ELSEVIER

Tetrahedron

Tetrahedron Vol. 62, No. 32, 2006

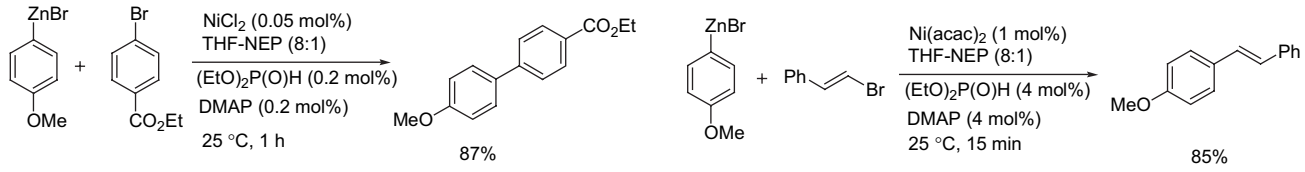
Tetrahedron Symposium-in-Print Number 124

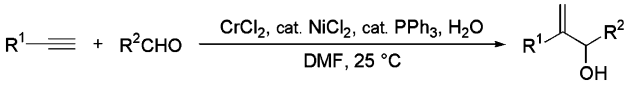
Recent advances in organonickel chemistry

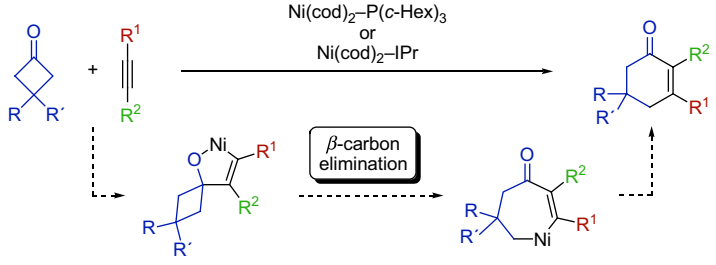
Guest editor: Tim Jamison

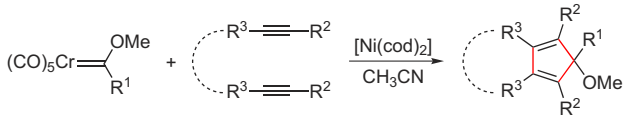
Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, United States

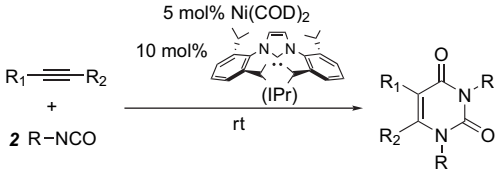
Contents

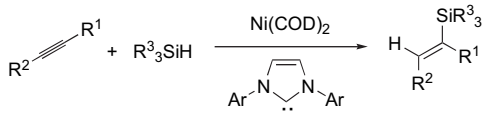


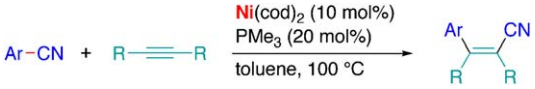


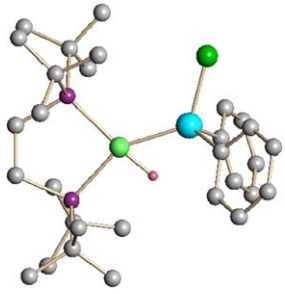


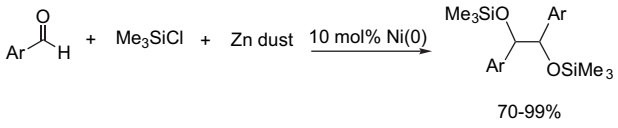




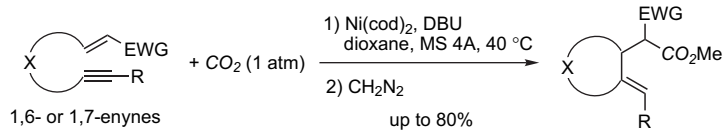


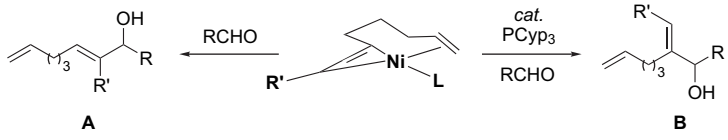






Arylaldehydes reacts with nickel(0) and Me_3SiCl to give η^1:η^1-siloxybenzylnickel complex. In the presence of zinc dust, the reductive homocoupling reaction of arylaldehyde proceeded catalytically to form pinacol derivatives.





Nickel-catalyzed reductive coupling reactions of aldehydes and 1,6-enynes proceed in excellent regioselectivity in the absence of a phosphine, and the use of a monodentate phosphine additive leads to the formation of the opposite regioisomer with equally high selectivity. Both products are the result of the same fundamental mechanism, with the inversion of regioselectivity being the result of stereospecific ligand substitution at the metal center.

OTHER CONTENT

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

The cover graphic depicts one molecule from each of the thirteen articles this issue, in the order of appearance (top left to bottom right). The red bonds indicate those that were constructed in a nickel-mediated transformation.

Abstracted/indexed 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. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®

ELSEVIER

ISSN 0040-4020

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.
96. Recent developments in dendrimer chemistry, David K. Smith, Ed. *Tetrahedron* **2003**, *59*, 3787–4024.
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.
113. Development and application of highly active and selective palladium catalysts, Ian J. S. Fairlamb, Ed. *Tetrahedron* **2005**, *61*, 9647–9918.
114. Multicomponent reactions, Ilan Marek, Ed. *Tetrahedron* **2005**, *61*, 11299–11520.
115. Polymer-supported reagents and catalysts: increasingly important tools for organic synthesis, Patrick Toy and Min Shi, Eds. *Tetrahedron* **2005**, *61*, 12013–12192.
116. Organocatalysis in organic synthesis, Pavel Kočovský and Anderi V. Malkov, Eds. *Tetrahedron* **2006**, *62*, 243–502.
117. Supramolecular chemistry of fullerenes, Nazario Martín and Jean-François Nierengarten, Eds. *Tetrahedron* **2006**, *62*, 1905–2132.
118. Chemistry of electron-deficient ynamines and ynamides, Richard P. Hsung, Ed. *Tetrahedron* **2006**, *62*, 3771–3938.
119. Microwave assisted organic synthesis, Nicholas E. Leadbeater, Ed. *Tetrahedron* **2006**, *62*, 4623–4732.
120. Nature-inspired approaches to chemical synthesis, Erik J. Sorensen and Emmanuel A. Theodorakis, Eds. *Tetrahedron* **2006**, *62*, 5159–5354.
121. The chemistry of radical ions, Paul E. Floreancig, Ed. *Tetrahedron* **2006**, *62*, 6447–6594.
122. Recent advances in oxidation chemistry, Dan Yang, Ed. *Tetrahedron* **2006**, *62*, 6595–6718.
123. Stereoselective and catalyzed halogenation reactions, Thomas Lectka, Ed. *Tetrahedron* **2006**, *62*, 7141–7204.
124. Recent advances in organonickel chemistry, Timothy F. Jamison, Ed. *Tetrahedron* **2006**, *62*, 7493–7610.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 62 (2006) 7503

Preface

Recent advances in organonickel chemistry

It is my great pleasure to serve as Guest Editor of this *Tetrahedron Symposium-in-Print*. This is the second *Tetrahedron Symposium-in-Print* dedicated entirely to organonickel chemistry. Appearing in 1998 as TSIP number 69, the first of these was edited by Prof. Bruce Lipshutz and provided an excellent snapshot of the field at the time. On one hand, it may seem that a second organonickel *Symposium-in-Print* may not be warranted after such a short period of time has elapsed, but this relatively small, eight-year gap is more reflective of the fact that this area of chemistry continues to expand and flourish, as also demonstrated by the diversity of chemistry that appears herein.

