	>99	99
12	**14f** R=*p*-OCH_3	**11d**	100	50 °C	96	94
13	**14g** R=*p*-OCF_3	**11d**	100	50 °C	84	95

[a] For a general procedure, see Section 4.
[b] The conversions were determined by GC.
[c] The enantiomeric excesses were determined by chiral HPLC (Chiralcel OJ-H) or chiral GC (Chiralselect 1000). The absolute configuration was assigned by comparison of the retention times of two enantiomers with reported data.[15g]

Table 3. Pd-Catalyzed asymmetric allylic alkylation of **16**



Entry	Ligand	Temperature	Time (h)	Yield (%)	ee (%)[a]
1	**3a**	rt	12	97	93(*S*)
2	**3b**	rt	12	93	2(*S*)
3	**3c**	rt	12	86	93(*S*)
4	**3d**	rt	12	91	97(*S*)
5	**3a**	0 °C	12	85	88(*S*)
6	**3a**	40 °C	4	97	98(*S*)
7	**3d**	40 °C	4	90	97(*S*)
8[b]	**3a**	40 °C	12	73	98(*S*)

[a] The ee values were determined by chiral HPLC (Chiral AD column) and the absolute configuration was assigned by comparison of the sign of the optical rotation with reported data.[4c]
[b] 0.1 mol% of $[Pd(C_3H_5)Cl]_2$ and 0.2 mol% of **3a** were used.

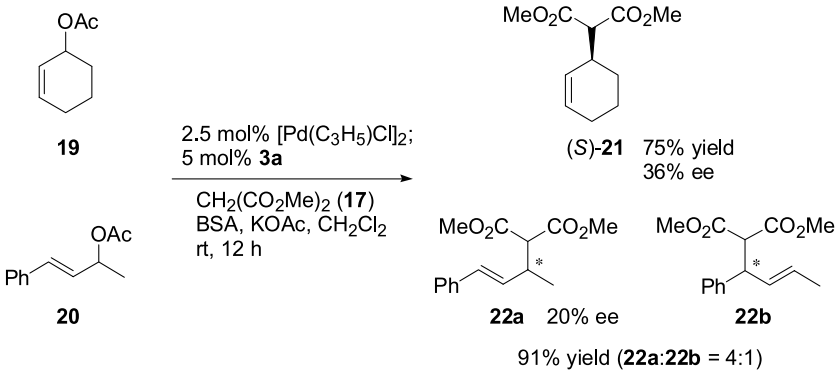
was then examined as the substrate with a few of the best catalysts (**11a**, **11d**, and **11e**). Complete conversions and very high enantioselectivities were obtained with **11a** and **11d** (entries 10 and 11), while **11e**, the most reactive catalyst, gave a little lower selectivity (entry 12). Thus, the overall results for asymmetric hydrogenation of biaryl alkenes with ligands **3** compare favorably with those obtained with JM-Phos **2** (95% ee for **12a** and 93% ee for **12b**).[15i]

Asymmetric hydrogenation of β-methyl cinnamic esters, followed by reduction of the ester function, can efficiently form chiral 3-arylbutanols, which are important intermediates for the synthesis of aromatic sesquiterpenes of the bisabolane family.[17] Few systems have been reported to be highly selective for this type of substrates.[15a,g] We were certainly interested in examining these important hydrogenation substrates with the air-stable catalysts **11**. Methyl-(*E*)-β-methyl cinnamate (**14a**) was initially selected as the substrate to screen ligands and reaction conditions. Complete conversions and extremely high enantioselectivities were observed with complexes **11a** and **11d** under 100 bar at rt (entries 1–3). The ee values are significantly higher than that with PHOX as a ligand (84% ee). However, when substrate **14b** having a *para*-fluoro substituent on the phenyl ring was subjected to hydrogenation, the conversion was not complete even at elevated temperature. The best result (96% ee and 90% conversion) for **14b** were obtained with **11d** at 50 °C under 100 bar (entry 7). We therefore used **11d** as catalyst and these optimized conditions for hydrogenation of several other aryl-(*E*)-β-methylcinnamic esters **14c–g**. Excellent ee values (94–99%) were obtained regardless of the substitution pattern on the phenyl ring, which were comparable to the best reported to date.[15a,g] The reactivities seemed quite substrate dependent. However, no obvious trend could be observed.

2.3. Pd-Catalyzed asymmetric C–C bond formations

2.3.1. Asymmetric allylic substitutions. Our next exploration of ligands **3** in asymmetric catalysis was focused on Pd-catalyzed allylic substitutions, a extensively studied reaction due to its synthetic potential.[18] A typical substrate 1,3-diphenylpropenyl acetate (**16**) in conjunction with the anion of dimethyl malonate (**17**) as a nucleophile was first tested with ligands **3a–d**. Under standard reaction conditions with $[Pd(\pi\text{-}C_3H_5)Cl]_2$ as a catalyst precursor, BSA as a base and KOAc as an additive in CH_2Cl_2 at rt, all the catalysts derived from **3a–d** provided product **18** in very good yields (86–97%) and high enantiomeric excesses (93–97%) (Table 3, entries 1–4), except that the catalyst derived from ligand **3b** showed essentially no enantioselectivity for this transformation. Lowering the reaction temperature has proven to be effective to improve the enantioselectivities in some allylic substitutions.[19] Thus, we carried out the same reaction with ligand **3a** at 0 °C instead of rt. Surprisingly, not only the yield was diminished as expected, but also the enantioselectivity dropped from 93–88% (entry 1 vs entry 5). On the opposite, when we increased the reaction temperature from rt to 40 °C, product **18** was obtained in the same yield but a higher ee value of 98% (entry 6). While for ligand **3d**, little difference was observed regarding both yields and ee values of **18** at a higher temperature (entry 7). In general, higher temperature increases the catalyst reactivity. Thus, this relatively uncommon property of ligand **3a** (higher ee at higher temperature) prompted us to test the possibility of lowering the catalyst loading for this reaction, which is generally used in 1–10 mol%, while maintaining high enantioselectivity. As shown in entry 8, when the reaction was carried out with only 0.2 mol% of Pd catalyst at 40 °C for 12 h, product **18** was obtained in 73% yield without any diminishment of enantioselectivity (98% ee). Such a low catalyst loading ($S/C = 500$) is rarely reported for Pd-catalyzed allylic substitution reactions with P,N-ligands, showing the superior reactivity of the catalyst of ligand **3a**. However, further decreasing the catalyst loading to 0.1 mol% was not satisfactory with only 38% yield of **18**.