A particularly noteworthy aspect of this TSIP is that *all* 13 papers in this issue have been individually dedicated to the same person, Prof. Dr. Günther Wilke of the Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany), in honor of his innumerable groundbreaking contributions to organonickel chemistry. Without Prof. Wilke, much if not all of the research described in this issue would not have been possible.[1]

The articles are organized thematically to some extent. The first (Wender) and second (Tamaru) both feature nickel-catalyzed coupling reactions of 1,3-dienes, but the similarities end there. The former details a [4+4] cycloaddition in the context of a natural product synthesis, and the latter describes the development of a coupling reaction of 1,3-dienes and imines.

Next, Knochel provides us with an account of the development of a cross-coupling reaction, and then a series of papers describing reactions of alkynes appears. Nickel-catalyzed cyclotrimerization and tetramerization of alkynes to give arenes and cyclooctatetraenes, respectively, are two of the earliest transition metal-catalyzed, carbon–carbon bond-forming reactions ever described, developed primarily by Reppe in the late 1940's and 1950's. In the articles in these papers, however, such processes are not the desired outcome and are often competing processes, especially cyclotrimerization.

What is especially striking about this collection of papers is that the species that couple with the alkyne differ greatly from one another, highlighting the diversity of chemistry catalyzed by nickel mentioned above. The coupling partner is an aldehyde in the case of Takai's intermolecular reductive coupling and, in three subsequent formal cycloaddition reactions, is a cyclobutanone (Murakami), a chromium carbene (Barluenga), or an isocyanate (Louie). In the final two papers of this subset, Montgomery and Hiyama each report an addition reaction, a hydrosilylation and an arylcyanation, respectively.

Two of the themes of the next two articles are reaction mechanism and X-ray crystallography of nickel complexes. Hillhouse focuses on several of the steps involved in oxidative addition reactions between Ni(0) and the Si–H bonds of silanes, and Ogoshi describes investigations of a dimerization reaction of aldehydes that gives pinacol derivatives.

In each of the final two articles, 1,6-enynes are involved, but play very different roles in the two cases. In the contribution from Mori and Sato, nickel effects a tandem carbocyclization–carboxylation, whereas in the case of the work from my laboratory, the alkene does not react, but rather directs the regioselectivity of addition to the alkyne.

I would like to thank Prof. Harry Wasserman for the invitation to be the Guest Editor of this *Symposium-in-Print* and for all of his help throughout the process. I am delighted to have had the opportunity not only to be involved with the production of this issue, but also to be able to contribute an article to it. Finally, I would like to thank all of the other contributors and reviewers, without whom, of course, this issue would not have been possible.

T. F. Jamison
Department of Chemistry,
Massachusetts Institute of Technology,
77 Massachusetts Avenue,
Cambridge, MA 02139, United States
E-mail address: tfj@mit.edu

Available online 5 June 2006

[1] For a very readable personal account of not only Prof. Wilke's contributions, but of also the history of the field through the mid-1980's, see: Wilke, G. Contributions to Organo-Nickel Chemistry. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 185–206.

0040–4020/$ - see front matter
doi:10.1016/j.tet.2006.04.078

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7505–7511
Tetrahedron

New reactions and step economy: the total synthesis of (±)-salsolene oxide based on the type II transition metal-catalyzed intramolecular [4+4] cycloaddition

Paul A. Wender,[a,*] Mitchell P. Croatt[a] and Bernhard Witulski[b]

[a]*Department of Chemistry, Stanford University, Stanford, CA 94305, USA*
[b]*Institut für Organische Chemie, Johannes Gutenberg-Universität Mainz, Duesbergweb 10-14, 55099 Mainz, Germany*

Received 5 January 2006; revised 28 February 2006; accepted 28 February 2006
Available online 12 June 2006

Dedicated to Professor Wilke whose pioneering and innovative studies in organometallic chemistry have enabled advances of profound fundamental and practical value and inspirations for the future of the field

Abstract—Studies on the viability of the type II nickel-catalyzed intramolecular [4+4] cycloaddition of bis-dienes show that it is influenced by both diene substitution and geometry. Both *E*- and *Z*-isomers of **19** and **20** react, albeit at markedly different rates, to afford cycloadducts, whereas only the *Z*-isomer of **9** (and not the *E*-isomer) reacts to give **8** and **25**. Chemoselective elaboration of **8** to (±)-salsolene oxide (**7**) was used to confirm the cycloadduct structure while establishing a step economical route to the natural product.

1. Introduction

Step economy is a preeminent goal of organic synthesis.[1] It influences the length, efficiency, cost, development time, execution time, effort, separation science, and environmental impact of a synthesis and therefore its capacity to efficaciously deliver a meaningful supply of target. Step economy is in turn influenced by reaction selection and is generally favored by the use of reactions that allow the greatest increase in target relevant complexity.[2] The ability to access more complex targets with step economy is thus principally determined and limited by the lexicon of known organic reactions (Fig. 1). The introduction of new reactions is thus a critical if not unique requirement for extending the reach of contemporary synthesis and thereby its impact on fundamental and applied aspects of chemistry, biology, medicine, materials, and environmental sciences.

Prompted by the above considerations, we have focused effort on the design or discovery of novel or new reactions[3] that provide fundamentally new ways of accessing ring systems commonly encountered in natural and designed polycyclic targets. A special emphasis has been placed on reactions that in the absence of catalysts are forbidden or difficult to achieve. Following the pioneering work of Reppe,[4] Reed,[5] Wilke,[6] and others,[7] we reported early on in this series the first examples of the intramolecular, metal-catalyzed [4+4] cycloaddition of bis-dienes.[8,9] As a consequence of its intramolecularity, this reaction allows for control over selectivity and for the introduction of substituents that are not possible with its intermolecular counterpart. This process has been used to readily access the fused eight-membered ring core of taxol (**3**)[10] and of asteriscanolide (**6**: Scheme 1).[11] The use of this cycloaddition to access *bridged* bicycles containing an eight-membered ring as are found in various natural products[12] has in contrast received little attention.[13] We report herein an exploratory mechanistic study on the utility of the type II intramolecular nickel(0)-catalyzed [4+4] cycloaddition for the synthesis of bicyclo[5.3.1]undecane derivatives, the influence of diene geometry and substitution on the type II process, and the preliminary application