To test the substrate scope and limitations of our new catalysts in allylation reactions of dimethyl malonate, a couple of more demanding substrates **19** and **20** were tested with ligand **3a**. Under standard reaction conditions, products **21** and **22** were obtained in good yields but disappointing ee values (Scheme 3). For the reaction of a cyclic substrate **19**,[20] only 36% ee was observed. For the reaction of an unsymmetric substrate **20**,[21] the product was obtained as a mixture of two regio-isomers in 4:1 ratio with 20% ee for



Scheme 3.

the major isomer 2-(1-methyl-3-phenylallyl) malonic acid dimethyl ester (**22a**). These results indicate this transformation is highly substrate dependent.

2.3.2. Asymmetric intermolecular Heck reaction. To further demonstrate the utility of ligand **3**, Pd-catalyzed asymmetric intermolecular Heck reaction[22] of 2,3-dihydrofuran (**23**) and phenyl triflate (**24**) was also investigated. Under typical conditions with $Pd_2(dba)_3 \cdot dba$ as the catalyst precursor and *N*,*N*-diisopropylethylamine as a base in benzene, ligands **3a** and **3d** provided product **25** in good yield and high ee value (entries 1 and 4). While much poorer yield and ee value of **25** were observed with **3b** and **3c** (entries 2 and 3), implying that a bulky substituent R^2 on the oxazoline ring of the ligand is beneficial for both higher reactivity and enantioselectivity in this reaction. Another regioisomer **26**, generated via C–C double bond migration in this reaction, was not observed under these conditions. Changing the catalyst precursor from $Pd_2(dba)_3 \cdot dba$ to $Pd_2(dba)_3 \cdot CHCl_3$ resulted in a mixture of **25** and **26** (93:7), though the overall yield and the ee value of the major product **25** were not affected significantly (entry 1 vs entry 5). Using THF in place of benzene as a solvent improved both yield and ee value of **25** (entry 1 vs entry 6 and entry 5 vs entry 7). Therefore, **25** was obtained almost quantitatively in 94% ee (entry 6), which is comparable to the best obtained with other P,N-ligands. Somewhat surprisingly, proton sponge, another commonly used base in this transformation, did not promote the reaction at all (entry 8) (Table 4).

3. Conclusion

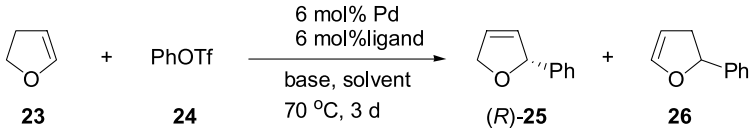
In summary, we have established a novel and efficient method of *ortho*-substitution of phenyl glycinol. Using this strategy as the key step, a new class of conformationally rigid phosphino-oxazoline ligands **3** were synthesized via divergent synthetic routes. A procedure that is suitable for scale-up ligand preparation was also developed, making this new class of ligands readily available from inexpensive phenyl glycinol. Their catalytic potential has been demonstrated in the highly enantioselective Ir-catalyzed hydrogenation of alkenes and Pd-catalyzed allylic substitution and intermolecular Heck reactions.

4. Experimental

4.1. General methods

All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. THF, ether, and benzene

Table 4. Pd-Catalyzed intermolecular Heck reaction[a]



Entry	Ligand	Pd complex	Base	Solvent	Yield(%)(**25**:**26**)[b]	ee(%)[c]
1	**3a**	$Pd_2(dba)_3 \cdot dba$	$^iPr_2EtN$	Benzene	87(>99:1)	91
2	**3b**	$Pd_2(dba)_3 \cdot dba$	$^iPr_2EtN$	Benzene	32(>99:1)	88
3	**3c**	$Pd_2(dba)_3 \cdot dba$	$^iPr_2EtN$	Benzene	45(>99:1)	78
4	**3d**	$Pd_2(dba)_3 \cdot dba$	$^iPr_2EtN$	Benzene	91(>99:1)	90
5	**3a**	$Pd_2(dba)_3 \cdot CHCl_3$	$^iPr_2EtN$	Benzene	90 (93:7)	90 (86)
6	**3a**	$Pd_2(dba)_3 \cdot dba$	$^iPr_2EtN$	THF	99(>99:1)	94
7	**3a**	$Pd_2(dba)_3 \cdot CHCl_3$	$^iPr_2EtN$	THF	93 (93:7)	93 (91)
8	**3a**	$Pd_2(dba)_3 \cdot dba$	Proton sponge	Benzene	No reaction	n/a

[a] For a typical reaction precedure, see Section 4.
[b] The total isolated yield of **25** and **26**. The ratio of **25**:**26** was determined by GC.
[c] The enantiomeric excesses of major isomer **25**. The data in parentheses were enantiomeric excesses of the minor isomer **26**, if detectable. They were all determined by chiral GC (β-DEX 120 column). The absolution configuration of **25** was assigned by comparison of the sign of the optical rotation with reported data.[23]

were dried and distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride was dried over CaH_2 under nitrogen. Column chromatography was performed using sorbent silica gel 60 Å (230×450 mesh). ^1H, ^{13}C, and ^{31}P were recorded on Bruker AM-300, AMX-360, and APX-400 spectrometers. Chemical shifts were reported in ppm up field to tetramethylsilane with the solvent resonance as the internal standard. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-ESI and HR-ESI or LR-APCI and HR-APCI. GC analysis was carried on Helwett–Packard 6890 gas chromatography using chiral capillary columns. HPLC analysis was carried on WatersTM 600 chromatography.

4.1.1. 2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-(2-iodophenyl)-ethylamine (6). To a suspention of (*R*)-α-methylbenzylamine **4** (1.37 g, 10.0 mmol) in 40 mL of THF at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 8 mL) dropwise. The resulting purple solution was stirred at −78 °C for 30 min before a solution of TBSCl (*tert*-butyldimethylsilyl chloride) (3.17 g, 21.0 mmol) in 20 mL of THF was added at the same temperature. The reaction mixture was allowed to warm to rt naturally and was stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 50 mL of ether. To this solution at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 12 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and stirred at rt for 1 h. I_2 (5.08 g, 20.0 mmol) was added at −78 °C and the reaction mixture was allowed to warm to rt and stirred at rt for 1 h. 10% $Na_2S_2O_3$ solution (20 mL) was added and the resulting mixture was stirred vigorously for 10 min. After usual work up, the product **7** was isolated by flash column chromatography (hexane/EtOAc=80:20) as a brown oil (2.27 g, 60%). $[\alpha]_D^{20}$ −49.4 (*c* 0.82, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.79 (dd, J=1.1, 7.9 Hz, 1H), 7.57 (dd, J=1.6, 7.8 Hz, 1H), 7.32 (dt, J=1.0, 7.8 Hz, 1H), 6.93 (dt, J=1.7, 7.7 Hz, 1H), 4.33 (dd, J=3.6, 7.9 Hz, 1H), 3.80 (dd, J=3.6, 9.9 Hz, 1H), 3.42 (dd, J=7.9, 9.9 Hz, 1H), 1.82 (s, 2H), 0.91 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 144.5, 139.5, 129.1, 128.3, 99.9, 67.6, 60.9, 26.1, 18.4, −5.1, −5.2; HRMS (M^++1) *m*/*z* calcd for $C_{14}H_{25}NOSiI$ 378.07447, found 378.07638.

4.1.2. 2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-ethylamine (8a). To a suspention of (*R*)-α-methylbenzylamine **4** (1.37 g, 10.0 mmol, 1 equiv) in 40 mL THF at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 8 mL) dropwise. The resulting purple solution was stirred at −78 °C for 30 min before a solution of TBSCl (3.17 g, 21.0 mmol) in 20 mL THF was added at the same temperature. The reaction mixture was allowed to warm to rt naturally and stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 50 mL ether. To this solution at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 12 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and stirred at rt for 1 h. Diphenylchlorophosphine (4.42 g, 20.0 mmol) was slowly added at −78 °C and the resulting solution was allowed to warm to rt and stirred overnight. Sulfur (0.960 g, 30.0 mmol) was added at rt and the mixture was stirred for 1 h before water was added. After usual work up, the product **9a** was isolated by flash column chromatography (hexane/EtOAc=90:10) as a white solid (3.03 g, 65%). $[\alpha]_D^{20}$ −66.6 (*c* 1.6, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 7.85–7.74 (m, 5H), 7.56–7.46 (m, 7H), 7.14 (m, 1H), 6.87 (dd, J=7.8, 14.7 Hz, 1H), 4.80 (dd, J=3.6, 8.0 Hz, 1H), 3.60–3.47 (m, 2H), 1.73 (s, 2H), 0.83 (s, 9H), −0.04 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2 (d, J=9.0 Hz), 133.5–131.6 (m), 130.2 (d, J=10.2 Hz), 128.6 (d, J=1.2 Hz), 128.4 (d, J=1.6 Hz), 126.8 (d, J=12.7 Hz), 66.9, 53.6 (d, J=7.0 Hz), 25.8, 18.2, −5.3, −5.5; ^{31}P NMR (145 MHz, $CDCl_3$) δ 42.11; HRMS (M^++1) *m*/*z* calcd for $C_{26}H_{35}NOSiPS$ 468.19408, found 468.19092.

4.1.3. 2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-[2-(dicyclohexyl-phosphinothioyl)-phenyl]-ethylamine (8b). To a suspention of (*R*)-α-methylbenzylamine **4** (0.343 g, 2.50 mmol, 1 equiv) in 10 mL THF at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 2 mL) dropwise. The resulting purple solution was stirred at −78 °C for 30 min before a solution of TBSCl (0.791 g, 5.25 mmol) in 5 mL THF was added at the same temperature. The reaction mixture was allowed to warm to rt naturally and was stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 15 mL ether. To this solution at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 3 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and was stirred at rt for 1 h. Dicyclohexylchlorophosphine (0.873 g, 3.75 mmol) was slowly added at −78 °C and the resulting solution was allowed to warm to rt and was stirred overnight. Sulfur (0.240 g, 7.50 mmol) was added at rt and the mixture was stirred for 1 h before water was added. After usual work up, the product **9b** was isolated by flash column chromatography (hexane/EtOAc=90:10) as a yellow oil (0.660 g, 55%). $[\alpha]_D^{20}$ −48.6 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ 8.00 (br s, 1H), 7.72–7.69 (m, 1H), 7.52–7.47 (m, 1H), 7.38–7.34 (m, 1H), 5.18 (br s, 1H), 3.82–3.70 (m, 2H), 2.41–2.35 (m, 2H), 2.11–2.08 (m, 2H), 1.87–1.19 (m, 20H), 0.95 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 147.1, 133.5 (m), 130.9, 128.5 (m), 127.0, 126.6, 126.5, 126.3, 68.2, 53.1, 39.8 (d, J=44.6 Hz), 39.3 (d, J=48.9 Hz), 27.0, 26.8, 26.4–26.1 (m), 25.7, 25.5, 18.0, −5.4, −5.5; ^{31}P NMR ($CDCl_3$, 145 MHz) δ 61.43 (br s); HRMS (M^++1) *m*/*z* calcd for $C_{26}H_{46}NOSiPS$ 480.28798, found 480.28543.

4.2. General procedure for preparation of oxazolines 7 and 9b–e

A mixture of **8a** (437 mg, 0.934 mmol), EDC·HCl (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (357 mg, 1.87 mmol), HOBT·H_2O (1-hydroxy-benzotriazole hydrate) (126 mg, 0.934 mmol), 1-adamantanecarboxylic acid (168 mg, 0.934 mmol), and TEA (triethylamine) (0.53 mL, 3.7 mmol) in 10 mL DMF was stirred at 70 °C overnight. To the cooled mixture was added 10 mL 2 N HCl solution followed by 20 mL EtOAc. The resulting mixture was stirred at rt for 30 min and then the two layers were separated. The aqueous layer was extracted with EtOAc (10 mL×2). The combined organic layer was washed with water and brine, dried with Na_2SO_4. After removal of the solvent, the resulting residue was purified by column flash chromatography (hexane/EtOAc/

CH_2Cl_2=70:20:10) to give condensation product as a white solid (336 mg). To a mixture of the above condensation product (316 mg, 0.613 mmol), DIPEA (*N*,*N*-diisopropylethylamine) (0.73 mL, 2.5 mmol) and TEA (0.51 mL, 6.1 mmol) in 10 mL CH_2Cl_2, was added methanesulfonyl chloride (95 μL, 1.2 mmol) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. After removal of the solvent and the excessive DIPEA and TEA under reduced pressure, **9d** was isolated by column flash chromatography (hexane/EtOAc=85:15) as a white solid (235 mg, 54% two steps).