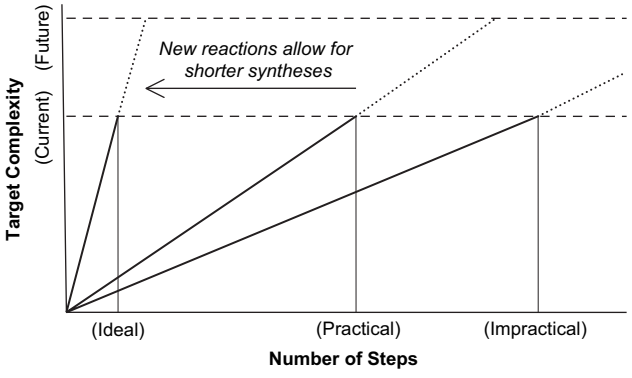
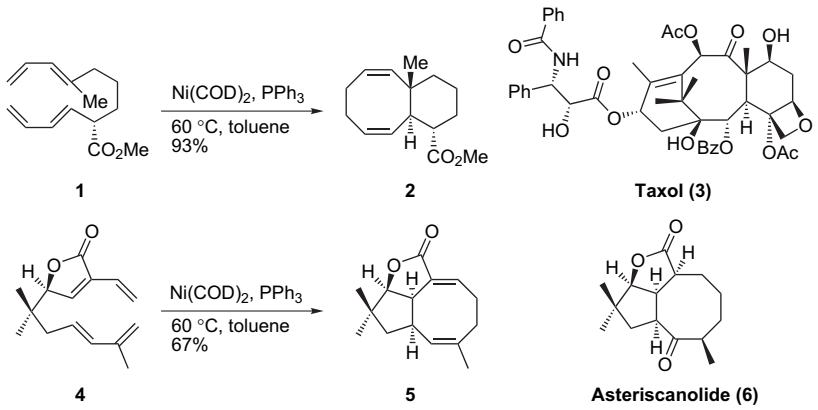


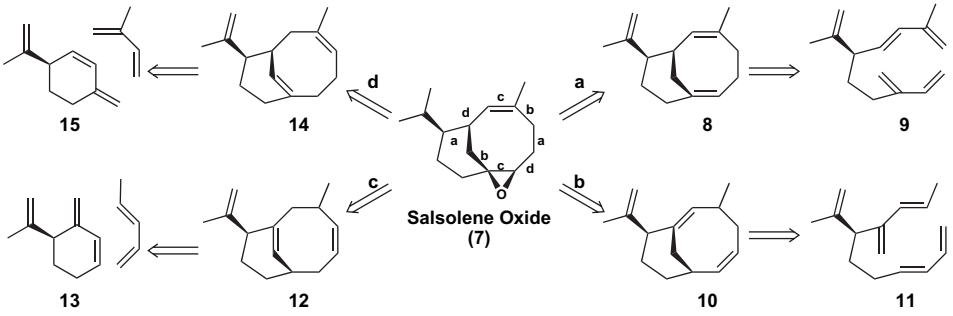
Figure 1. The relationship of step economy to complexity and new reactions.

* Corresponding author. Tel.: +1 650 723 0208; fax: +1 650 725 0259; e-mail: wenderp@leland.stanford.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.085



Scheme 1. Representative examples of type I metal-catalyzed [4+4] cycloadditions.



Scheme 2. Connectivity analyses of salsolene oxide using a type II [4+4] cycloaddition.

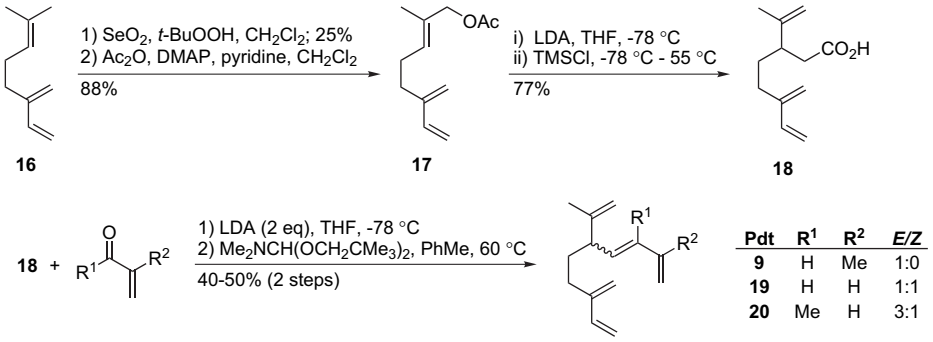
of this type II process to the total synthesis of (±)-salsolene oxide (**7**: Scheme 2).

2. Results and discussion

Salsolene oxide (**7**) is a tricyclic sesquiterpene reported by Weyerstahl in 1991 as an isolate of the Himalayan plant *Artemisia salsoloides*.[14] Its synthesis has been reported by Paquette and coworkers and entails an impressive 16-step route in which (*R*)-(−)-carvone is cleaved to an acyclic bromoester, which is then converted using a [2+2] cycloaddition to a bicyclo[3.1.1]heptanone. The bicyclo[5.3.1]undecenone core structure of the target is then derived through a ring expansion of a four- to an eight-membered ring.[15]

In considering a synthesis of salsolene oxide (**7**: Scheme 2), one is confronted with the task of assembling its bicyclo[5.3.1]undecane ring system, also found in taxanes and other natural products,[12] along with an uncommonly encountered bridgehead epoxide. Connectivity analysis[16] suggests four general ways in which this ring system could be assembled using a [4+4] cycloaddition strategy: connections of paired-bonds labeled **a**, **b**, **c**, or **d** (Scheme 2). The two intermolecular options (**c** and **d**) are excluded on mechanistic grounds as they would require formation of a highly strained bridgehead alkene. The intramolecular strategies using a type II [4+4] cycloaddition (**a** and **b**) are not without concerns as well as they too would lead to cycloadducts with bridgehead alkenes, albeit ones which would be less strained. If successful, however, route **a** would afford several important synthetic advantages. It positions all of the alkenes in the cycloadduct in exactly the locations needed for accessing the target functionality, offering an advantage over the other type II process (route **b**). Moreover, the three alkenes in cycloadduct **8** would be expected to exhibit differentiated reactivity. The more reactive bridgehead alkene would be expected to undergo epoxidation with chemo- and diastereoselectivity to provide the bridgehead epoxide of the target allowing then for selective reduction of the sterically less encumbered isopropenyl pi-system. In addition, the required bis-diene precursor **9** could be assembled readily from commercially available building blocks (Scheme 3). Ten carbons would come from the monoterpene myrcene (**16**), one from acetate, and four from methacrolein. The simplicity and brevity of this plan are a direct and unique consequence of the value of new strategy level reactions,[2a] in this case the type II [4+4] cycloaddition, as tools for achieving step economical syntheses.

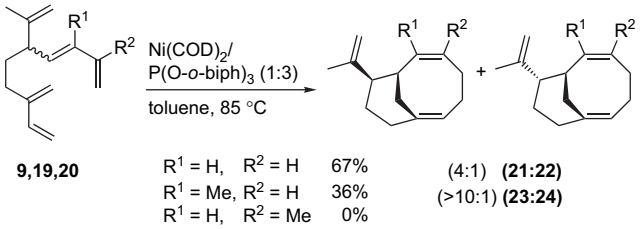
The synthesis of the tethered bis-dienes (**9**, **19**, and **20**: Scheme 3) required for testing the viability of this type II [4+4] process (route **a**: Scheme 2) began with the previously reported Büchi–Sharpless oxidation of commercially available myrcene (**16**) to myrcenol.[17] Conversion of the latter to its acetate **17** (88%) followed by Ireland–Claisen rearrangement[18] provided carboxylic acid **18** in 77% yield. The second diene subunit was then introduced through a two-step procedure involving condensation of the dianion of **18** individually with methacrolein, acrolein, or methylvinylketone, and subsequent decarboxylative dehydration of each resulting hydroxy acid to afford bis-dienes **9** (*E*-isomer only), **19** (*E*:*Z*=1:1), and **20** (*E*:*Z*=3:1) in comparable overall yields (40–50%). This strategy serves as an expedient and



Scheme 3. Synthesis of the bis-diene precursors for type II [4+4] cycloadditions.

general route to the bis-dienes required for type II [4+4] cycloadditions.