4.2.1. 2-*tert*-Butyl-(4*R*)-(2-iodo-phenyl)-4,5-dihydro-oxazole (7). This compound was produced from **6** and dimethyl acetic acid following the general procedure as a colorless oil (60%). $[\alpha]_D^{20}-87.5$ (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.79 (dd, *J*=1.2, 7.9 Hz, 1H), 7.32 (dt, *J*=1.2, 7.7 Hz, 1H), 7.20 (dd, *J*=1.7, 7.8 Hz, 1H), 6.94 (dt, *J*=1.8, 7.6 Hz, 1H), 5.37 (dd, *J*=7.8, 10.3 Hz, 1H), 4.76 (dd, *J*=8.5, 10.3 Hz, 1H), 3.85 (t, *J*=8.1 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 176.3, 146.0, 139.2, 129.1 (d, *J*=22.0 Hz), 128.6, 127.4, 98.3, 74.3, 72.8, 33.6, 28.1; HRMS (M^++1) *m*/*z* calcd for $C_{13}H_{17}NOI$ 330.03494, found 330.03633.

4.2.2. 2-Benzhydryl-(4*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-4,5-dihydro-oxazole (9b). This compound was produced from **8a** and diphenyl acetic acid following the general procedure as a white solid (52%). $[\alpha]_D^{20}+35.4$ (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.83–7.71 (m, 4H), 7.56–7.45 (m, 7H), 7.41–7.24 (m, 11H), 7.16 (m, 1H), 6.87 (dd, *J*=7.7, 14.8 Hz, 1H), 5.91 (t, *J*=9.1 Hz, 1H), 5.26 (s, 1H), 4.72 (t, *J*=9.6 Hz, 1H), 3.96 (t, *J*=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 146.8 (d, *J*=8.5 Hz), 139.2 (d, *J*=8.7 Hz), 133.1–130.1 (m), 129.0–128.5 (m), 127.2 (d, *J*=4.2 Hz), 127.0 (d, *J*=12.5 Hz), 76.3, 66.8 (d, *J*=7.2 Hz), 51.2; ^{31}P NMR ($CDCl_3$, 145 MHz) δ 42.38; HRMS (M^++1) *m*/*z* calcd for $C_{34}H_{29}NOPS$ 530.17020, found 530.17347.

4.2.3. 2-(3,5-Di-*tert*-butyl-phenyl)-(4*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-4,5-dihydro-oxazole (9c). This compound was produced from **8a** and 3,5-di-*tert*-butylbenzoic acid following the general procedure as a white solid (50%). $[\alpha]_D^{20}+34.0$ (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.92–7.76 (m, 6H), 7.57–7.49 (m, 9H), 7.19 (t, *J*=7.4 Hz, 1H), 6.95 (dd, *J*=7.7, 14.8 Hz, 1H), 6.03 (t, *J*=8.9 Hz, 1H), 4.72 (t, *J*=9.7 Hz, 1H), 4.07 (t, *J*=8.5 Hz, 1H), 1.35 (s, 18H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 166.6, 151.1, 147.5 (d, *J*=8.5 Hz), 133.4–131.6 (m), 130.7, 129.6–129.0 (m), 127.1, 125.9, 123.0, 75.9, 68.0, 35.2, 31.6; ^{31}P NMR ($CDCl_3$, 145 MHz) δ 42.30; HRMS (M^++1) *m*/*z* calcd for $C_{35}H_{39}NOPS$ 552.24845, found 552.24701.

4.2.4. 2-Adamantan-1-yl-(4*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-4,5-dihydro-oxazole (9d). $[\alpha]_D^{20}+9.35$ (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.83–7.66 (m, 4H), 7.52–7.40 (m, 7H), 7.32 (dd, *J*=4.8, 6.8 Hz, 1H), 7.12 (m, 1H), 6.85 (ddd, *J*=0.7, 7.8, 14.8 Hz, 1H), 5.74 (t, *J*=9.0 Hz, 1H), 4.49 (dd, *J*=9.0, 9.9 Hz, 1H), 3.78 (t, *J*=8.4 Hz, 1H), 1.98 (s, 3H), 1.91 (s, 6H), 1.69 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5, 147.4 (d, *J*=8.5 Hz), 133.0 (d, *J*=5.5 Hz), 132.7–132.3 (m), 131.9–131.7 (m), 131.6 (d, *J*=2.9 Hz), 130.5 (d, *J*=83.4 Hz), 128.8–128.4 (m), 126.7 (d, *J*=12.5 Hz), 75.3, 66.6 (d, *J*=7.0 Hz), 39.6, 36.5, 35.3, 27.8; ^{31}P NMR ($CDCl_3$, 145 MHz) δ 42.30; HRMS (M^++1) *m*/*z* calcd for $C_{31}H_{33}NOPS$ 498.20150, found 498.19902.

4.2.5. 2-*tert*-Butyl-(4*R*)-[2-(dicyclohexyl-phosphinothioyl)-phenyl]-4,5-dihydro-oxazole (9e). This compound was produced from **8b** and dimethyl acetic acid following the general procedure as a colorless oil (52%). $[\alpha]_D^{20}-78.0$ (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54–7.49 (m, 2H), 7.37–7.31 (m, 2H), 6.53 (m, 1H), 4.94 (t, *J*=9.5 Hz, 1H), 3.92 (t, *J*=8.0 Hz, 1H), 2.54 (m, 1H), 2.31 (m, 1H), 2.09 (m, 1H), 1.91–1.13 (m, 19H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 149.2, 131.7 (d, *J*=2.6 Hz), 131.3, 128.6 (d, *J*=9.0 Hz), 126.3 (d, *J*=10.5 Hz), 125.0 (d, *J*=63.8 Hz), 76.2, 66.5 (d, *J*=3.7 Hz), 41.2 (d, *J*=48.2 Hz), 36.5 (d, *J*=51.2 Hz), 33.3, 27.9, 26.6–25.2 (m); ^{31}P NMR ($CDCl_3$, 145 MHz) δ 57.27 (br); HRMS (M^++1) *m*/*z* calcd for $C_{25}H_{39}NOPS$ 432.24845, found 432.24619.

4.2.6. 2-*tert*-Butyl-(4*R*)-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (3a). To a solution of **7** (94 mg, 0.286 mmol) in 4 mL ether was added *t*-BuLi (1.7 M solution, 0.34 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min before diphenylchlorophosphine (2.43 g, 11.0 mmol) was added slowly. The solution was allowed to warm to rt and was stirred overnight. Water was added. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to give **3a** as a white solid (40%). $[\alpha]_D^{20}-50.9$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.40–7.26 (m, 12H), 7.19 (dt, *J*=1.5, 7.5 Hz, 1H), 6.93–6.89 (m, 1H), 5.82–5.75 (m, 1H), 4.24 (dd, *J*=8.4, 10.2 Hz, 1H), 3.64 (dt, *J*=0.5, 8.4 Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (CD_2Cl_2, 90 MHz) δ 175.8, 148.4 (d, *J*=24.0 Hz), 136.9 (d, *J*=10.2 Hz), 135.4–134.2 (m), 130.0–129.3 (m), 127.9 (br s), 126.8 (br s), 75.4 (d, *J*=4.4 Hz), 67.5 (m), 33.9, 28.3; ^{31}P NMR (CD_2Cl_2, 145 MHz) δ −14.97; HRMS (M^++1) *m*/*z* calcd for $C_{25}H_{27}NOP$ 388.18248, found 388.17930.

4.3. General procedure for preparation of ligands 3b–e

To a N_2-flushed Schlenk flask was loaded about 1 g of Raney-Ni 2800 slurry. The Raney-Ni was washed sequentially with methanol (3 mL×3), ether (3 mL×3), and dried degassed CH_3CN (3 mL×3). To this flask was then transferred a solution of **9d** (190 mg, 0.382 mmol) in 6 mL CH_3CN. The resulting mixture was stirred under N_2 at rt for 1 d. The mixture was filtered under N_2. The Raney-Ni solid was washed with CH_3CN (3 mL×3). The combined filtrate was concentrated under reduced pressure and the residue was passed through a short silica gel plug under N_2 to give pure product **3d** as a white solid (91%).

4.3.1. 2-Benzhydryl-(4*R*)-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (3b). This compound was produced from **9b** following the general procedure as a white solid (94%). $[\alpha]_D^{20}-67.9$ (*c* 0.66, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.44–7.21 (m, 23H), 6.98–6.95 (m, 1H), 5.97 (dt, *J*=5.6, 9.4 Hz, 1H), 5.24 (s, 1H), 4.38 (dd,

J=8.6, 10.3 Hz), 3.74 (t, J=8.6 Hz); ^{13}C NMR (CD_2Cl_2, 90 MHz) δ 169.3, 147.9 (d, J=24.4 Hz), 140.4 (d, J=3.6 Hz), 136.7 (d, J=10.3 Hz), 135.5–134.0 (m), 130.1–126.9 (m), 75.6 (d, J=5.3 Hz), 68.0, 51.7; ^{31}P NMR (CD_2Cl_2, 145 MHz) δ −15.10; HRMS (M^++1) *m/z* calcd for $C_{34}H_{29}NOP$ 498.19813, found 498.19772.

4.3.2. 2-(3,5-Di-*tert*-butyl-phenyl)-(4*R*)-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (3c). This compound was produced from **9c** following the general procedure as a white solid (95%). $[\alpha]_D^{20}$ −48.3 (*c* 0.87, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.95 (d, J=1.8 Hz, 2H), 7.67 (t, J=1.8 Hz, 1H), 7.50–7.47 (m, 1H), 7.43–7.34 (m, 1H), 7.24 (dt, J=1.3, 7.5 Hz, 1H), 7.01 (ddd, J=1.1, 4.4, 7.6 Hz, 1H), 6.11 (ddd, J=5.9, 8.7, 14.5 Hz, 1H), 4.48 (dd, J=8.4, 10.2 Hz, 1H), 3.90 (t, J=8.5 Hz, 1H), 1.42 (s, 18H); ^{13}C NMR (CD_2Cl_2, 90 MHz) δ 166.1, 151.7, 148.2 (d, J=23.9 Hz), 137.0 (m), 135.6–133.9 (m), 130.2–126.3 (m), 123.3, 75.4 (d, J=4.2 Hz), 68.6, 35.5, 31.9; ^{31}P NMR (CD_2Cl_2, 145 MHz) δ −14.83; HRMS (M^++1) *m/z* calcd for $C_{35}H_{39}NOP$ 520.27638, found 520.27501.

4.3.3. 2-Adamantan-1-yl-(4*R*)-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (3d). $[\alpha]_D^{20}$ −66.1 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.05 (m, 12H), 6.79 (ddd, J=0.9, 4.4, 7.8 Hz, 1H), 5.74 (ddd, J=5.1, 8.3, 13.4 Hz, 1H), 4.15 (dd, J=8.5, 10.3 Hz, 1H), 3.53 (t, J=8.3 Hz, 1H), 1.96 (s, 3H), 1.90 (s, 6H), 1.66 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2, 147.8 (d, J=24.3 Hz), 136.4–136.1 (m), 134.7, 134.4, 134.0, 133.7, 133.5, 129.7, 129.2, 128.9, 128.8, 128.7, 127.6, 126.1 (d, J=5.7 Hz), 74.6 (d, J=5.0 Hz), 66.8 (d, J=24.2 Hz), 39.9, 36.8, 35.6, 28.2; ^{31}P NMR ($CDCl_3$, 145 MHz) δ −15.14; HRMS (M^++1) *m/z* calcd for $C_{31}H_{33}NOP$ 466.22943, found 466.22620.

4.3.4. 2-*tert*-Butyl-(4*R*)-(2-dicyclohexylphosphanyl-phenyl)-4,5-dihydro-oxazole (3e). This compound was produced from **9e** following the general procedure as a colorless oil (90%). $[\alpha]_D^{20}$ −70.9 (*c* 0.53, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.49–7.47 (m, 1H), 7.37–7.24 (m, 3H), 6.02 (ddd, J=5.7, 8.4, 14.1 Hz, 1H), 4.76 (dd, J=8.3, 10.3 Hz, 1H), 3.79 (t, J=8.3 Hz, 1H), 2.00–0.85 (m, 31H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 175.2, 151.0 (d, J=25.3 Hz), 133.2 (d, J=20.8 Hz), 133.1 (d, J=3.4 Hz), 129.5, 126.7, 126.2 (d, J=6.3 Hz), 75.9 (d, J=7.2 Hz), 67.9 (d, J=25.9 Hz), 35.2 (d, J=12.9 Hz), 34.0 (d, J=11.7 Hz), 33.7, 31.3–30.9 (m), 30.0 (d, J=10.2 Hz), 29.2 (d, J=6.2 Hz), 28.1, 27.7–27.3 (m), 26.8 (d, J=3.9 Hz); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ −14.46; HRMS (M^++1) *m/z* calcd for $C_{25}H_{39}NOP$ 400.27638, found 400.27262.