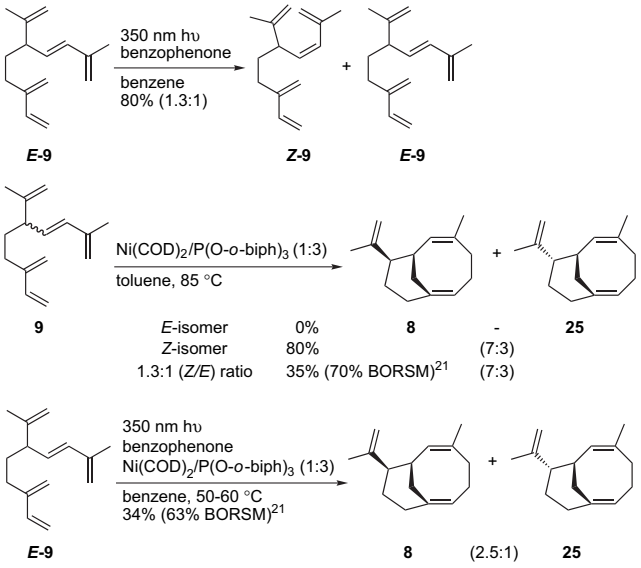
The viability of the key type II [4+4] cycloaddition was explored using various catalysts, ligands, and solvents with substrates **9**, **19**, and **20**. An effective procedure involved treatment of the bis-dienes **19** (*E*/*Z*=1:1) with $Ni(COD)_2$ (10 mol %) and P(*O*-*o*-biph)$_3$ (30 mol %) in toluene at 85 °C, which provided cycloadducts **21** and **22** (4:1) in 67% yield (Scheme 4). For comparative purposes, reaction of the 3-methyl substituted bis-dienes **20** (*E*:*Z*=1.4:1) was conducted under similar conditions and gave the cycloadduct **23** although in lower yield (36%). While unoptimized, these results offered encouragement for the viability of the key cycloaddition involving bis-diene *E*-**9**. Rather remarkably, however, when 2-methyl substituted bis-diene *E*-**9**, the potential precursor to salsolene oxide, was subjected to the above conditions, intramolecular cycloaddition did not occur. At extended reaction times, only intermolecular [4+4] cycloadducts formed slowly. Changes in solvent (THF and toluene), ligand (phosphines and phosphites), and metal-to-ligand ratios (from 1:1 to 1:3) did not alter this outcome. While the effect of substitution on the diene is of general mechanistic interest, the absence of type II cycloadducts in the reaction of *E*-**9** presented a significant problem with respect to the specific application of this reaction to the synthesis of salsolene oxide.



Scheme 4. Initial results of the type II [4+4] cycloaddition.

In our previous studies on nickel-catalyzed [4+2] cycloadditions, we observed that *E*- and *Z*-diene isomers reacted at different rates,[19] suggesting a potential solution to the above problem involving *E*-**9**. To address this point and to establish a more detailed analysis of the time course of these reactions, the cycloadditions of **19** and **20** were monitored by gas chromatography. As observed in [4+2] cycloadditions, the *Z*-isomers of **19** and **20** underwent [4+4] cycloaddition more rapidly than the *E*-isomers, reacting readily even at lower temperatures (60 °C). Typically, at 85 °C in the presence of $Ni(COD)_2$ (25 mol %) and P(*O*-*o*-biph)$_3$ (75 mol %) in toluene, *Z*-**19** was consumed completely within 25 min, during which time less than 20% of the corresponding *E*-**19** had reacted. Complete conversion of the latter required 5–6 h. Similar results were obtained for **20**; the *Z*-isomer was consumed in 2 h while the *E*-isomer required excess of 12 h for complete conversion.

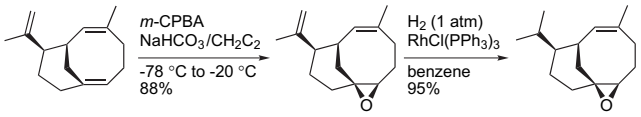
Guided by these encouraging results, a study of the behavior of *Z*-**9** was conducted. For this purpose, *E*-**9** was photoequilibrated (Rayonet reactor, 350 nm) in benzene in the presence of benzophenone as a sensitizer (10 mol %) to provide a 1.3:1 mixture of *Z*-**9** and *E*-**9** (80% yield) from which the *Z*-isomer could be obtained by chromatographic purification. In contrast to the behavior of *E*-**9**, when *Z*-**9** was subjected to typical reaction conditions cycloadducts **8** and **25** (7:3) were obtained in 80% yield (Scheme 5). In accord with the above stereochemical effects, when mixtures of *Z*-**9** and *E*-**9** were submitted to these reaction conditions, the *Z*-isomer was completely consumed in 10 min at 80 °C while the *E*-isomer remained unchanged. This striking difference in reactivity allowed convenient recycling of the unreactive isomer by photo-equilibration, thereby increasing the overall throughput of this route to salsolene oxide. Significantly, both processes, an in situ photo-equilibration and the [4+4] cycloaddition, could be achieved in one



Scheme 5. Serial photoisomerization and [4+4] reaction of **9**.

operation. This unoptimized procedure allowed the more reactive bis-diene isomer (*Z*-**9**) to be siphoned off through a [4+4] cycloaddition. A direct synthesis of the *Z*-isomer was not pursued as this photo-equilibration–cycloaddition process served to address both the mechanistic and strategic proof of concept goals of this initial study.

Chemoselective mono-epoxidation of triene **8** was achieved with *m*-CPBA at −78 °C to −20 °C to provide the desired epoxide **26** in 88% yield (Scheme 6). The presence of solid sodium bicarbonate in this reaction serves to suppress an acid-catalyzed rearrangement of the desired product. Finally, chemoselective hydrogenation of diene **26** was accomplished with Wilkinson's catalyst, providing salsolene oxide (**7**) in 95% yield.



Scheme 6. Completion of the synthesis of (±)-salsolene oxide.

3. Conclusion

The type II [4+4] cycloaddition has been shown to be a powerful tool in the synthesis of bicyclo[5.3.1]undecadienes, the core of a number of important natural products. An initial mechanistic study, examining the effects of substitution and alkene geometry on the cycloaddition, showed that both factors influence the reaction outcome. The most remarkable illustration of this influence was with the *E*- and *Z*-isomers of **9**, the former being unreactive while the latter reacting in high yield to provide bicyclo[5.3.1]undecadiene cycloadducts **8** and **25**. The use of a novel serial photoisomerization–cycloaddition process allowed the unreactive *E*-isomer to be photoequilibrated with the reactive *Z*-isomer and the latter to be siphoned off through a type II [4+4] cycloaddition. Type II cycloadduct **8** was converted to (±)-salsolene oxide (**7**) in two chemoselective steps. The value of new complexity increasing reactions in achieving step economical syntheses is suggested in part by the reduction in total step count (16–8 steps) made possible with this novel type II [4+4] cycloaddition.[15]

4. Experimental

4.1. Myrcenol

To a solution of myrcene (**16**, 35.6 g, 0.26 mol) in 250 mL CH_2Cl_2 was slowly added a mixture containing SeO_2 (14.3 g, 0.13 mol), 60 mL of a 90% aqueous *t*-butylhydroperoxide solution and an additional 150 mL CH_2Cl_2. During this period the reaction temperature was carefully controlled not to exceed 10 °C. After an additional 4 h at 10 °C, the reaction mixture was brought to room temperature and stirred overnight. Benzene was added to the reaction mixture and CH_2Cl_2 was removed in vacuo. The remaining benzene solution was diluted with Et_2O and washed twice with 10% aqueous NaOH and three times with a 10% aqueous $NaHSO_3$ solution, followed by washing with brine and drying with $MgSO_4$. After removal of the combined organic solvents in vacuo, the crude material was dissolved in methanol, cooled to 0 °C, and treated with an excess $NaBH_4$ (5 g) in small portions. After stirring overnight at room temperature the reaction mixture was hydrolyzed with a saturated aqueous NH_4Cl solution. Extraction with Et_2O, drying with $MgSO_4$, filtration, and concentration in vacuo gave crude myrcenol, which was purified via flash chromatography (SiO_2; hexane/ethyl acetate = 9:1 (v/v)). After purification 10.7 g (0.0703 mol, 25%) myrcenol was obtained as a colorless oil.

Spectral data matched that of the known compound.[17a]

4.2. Acetate 17

Myrcenol (8.8 g, 58 mmol) was dissolved in 50 mL dry pyridine. Acetic anhydride (11.8 g, 112 mmol) and a catalytic amount of DMAP (5.8 mmol) were added. The reaction mixture was stirred at 0 °C overnight. Removal of the solvent in vacuo, followed by flash chromatography (SiO_2; hexane/ethyl acetate = 9:1 (v/v)) gave 9.9 g (51 mmol, 88%) of the acetate as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): 6.38 (dd, *J*=17.6, 11.0 Hz, 1H); 5.52–5.50 (m, 1H); 5.26 (d, *J*=17.6 Hz, 1H); 5.08 (d, *J*=11.0 Hz, 1H); 5.04 (s, 1H); 5.00 (s, 1H); 4.47 (s, 2H); 2.27 (br s, 4H); 2.10 (s, 3H); 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 145.6, 138.7, 130.6, 129.1, 115.9, 113.1, 70.1, 30.8, 26.3, 21.0, 13.9. IR (thin film): ν 3089 (m); 2934 (m); 1741 (s); 1596 (m); 1458 (m); 1376 (m); 1232 (s); 1023 (s) cm^{-1}. MS (70 eV): *m/z* (%) 159 (4); 135 (16); 119 (87); 93 (100); 92 (26); 91 (45); 79 (42).

4.3. Carboxylic acid 18

To a solution of diisopropylamine (3.5 g, 34.1 mmol) in 50 mL THF was added *n*-BuLi in hexane (14.2 mL of a 2.5 M solution, 35.5 mmol) at 0 °C. After 20 min at 0 °C the solution was cooled to −78 °C and a precooled solution (−78 °C) of acetate **17** (4.73 g, 24.4 mmol) in 50 mL THF was added slowly via cannula transfer. The reaction mixture was stirred at −78 °C for 20 min followed by adding chlorotrimethylsilane (3.7 g, 29 mmol, freshly distilled from CaH) in one batch. The reaction mixture was brought to room temperature and then refluxed for 5 h. After cooling, 10 mL methanol was added, followed by adding 1 g LiOH and 20 mL water. The resulting mixture was stirred overnight, concentrated, diluted with water, and extracted with Et_2O (2×10 mL). The aqueous layer was acidified with 1 N HCl and extracted several times with Et_2O, followed by washing with brine. The combined organic fractions were dried with $MgSO_4$ and concentrated in vacuo. Purification of the crude material by filtration through a plug of SiO_2 (hexane/ethyl acetate = 1:1 as eluent) yielded 3.66 g (18.9 mmol, 77%) carboxylic acid **18** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.36 (dd, *J*=17.6, 10.8 Hz, 1H); 5.20 (d, *J*=17.6 Hz, 1H); 5.05 (d, *J*=10.8 Hz, 1H); 5.00 (s, 1H); 4.99 (s, 1H); 4.84 (s, 1H); 4.81 (s, 1H); 2.62 (m, 1H); 2.42–2.45 (m, 2H); 2.14 (m, 2H); 1.70 (s, 3H); 1.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 146.0, 145.5, 138.8, 115.8, 113.1, 112.6, 43.3, 39.0, 31.4, 28.9,

18.7. IR (thin film): ν 3078 (s); 2932 (s); 1707 (s); 1644 (m); 1597 (m); 1440 (m); 1409 (m); 1293 (m) cm^{-1}. HRMS: calcd for $C_{12}H_{18}O_2$ 194.1306, found 194.1308.

4.4. General preparation of bis-dienes

A solution of lithium diisopropylamine in THF was prepared by adding *n*-BuLi (15.5 mL of a 2.4 M solution in hexane, 37.1 mmol) to diisopropylamine (3.75 g, 37.1 mmol) in 100 mL abs THF at 0 °C. To this freshly prepared solution was added acid **18** (3.0 g, 15.4 mmol) in 50 mL THF. The complete generation of the desired dianion was ensured by warming the resulting mixture to 50 °C. After 1.5 h the reaction was cooled down to −78 °C and freshly distilled methacrolein (1.8 g, 26 mmol, distilled over $CaSO_4$) was added and the mixture stirred overnight. Water was added to the reaction and the THF removed in vacuo. The crude β-hydroxy acid was obtained after acidifying with 1 N HCl, extracting with Et_2O, drying the combined organic layers with $MgSO_4$, and washing with brine, followed by filtration and removal of the organic solvent in vacuo.

The crude β-hydroxy acid was dissolved in 200 mL toluene and *N*,*N*-dimethyl-dineopentylketal-formamide (10 mL, 8.29 g, 36 mmol) and pyridine (0.5 mL) were added. The reaction mixture was heated to 60 °C for 1 h while a slight evolution of CO_2 was visible. When complete conversion was reached (TLC) the solution was concentrated in vacuo and acidified with 0.5 N HCl. Extraction with Et_2O, washing with brine, drying with $MgSO_4$, filtration, and evaporation of the combined fractions were followed by flash chromatography (SiO_2, hexane) yielding bis-diene *E*-**9** (1.3 g, 6 mmol, 40%).

4.4.1. Bis-diene *E*-9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.4 (dd, J=17.6, 11.0 Hz, 1H); 6.18 (d, J=15.7 Hz, 1H); 5.57 (dd, J=15.7, 8.0 Hz, 1H); 5.22 (d, J=17.6 Hz, 1H); 5.06 (d, J=11.0 Hz, 1H); 5.02 (m, 2H); 4.92 (br s, 2H); 4.80 (br s, 2H); 2.75 (m, 1H); 2.19 (m, 2H); 1.85 (s, 3H); 1.71 (s, 3H); 1.89–1.61 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 146.4, 142.0, 138.9, 133.0, 132.8, 115.7, 115.0, 113.2, 110.7, 50.3, 31.6, 29.2, 20.1, 18.7. IR (thin film): ν 3081 (m); 2969 (m); 2937 (s); 1786 (w); 1734 (w); 1644 (m); 1595 (m); 1452 (m); 1438 (m); 991 (m); 966 (s) cm^{-1}. HRMS: calcd for $C_{15}H_{22}$ 202.1721, found 202.1719.