4.4. Multigram scale synthesis of ligand 3a via route C

4.4.1. 2-Hydroxyl-(1*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-ethylamine (10). To a suspention of (*R*)-α-methylbenzylamine **4** (5.46 g, 0.04 mol) in 150 mL of THF at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 32 mL) dropwise. The resulting purple solution was stirred at −78 °C for 30 min before a solution of TBSCl (12.7 g, 0.084 mol) in 80 mL of THF was added at the same temperature. The reaction mixture was allowed to warm to rt naturally and stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 200 mL of ether. To this solution at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 48 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and stirred at rt for 1 h. Diphenylchlorophosphine (17.7 g, 0.08 mol) was slowly added at −78 °C and the resulting solution was allowed to warm to rt and stirred overnight. Sulfur (3.84 g, 0.12 mol) was added at rt and the mixture was stirred for 1 h. The solvent was removed and the residue was dissolved in 100 mL of methanol followed by addition of 20 mL of conc. HCl. The mixture was heated at 50 °C for 4 h. After removal of methanol the yellow solid residue was redissolved in 150 mL of water and washed with ether (80 mL×3). The aqueous layer was then basicified by adding 60 mL of 4 N NaOH solution. The precipitate was dissolved in CH_2Cl_2 and extracted from the aqueous layer. After removal of the solvent, the crude product **10** was obtained as an offwhite solid (7.88 g, 56%, about 90% purity shown by NMR); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.68–7.72 (m, 4H), 7.41–7.49 (m, 8H), 7.10 (m, 1H), 6.81 (m, 1H), 4.69 (dd, J=1.3, 6.6 Hz, 1H), 3.48 (d, J=6.9 Hz, 2H), 1.88 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.3–132.9 (m), 129.0–129.3 (m), 127.4 (d, J=13.1 Hz), 67.1, 53.9; ^{31}P NMR (145 MHz, $CDCl_3$) δ 42.4.

4.4.2. 2-*tert*-Butyl-(4*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-4,5-dihydro-oxazole (9a). A mixture of **10** (7.88 g, 22.3 mmol), trimethyl acetyl chloride (3.0 mL, 24.5 mmol), and TEA (13.0 mL, 89.2 mmol) in 200 mL of CH_2Cl_2 was stirred at 0 °C for 2 h. 10 equiv of TEA (32.5 mL, 0.223 mol), 4 equiv of DIPEA (15.6 mL, 89.2 mmol) and 2 equiv of methanesulfonyl chloride (3.45 mL, 44.6 mmol) was added sequentially at the same temperature. The resulting mixture was allowed to warm to rt during 2 h and stirred for another 24 h. TLC showed the completion of the reaction. After removal of the solvent and the excessive TEA and DIPEA under reduced pressure, **9a** was isolated by column flash chromatography (hexane/EtOAc=85:15) as a white solid (4.4 g, 47% yield).

4.4.3. 2-*tert*-Butyl-(4*R*)-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (3a). To a N_2-flushed Schlenk flask was loaded about 20 g of Raney-Ni 2800 slurry. The Raney-Ni was washed sequentially with methanol (30 mL×3), ether (30 mL×3), and dried degassed CH_3CN (30 mL×3). To this flask was then transferred a solution of **9a** (4.4 g, 10.5 mmol) in CH_3CN (100 mL). The resulting mixture was stirred under N_2 at rt for 1 d. The reaction mixture was filtered under N_2 and washed with CH_3CN (50 mL×3). The combined filtrate was concentrated under reduced pressure and the residue was passed through a short silica gel plug under N_2 to give **3a** as a white solid (3.66 g, 90% yield).

4.5. General procedure for preparation of complex 11a–e

To a Schlenk tube was added **3d** (76 mg, 0.163 mmol), $[Ir(COD)Cl]_2$ (54.8 mg, 0.0816 mmol) and dried CH_2Cl_2 (3 mL). The resulting red solution was heated under N_2 at 50 °C for 1 h. TLC indicated that **3d** was consumed completely. After the solution was cooled to rt, Na[BARF] (217 mg, 0.245 mmol) was added followed by H_2O (3 mL). The resulting mixture was stirred vigorously for 30 min. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 mL×2). The combined organic

layer was dried with Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (hexanes/CH_2Cl_2=1:1) to give **11d** as an orange solid (57%).

4.5.1. Compound 11a. This compound was produced from **2a** following the general procedure as a yellow solid (52%); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.74 (s, 8H), 7.60–6.54 (m, 8H), 7.46–7.31 (m, 6H), 7.25–7.17 (m, 3H), 7.05 (ddd, J=1.2, 7.9, 10.9 Hz, 1H), 5.81 (dd, J=3.7, 9.7 Hz, 1H), 4.96 (m, 1H), 4.94 (dd, J=4.2, 9.4 Hz, 1H), 4.81 (t, J=9.7 Hz, 1H), 4.26 (m, 1H), 4.16 (m, 1H), 3.22 (m, 1H), 2.50–2.33 (m, 2H), 2.24 (m, 1H), 2.13–2.00 (m, 2H), 1.71 (m, 1H), 1.55 (m, 1H), 0.93 (s, 9H); ^{31}P NMR ($CDCl_3$, 145 MHz) δ 15.55; HRMS (cation) m/z calcd for $C_{33}H_{38}NOPIr$ 688.23150, found 688.22827; HRMS (anion) m/z calcd for $C_{32}H_{12}BF_{24}$ 863.06434, found 863.06754.

4.5.2. Compound 11b. This compound was produced from **2b** following the general procedure as a red solid (50%); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.77–6.78 (m, 34H), 5.93 (d, J=7.2 Hz, 2H), 5.76 (dd, J=5.6, 9.7 Hz, 1H), 5.20–5.11 (m, 2H), 4.90–4.80 (m, 2H), 3.95 (m, 1H), 3.80 (m, 1H), 3.00 (m, 1H), 2.53–2.45 (m, 2H), 2.35–2.19 (m, 2H), 1.90 (m, 1H), 1.75 (m, 1H), 1.52–1.34 (m, 2H); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 16.33; HRMS (cation) m/z calcd for $C_{42}H_{40}NOPIr$ 798.24715, found 798.24948; HRMS (anion) m/z calcd for $C_{32}H_{12}BF_{24}$ 863.06434, found 863.07128.