4.4.2. Bis-diene *E*-19 (isolated as a mixture of *E*- and *Z*-isomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.27–6.42 (m, 2H); 6.08 (dd, J=15.0, 10.4 Hz, 1H); 5.65 (dd, J=8.0, 15.0 Hz, 1H); 5.22 (d, J=17.6 Hz, 1H); 5.13 (d, J=16.8 Hz, 1H); 5.05 (d, J=11.0 Hz, 1H); 5.00–5.02 (m, 3H); 4.79 (br s, 2H); 2.74 (q, J=7 Hz, 1H); 2.20 (m, 2H); 1.60–1.80 (m, 2H); 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 146.3, 138.8, 137.2, 137.1, 131.1, 115.7, 115.5, 113.2, 110.9, 50.0, 31.2, 29.2, 20.0. IR (thin film): ν 3086 (w); 2925 (s); 2854 (m); 1797 (w); 1738 (w); 1643 (m); 1452 (m); 1375 (w); 1248 (w); 1003 (m) cm^{-1}. HRMS: calcd for $C_{14}H_{20}$ 188.1565, found 188.1565.

4.4.3. Bis-diene *Z*-19 (isolated as a mixture of *E*- and *Z*-isomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (m, 1H); 6.35 (m, 1H); 6.09 (dd, J=11.0, 9.0 Hz, 1H); 5.34 (dd, J=11.0, 11.0 Hz, 1H); 5.00–5.20 (m, 6H); 4.78 (br s, 2H); 3.18 (m, 1H); 2.10–2.30 (m, 2H); 1.60–1.80 (m, 2H); 1.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 146.2, 138.8, 134.8, 132.2, 129.8, 117.7, 115.7, 113.2, 110.3, 45.0, 32.1, 29.1, 20.4. See Section 4.4.2 for IR and HRMS data.

4.4.4. Bis-diene *E*-20 (isolated as a mixture of *E*- and *Z*-isomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.38 (m, 2H); 5.40 (d, J=9.6 Hz, 1H); 5.21 (d, J=17.6 Hz, 1H); 5.13 (d, J=17.3 Hz, 1H); 5.06 (d, J=11.0 Hz, 1H); 5.00 (m, 3H); 4.70 (br s, 2H); 3.05 (m, 1H); 2.16 (m, 2H); 1.50–1.70 (m, 2H); 1.78 (d, J=1.2 Hz, 3H); 1.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 146.3, 141.6, 138.9, 135.5, 134.5, 115.7, 113.2, 111.1, 110.3, 45.6, 32.2, 29.2, 20.3, 12.1. IR (thin film): ν 3088 (m); 2979 (m); 2940 (s); 2863 (m); 1642 (m); 1595 (s); 1441 (m); 1373 (m) cm^{-1}. HRMS: calcd for $C_{15}H_{22}$ 202.1721, found 202.1714.

4.4.5. Bis-diene *Z*-20 (isolated as a mixture of *E*- and *Z*-isomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (dd, J=17.5, 10.8 Hz, 1H); 6.38 (m, 1H); 4.90–5.40 (m, 7H); 4.78 (br s, 2H); 3.15 (m, 1H); 2.16 (m, 2H); 1.50–1.70 (m, 2H); 1.87 (s, 3H); 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 141.5, 138.8, 133.8, 133.4, 132.8, 115.7, 114.0, 113.2, 110.1, 44.5, 32.4, 29.2, 20.3, 20.0. See Section 4.4.4 for IR and HRMS data.

4.5. Photochemical isomerization of bis-diene *E*-9

Bis-diene *E*-**9** (200 mg, 1.0 mmol), benzophenone (18 mg, 0.1 mmol), and dodecane (200 mg, internal standard) were dissolved in 200 mL benzene. The resulting solution was purged with argon for 0.5 h followed by irradiation with 350 nm light (Rayonett photoreactor). The photochemical induced *E*/*Z*-equilibration was followed by GC and stopped when an *E*/*Z*-ratio of 1.3:1.0 was reached. Evaporation of the solvent and filtration through a plug of SiO_2 (hexane) gave 80% of the bis-diene isomers *E*-**9** and *Z*-**9**.

4.5.1. Bis-diene *Z*-9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.37 (dd, J=17.6, 10.7 Hz, 1H); 5.94 (d, J=11.5 Hz, 1H); 5.34 (dd, J=11.5, 11.0 Hz, 1H); 5.21 (d, J=17.6 Hz, 1H); 5.05 (d, J=10.7 Hz, 1H); 5.01 (br s, 1H); 4.99 (br s, 1H); 4.95 (br s, 1H); 4.88 (br s, 1H); 4.77 (br s, 2H); 3.32 (m, 1H); 2.2 (m, 2H); 1.89 (s, 3H); 1.73 (s, 3H); 1.6–1.9 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 146.4, 141.6, 138.9, 133.6, 131.4, 115.6, 115.4, 113.1, 110.4, 45.2, 32.8, 29.2, 23.3, 20.3. IR (thin film): ν 3081 (m); 2939 (s); 1644 (m); 1595 (m); 1452 (m); 1373 (m) cm^{-1}.

4.6. General procedure for the [4+4] cycloaddition

To a 100 mL Schlenk flask were added bis-dienes *E*-**9** and *Z*-**9** (1.3:1 ratio, 47 mg, 0.223 mmol), toluene (70 mL), dodecane (47 mg, internal standard), and P(*O*-*o*-biph)$_3$ (96.8 mg, 0.180 mmol) under an atmosphere of argon. The flask was heated to 60 °C and Ni(COD)$_2$ (0.8 mL of a 0.07 M stock solution) was added via syringe, and the flask was sealed. The dodecane/bis-diene ratio was determined and its conversion monitored by GC. After 4 h the conversion of *Z*-bis-diene *Z*-**9** was complete and the reaction was stopped via cooling and exposure to air. Filtration of the toluene solution through a plug of silica and elution with Et_2O

removed the nickel salts. Concentration in vacuo was either followed by another cycle of irradiation–Ni(0)-cyclization or by flash chromatography (SiO_2, hexane). An effective separation of the stereoisomers **8** and **25** was achieved with a long chromatographic column (typically 90 cm× 2.5 cm for a 100 mg sample). For mechanistic purposes all trace bis-dienes and 1,3-diene containing side products could be removed from the product mixture prior to flash chromatography by treatment with tetracyanoethene, added in excess at room temperature to a solution of the crude product mixture in CH_2Cl_2 followed by stirring for several minutes. All 1,3-diene containing materials were converted to highly polar products and were easily removed from the nonpolar products **8** and **25** with flash chromatography.

4.6.1. Cyclooctadiene 8. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.24 (dd, J=8.3, 2.5 Hz, 1H); 5.11 (br s, 1H); 4.97 (d, J=1 Hz, 1H); 4.92 (br s, 1H); 3.06 (m, 1H); 2.93 (br s, 1H); 2.84 (dt, J=13.0, 2.0 Hz, 1H); 2.4 (m, 1H); 2.25 (m, 1H); 2.11 (m, 1H); 1.77 (s, 3H); 1.73 (br s, 3H); 1.65–2.10 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 142.6, 133.8, 130.5, 118.1, 111.6, 48.3, 41.2, 35.2, 31.8, 30.8, 30.3, 27.8, 25.1, 23.3. IR (thin film): ν 2930 (s); 1642 (m); 1495 (m); 1444 (m); 1006 (m) cm^{-1}. HRMS: calcd for $C_{15}H_{22}$ 202.1721, found 202.1719. Anal. Calcd for $C_{15}H_{22}$: C, 89.04%; H, 10.96%. Found: C, 89.00%; H, 10.85%.

4.6.2. Cyclooctadiene 25. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.26 (dd, J=8.4, 2.7 Hz, 1H); 5.02 (br s, 1H); 4.86 (d, J=1.4 Hz, 1H); 4.63 (s, 1H); 3.24 (m, 1H); 3.04 (m, 1H); 2.94 (br s, 1H); 2.42 (m, 1H); 1.95–2.22 (m, 4H); 1.69–1.83 (m, 3H); 1.77 (s, 3H); 1.70 (t, J=1.9 Hz, 3H); 1.49 (ddd, J=24.8, 12.5, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 141.5, 134.0, 123.5, 118.6, 110.2, 49.8, 39.9, 37.2, 36.4, 32.2, 31.5, 27.3, 24.6, 22.7. IR (thin film): ν 2964 (s); 2928 (s); 2875 (m); 2844 (m); 1642 (m); 1495 (w); 1439 (m); 1374 (w); 1058 (w); 1017 (w) cm^{-1}.

4.6.3. Cyclooctadiene 21. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.49 (m, 1H); 5.37 (d, J=11.3 Hz, 1H); 5.28 (m, 1H); 4.97 (br s, 1H); 4.95 (br s, 1H); 3.00 (br s, 1H); 2.85 (m, 2H); 2.47 (m, 1H); 2.27 (t, J=11.0 Hz, 1H); 2.16 (br s, 1H); 1.92–2.10 (m, 5H); 1.78 (s, 3H); 1.70 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.8, 142.0, 136.7, 126.4, 118.1, 111.2, 47.0, 42.1, 34.6, 30.4, 29.9, 26.8, 25.7, 22.8. IR (thin film): ν 2934 (s); 1641 (m); 1456 (m); 1024 (m) cm^{-1}. HRMS: calcd for $C_{14}H_{20}$ 188.1565, found 188.1566.

4.6.4. Cyclooctadiene 22. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.48 (m, 1H); 5.27 (m, 2H); 4.86 (d, J=1.3 Hz, 1H); 4.63 (s, 1H); 3.2 (dt, J=7.0, 3.0 Hz, 1H); 2.92 (m, 1H); 2.47 (m, 1H); 1.70–2.30 (m, 7H); 1.77 (s, 3H); 1.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.0, 141.5, 130.5, 127.1, 118.8, 110.2, 49.2, 41.2, 37.3, 36.2, 31.7, 27.4, 25.6, 22.8. IR (thin film): ν 3008 (m); 2932 (s); 2875 (s); 1643 (m); 1492 (m); 1440 (m); 1375 (m); 1038 (w); 999 (w) cm^{-1}. HRMS: calcd for $C_{14}H_{20}$ 188.1565, found 188.1564.

4.6.5. Cyclooctadiene 23. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.43 (m, 1H); 5.27 (dd, J=7.0, 3.0 Hz, 1H); 4.97 (d, J=1.4 Hz, 1H); 4.96 (br s, 1H); 2.98 (dd, J=13.0, 1.7 Hz, 1H); 2.89 (m, 2H); 2.29–2.51 (m, 3H); 1.85–2.10 (m, 5H); 1.77 (s, 3H); 1.74 (s, 3H); 1.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 141.8, 139.5, 123.9, 118.5, 111.3, 45.4, 43.1, 34.3, 30.1, 29.6, 27.8, 26.6, 25.1, 22.7. IR (thin film): ν 3025 (m); 2964 (s); 2934 (s); 2887 (s); 1641 (m); 1497 (m); 1376 (m); 1184 (w); 1099 (w); 1023(m); 888 (m) cm^{-1}. HRMS: calcd for $C_{15}H_{22}$ 202.1721, found 202.1729.

4.7. Photochemical and Ni(0)-catalyzed formation of 8 and 25

Isomerically pure *E*-**9** (49 mg, 0.243 mmol) was dissolved in 70 mL benzene and dodecane (54 mg, internal standard), benzophenone (14 mg, 0.073 mmol), and P(*O*-*o*-biph)$_3$ (98 mg, 0.183 mmol) were added. Argon was purged through the resulting reaction mixture for 0.5 h. A stock solution of Ni(COD)$_2$ in benzene (0.9 mL, 0.07 M) was added and the resulting reaction mixture was irradiated (350 nm, Rayonett chamber) at 50–60 °C. The reaction was monitored by GC. After 2.5 h, 54% of the initial *E*-**9** was converted and at this point a 34% yield (63% BORSM)[20] of **8** and **25** (2.5:1 ratio) was obtained (GC). A longer reaction time did not significantly increase the observed yields.

4.7.1. Epoxide 26. Cyclooctadiene **8** (32 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (20 mL) and $NaHCO_3$ (34.4 mg, 0.41 mmol) was added. The reaction mixture was cooled to −78 °C, followed by addition of *m*-CPBA (33 mg, 0.19 mmol). During a period of 1–2 h the reaction was gradually allowed to warm to −20 °C and the epoxide formation was monitored by TLC. When a complete conversion was reached 1 mL triethylamine was added. After stirring for 0.5 h, the reaction mixture was filtered through a plug of SiO_2 (hexane/ethyl acetate). Concentration was followed by flash chromatography (SiO_2, hexane/ethyl acetate = 9:1 (v/v)) yielding epoxide **26** (31 mg, 0.14 mmol, 88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.16 (s, 1H); 5.01 (d, J=1.0 Hz, 1H); 4.93 (s, 1H); 3.0 (br s, 1H); 2.83 (m, 1H); 2.75 (dd, J=6.8, 1.8 Hz, 1H); 1.87–2.21 (m, 7H); 1.85 (m, 1H); 1.78 (br s, 6H); 1.69 (ddd, J=14.3, 5.5, 3.4 Hz, 1H); 1.04 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 134.2, 130.2, 111.7, 64.2, 61.5, 46.1, 38.0, 32.3, 29.6, 27.4, 27.1, 26.5, 24.0, 22.7. IR (thin film): ν 3018 (w); 2964 (s); 2938 (s); 2882 (m); 1640 (m); 1493 (m); 1447 (s); 1375 (m); 1239 (w); 1063 (w); 1003 (m) cm^{-1}. HRMS: calcd for $C_{15}H_{22}O$ 218.1670, found 218.1669. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52%; H, 10.16%. Found: C, 82.83%; H, 10.48%.

4.7.2. Salsolene oxide 7. To a solution of epoxide **26** (24 mg, 0.11 mmol) in benzene (30 mL) was added [RhCl(PPh$_3$)$_3$] (20 mg, 0.02 mmol). The reaction vessel was saturated with hydrogen by several cycles of evaporation and flushing with hydrogen. The product formation was monitored by GC and filtered through a plug of ALOX III (Et_2O). Flash chromatography (SiO_2, hexane/diethyl ether = 9:1 (v/v)) of the crude product gave (±)-salsolene oxide (23 mg, 0.10 mmol, 95%). The spectra are identical to the natural product.[14]

Acknowledgements

This research was supported by the National Science Foundation (CHE-040638). Fellowship support from Eli Lilly and Company (M.P.C.) and the Alexander von Humboldt Foundation (B.W.) are gratefully acknowledged. Mass spectra were provided by the Mass Spectrometry Facility, University of California, San Francisco supported by the NIH Division of Research Resources.