4.5.3. Compound 11c. This compound was produced from **2c** following the general procedure as an orange solid (63%); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.79 (m, 2H), 7.73 (s, 9H), 7.62 (m, 1H), 7.56 (br s, 4H), 7.50–7.36 (m, 12H), 7.22 (m, 1H), 6.04 (dd, J=4.2, 9.1 Hz, 1H), 5.21 (dd, J=4.4, 9.5 Hz, 1H), 5.07 (t, J=9.4 Hz, 1H), 5.04 (m, 1H), 4.08 (m, 1H), 3.87 (m, 1H), 3.52 (m, 1H), 2.54–2.39 (m, 2H), 2.30 (m, 1H), 2.22–2.14 (m, 2H), 1.90 (m, 1H), 1.70–1.64 (m, 2H), 1.31 (s, 18H); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 12.47; HRMS (cation) m/z calcd for $C_{43}H_{50}NOPIr$ 820.32540, found 820.32552; HRMS (anion) m/z calcd for $C_{32}H_{12}BF_{24}$ 863.06434, found 863.06159.

4.5.4. Compound 11d. ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.75 (s, 8H), 7.66–7.58 (m, 8H), 7.43–7.38 (m, 5H), 7.35–7.26 (m, 4H), 7.05 (m, 1H), 5.84 (dd, J=3.5, 9.8 Hz, 1H), 5.05 (m, 1H), 5.01 (dd, J=4.0, 9.4 Hz, 1H), 4.84 (t, J=9.6 Hz, 1H), 4.35 (m, 1H), 4.28 (m, 1H), 3.23 (m, 1H), 2.52–2.36 (m, 3H), 2.25 (m, 1H), 2.16–2.01 (m, 2H), 1.84–1.74 (m, 7H), 1.64–1.52 (m, 4H), 1.41–1.36 (m, 6H); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 15.89; HRMS (cation) m/z calcd for $C_{39}H_{44}NOPIr$ 766.27845, found 766.27163; HRMS (anion) m/z calcd for $C_{32}H_{12}BF_{24}$ 863.06434, found 863.07188.

4.5.5. Compound 11e. This compound was produced from **2e** following the general procedure as an orange solid (58%); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.74 (m, 8H), 7.65–7.51 (m, 7H), 7.39 (m, 1H), 5.67 (d, J=7.2 Hz, 1H), 5.28 (dd, J=1.2, 10.2 Hz, 1H), 5.06 (m, 1H), 4.92 (m, 1H), 4.43 (dd, J=7.5, 10.2 Hz, 1H), 3.76 (m, 1H), 3.56 (m, 1H), 2.97 (m, 1H), 2.60–2.51 (m, 2H), 2.39–2.10 (m, 5H), 1.94–1.63 (m, 12H), 1.52–1.32 (m, 19H); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 9.00; HRMS (cation) m/z calcd for $C_{33}H_{50}NOPIr$ 700.32540, found 700.32349; HRMS (anion) m/z calcd for $C_{32}H_{12}BF_{24}$ 863.06434, found 863.07146.

4.6. General procedure for enantioselective hydrogenations

α-Methylstilbene (25.9 mg, 0.133 mmol) and Ir-complex **11d** (1 mg, 0.614 μmol) was dissolved in CH_2CH_2 (2 mL). This solution was then transferred into an autoclave. The hydrogenation was performed at rt under 50 bar of H_2 (or under reaction conditions described in Tables 1 and 2) for 12 h. After carefully releasing the hydrogen, the reaction mixture was directly passed through a short silica gel plug and flashed with ether. After evaporation, the residue was directly used for chiral HPLC analysis to measure the enantiomeric excess and for GC to measure the conversion.

4.7. General procedure for enantioselective allylic substitutions

In a schlenk tube, allylpalladium chloride dimer (4.57 mg, 0.0125 mmol), ligand **3a** (9.68 mg, 0.025 mmol) and solid potassium acetate (4.9 mg, 0.05 mmol) were dissolved in 2 mL of CH_2Cl_2. The solution was stirred at rt for 15 min. Dimethyl malonate (0.172 mL, 1.5 mmol) and *N*,*O*-bis(trimethylsilyl) acetamide (0.37 mL, 1.5 mmol) and a solution of *rac*-(*E*)-1-acetoxy-1,3-diphenyl-2-propene (**17**) (126 mg, 0.5 mmol) in 1 mL of CH_2Cl_2 were added subsequently. The reaction mixture was stirred at rt for 12 h. The solvent was removed under vacuum and the residue was passed through a short silica gel column (EtOAc/hexanes=1:9) to give product **18**.

4.7.1. 2-(1,3-Diphenyl-allyl) malonic acid dimethyl ester (18). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.15–7.29 (m, 10H), 6.45 (d, J=15.8 Hz, 1H), 6.31 (dd, J=15.7, 8.5 Hz, 1H), 4.24 (dd, J=10.3, 8.8 Hz, 1H), 3.93 (d, J=10.9 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H). The ee of product was analyzed via chiral HPLC (AD column; eluting with 90:10 hexanes/2-propanol).

4.7.2. 2-Cyclohex-2-enylmalonic acid dimethyl ester (21). ^{1}H NMR (360 MHz) δ 5.68–5.71 (m, 1H), 5.43–5.46 (m, 1H), 3.66 (s, 6H), 3.21 (d, J=9.5 Hz, 1H), 2.82–2.84 (m, 3H), 1.27–1.92 (m, 6H). The ee of product was analyzed via chiral GC (Supelco Chiral Select 1000 column).

4.7.3. Compounds 22a and 22b. ^{1}H NMR showed an inseparable mixture of **22a** and **22b** (80:20) was obtained. 2-(1-Methyl-3-phenylallyl) malonic acid dimethyl ester (**22a**); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.11–7.21 (m, 5H), 6.31 (d, J=15.8 Hz, 1H), 5.98 (dd, J=15.8, 8.5 Hz, 1H), 3.60 (s, 3H), 3.53 (s, 3H), 3.25 (d, J=8.9 Hz, 1H), 2.97–3.00 (m, 1H), 1.05 (d, J=6.8 Hz, 3H); ^{1}H NMR for 2-(1-phenyl-but-2-enyl) malonic acid dimethyl ester (**22b**) can be found in literature.[21a] The ee of **22a** was analyzed via chiral HPLC (OJ-H column; eluting with 95:5 hexanes/2-propanol).

4.8. General procedure for enantioselective Heck reactions

2-Phenyl-2,5-dihydrofuran (**25**). In a schlenk tube, $[Pd_2(dba)_3 \cdot dba]$ (8.61 mg, 0.015 mmol), ligand **3a** (11.61 mg, 0.03 mmol) were dissolved in 3 mL of THF. The solution was stirred at 70 °C for 15 min. Phenyl triflate (**24**) (80.7 μL, 0.5 mmol), 2,3-dihydrofuran (**23**) (0.19 mL, 2.5 mmol) and *N*,*N*-diisopropylethylamine (0.26 mL, 1.5 mmol) were added subsequently. The reaction mixture was stirred at 70 °C for 3 d. The solvent was removed under reduced pressure and the residue was purified by a silica gel column (EtOAc/hexanes = 1:9) to afford **25**; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.20–7.25 (m, 5H), 5.92 (m, 1H), 5.79 (m, 1H), 5.70 (m, 1H), 4.76 (m, 1H), 4.69 (m, 1H). The product was analyzed via chiral GC (Supelco β-DEX 120 column).

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References and notes

1. For recent reviews, see: (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In Ojima, I., Ed. 2nd ed.; Catalytic asymmetric synthesis; Wiley: New York, 2000. (b) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Comprehensive asymmetric catalysis; Springer: Berlin, 1999; Vol. I–III. (c) Noyori, R.; Asymmetric catalysis in organic synthesis; Wiley-Interscience: New York, 1994.
2. Akerrnarj, B.; Krakenberger, S.; Hannsson, S.; Vitagliano, A. *Organometallics* **1987**, *6*, 620.
3. For recent reviews on chiral P,N-ligands, see: (a) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497. (b) Chelucci, G.; Orru, G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471. (c) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res* **2000**, *33*, 336.
4. (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (b) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149. (c) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769.
5. (a) Hou, D.; Reibenspies, J.; Colacot, T. J.; Burgess, K. *Chem. Eur. J.* **2001**, *7*, 5391. (b) Hou, D.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206. (c) Hou, D.; Burgess, K. *Org. Lett.* **1999**, *1*, 1745.
6. (a) Zhang, X. *Enantiomer* **1999**, *4*, 541. (b) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1612.
7. Brown, J. M.; Chaloner, P. A. In Pignolet, L. H., Ed.; Homogeneous catalysis with metal phosphine complexes; Plenum: New York, 1983; p 137.
8. Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513.
9. (a) Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817. (b) Davies, I. W.; Gerena, L.; Cai, D.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 1145. (c) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027.
10. O'Brien, P.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2519.
11. (a) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3212. (b) Almena Perea, J. J.; Börner, A.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 8073. (c) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
12. Burns, S. A.; Corriu, R. J. P.; Huynh, V.; Moreau, J. J. E. *J. Organomet. Chem.* **1987**, *333*, 281.
13. (a) Polniaszek, R. P.; Lichti, C. F. *Synth. Commun.* **1992**, *22*, 171. (b) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859.
14. Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161.
15. For a recent review of hydrogenation of olefin with P,N-ligands, see: (a) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hormann, E.; McIntyre, S.; Menges, F.; Schonleber, M.; Smidt, S. P.; Wustenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33 and references cited therein. (b) Kallstrom, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308–14309. (c) Durry, W. J., III; Zimmerman, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 70. (d) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3941. (e) Xu, G.; Gilbertson, S. R. *Tetrahedron Lett.* **2003**, *44*, 953. (f) Brauer, D. J.; Kottsieper, K. W.; Boßenbach, S.; Stelzer, O. *Eur. J. Inorg. Chem.* **2003**, 1748. (g) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 943. (h) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713. (i) Hou, D.; Reibenspies, J.; Colacot, T. J.; Burgess, K. *Chem. Eur. J.* **2001**, *7*, 5391.
16. Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2897.
17. (a) Fuganti, C.; Serra, S.; Dulio, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758. (b) Fuganti, C.; Serra, S.; Dulio, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 279. (c) Meyers, A. I.; Stoianova, D. *J. Org. Chem.* **1997**, *62*, 5219.
18. For reviews, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Trost, B. M.; Lee, C. In Ojima, I., Ed. 2nd ed.; Catalytic asymmetric synthesis; VCH: New York, 2000; pp 593–640. (c) Pfaltz, A.; Lautens, M. In Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Comprehensive asymmetric catalysis; Springer: Berlin, 1999; Vol. 2, pp 833–884. (d) Trost, B. M. *Acc. Chem. Res* **1996**, *29*, 355.
19. (a) Lyle, M. P. A.; Narine, A. A.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 5060. (b) Jones, G.; Richards, C. J. *Tetrahedron Lett.* **2001**, *42*, 5553.
20. (a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. (b) Vyskocil, S.; Smrcina, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7738.
21. (a) Pena-Cabrera, E.; Norrby, P.-O.; Sjogren, M.; Vitagliano, A.; De Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Akermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299. (b) Togni, A. *Tetrahedron: Asymmetry* **1991**, *2*, 683. (c) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723.
22. For some reviews of asymmetric Heck reaction, see: (a) Shibasaki, M.; Vogl, E. M. In Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Comprehensive asymmetric catalysis; Springer: Heidelberg, 1999; p 458; and Supplement 2004, 1, pp 73–81. (b) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16. For some recently published examples with P,N-ligands, see: (c) Kilroy, T. G.; Cozzi, P. G.; End, N.; Guiry, P. J. *Synthesis* **2004**, 1879. (d) Hou, X.-L.; Dong, D. X.; Yuan, K.

Tetrahedron: Asymmetry **2004**, *15*, 2189. (e) Kilroy, T. G.; Cozzi, P. G.; End, N.; Guiry, P. J. *Synlett* **2004**, 106. (f) Tu, T.; Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-C. *Chem. Eur. J.* **2003**, *9*, 3073. (g) Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brien, E. M.; Spinelli, E. M. *Org. Lett.* **2003**, *5*, 595.

23. Hashimoto, Y.; Horie, Y.; Hayashi, M.; Saigo, K. *Tetrahedron: Asymmetry* **2000**, *11*, 2205.