References and notes

1. (a) Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25–31; (b) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind. (London)* **1997**, 765–769; (c) Wender, P. A.; Miller, B. L. *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI: Greenwich, 1993; Vol. 2, pp 27–66.
2. (a) For a compelling example of step economy through new reactions, see: Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625–2628; (b) For discussions of complexity and connectivity analyses, see: Barone, R.; Chanon, M. *Tetrahedron* **2005**, *61*, 8916–8923; (c) Chanon, M.; Barone, R.; Baralotto, C.; Julliard, M.; Hendrickson, J. B. *Synthesis* **1998**, 1559–1583; (d) Bertz, S. H.; Sommer, T. J. *Chem. Commun.* **1997**, 2409–2410; (e) Ref. 1c.
3. (a) For the first metal-catalyzed intramolecular [4+2] reaction, see: Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432–6434; (b) For the first metal-catalyzed intramolecular [5+2] reaction, see: Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720–4721; (c) For the first metal-catalyzed intermolecular [5+2] reaction, see: Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976–10977; (d) For the first [5+2+1] reaction, see: Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876–2877; (e) For the first [5+2+1] reaction using allenes, see: Wegner, H. A.; de Meijere, A.; Wender, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 6530–6531; (f) For the first report of a diene–yne [4+2+1] and dienyl Pauson–Khand reaction, see: Wender, P. A.; Deschamps, N. M.; Gamber, G. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1853–1857; (g) For the first intermolecular dienyl Pauson–Khand reaction, see: Wender, P. A.; Deschamps, N. M.; Williams, T. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3076–3079; (h) For the first report of a diene–ene [2+2+1], see: Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *J. Am. Chem. Soc.* **2004**, *126*, 5948–5949; (i) For the first [5+1+2+1] reaction, see: Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 2836–2837.
4. Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Justus Liebigs Ann. Chem.* **1948**, *560*, 1–92.
5. Reed, H. W. B. *J. Chem. Soc.* **1954**, 1931–1941.
6. Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 105–115.
7. For reviews, see: (a) Jolly, P. W. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: New York, NY, 1982; Vol. 8, pp 671–711; (b) Keim, W.; Behr, A.; Roper, M. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: New York, NY, 1982; pp 371–461; (c) Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Academic: New York, NY, 1974; Vol. 1, pp 1–518; (d) Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Academic: New York, NY, 1975; Vol. 2, pp 1–416; (e) Heimbach, P.; Jolly, P. W.; Wilke, G. *Advances in Organometallic Chemistry*; Stone, F. G. A., West, R., Eds.; Academic: New York, NY, 1970; Vol. 8, pp 29–86.
8. Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678–4679.
9. (a) Murakami, M.; Itami, K.; Ito, Y. *Synlett* **1999**, 951–953; (b) Lee, P. H.; Lee, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3253–3256; (c) Takahashi, T.; Sun, W.-H.; Liu, Y.; Nakajima, K.; Kotora, M. *Organometallics* **1998**, *17*, 3841–3843.
10. Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221–2224.
11. Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904–5906.
12. Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881–930.
13. Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, *12*, 1089–1094.
14. Weyerstahl, P.; Marschall, H.; Wahlburg, H.-C.; Kaul, V. K. *Liebigs Ann. Chem.* **1991**, 1353–1355.
15. (a) Paquette, L. A.; Sun, L.-Q.; Watson, T. J. N.; Friedrich, D.; Freeman, B. T. *J. Am. Chem. Soc.* **1997**, *119*, 2767–2768; (b) Paquette, L. A.; Sun, L.-Q.; Watson, T. J. N.; Friedrich, D.; Freeman, B. T. *J. Org. Chem.* **1997**, *62*, 8155–8161.
16. (a) Barberis, F.; Barone, R.; Arbelot, M.; Baldy, A.; Chanon, M. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 467–471; (b) See Ref. 2a.
17. (a) Büchi, G.; Wüest, H. *Helv. Chim. Acta* **1967**, *50*, 2440–2445; (b) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528.
18. For a review, see: Chai, Y.; Hong, S.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905–2928.
19. (a) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962–2963; (b) Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255–1275.
20. BORSM yield is based on recovered starting material.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7512–7520
Tetrahedron

Nickel-catalyzed multi-component connection reaction of isoprene, aldimines (lactamines), and diphenylzinc

Keisuke Kojima,[a] Masanari Kimura,[a] Satoshi Ueda[b] and Yoshinao Tamaru[b,*]

[a]*Graduate School of Science and Technology, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan*
[b]*Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan*

Received 15 November 2005; revised 2 March 2006; accepted 2 March 2006
Available online 8 June 2006

This manuscript was dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry

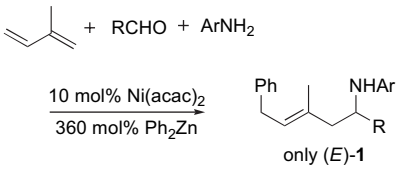
Abstract—$Ni(acac)_2$ catalyzes the four-component connection reaction of diphenylzinc, isoprene, aromatic aldehydes, and aromatic amines in this order and provides stereochemically homogeneous (*E*)-1-arylamino-1-aryl-3-methyl-5-phenyl-3-pentenes (**1**) in excellent yields. Aliphatic aldehydes react similarly and give (*E*)-1-arylamino-1-alkyl-3-methyl-5-phenyl-3-pentenes (**1**) in slightly reduced yields. When the alkyl groups are bulky, in addition to **1** are formed (*E*)-1-arylamino-1-alkyl-*4-methyl*-5-phenyl-3-pentenes (**1′**) as the minor products. Lactamines prepared in situ from five- and six-membered lactols and aromatic amines are more reactive than alkyl aldehyde aldimines and furnish (*E*)-4-arylamino-6-methyl-8-phenyl-6-octen-1-ols (**4**) and (*E*)-5-arylamino-7-methyl-9- phenyl-7-nonen-1-ols (**5**), respectively, in good yields with excellent *E*-stereoselectivity.

1. Introduction

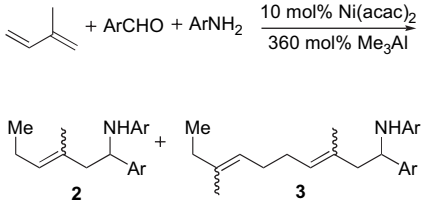
Multi-component connection reactions of simple molecules are straightforward and efficient methods to construct desired molecules which have been realized mostly by making the best use of transition-metal catalysis.[1] Isoprene and aldimines are among the most important building blocks; isoprene is a ubiquitous constituent of the carbon frameworks of natural products and aldimines serve as a nitrogen source of many physiologically interesting compounds. Regio- (C1 vs C4) and stereoselective (*E* vs *Z*) incorporation of isoprene into molecules is a rather difficult task and it has been a challenge for synthetic organic chemists to establish methods to manipulate isoprene in desired ways.[2] Aldimines are among the least reactive carbonyl compounds and many studies, particularly in the past decade, have been devoted to their activation and utilization as electrophiles toward carbonucleophiles.

Recently, we demonstrated that a nickel(0) species nicely catalyzed the three-component connection reaction of organometals (M=Zn and B), isoprene, and aldehydes to afford homoallyl alcohols, where isoprene reacted regioselectively with aldehydes at the C1 position and with organometals at the C4 position.[3]

We also clarified that a similar methodology could be applied to the reactions with aldimines; phenylative multi-component connection reaction was best performed with diphenylzinc (Eq. 1), while methylative reaction was most successful with trimethylaluminum (Eq. 2).[4,5] Methylative reaction, however, is still not at a practically useful level; the reaction yields **2** with modest stereoselectivity (*E*:*Z*= 2:1–10:1) along with **3** as minor products, both being inseparable by conventional column chromatography. Further improvement of the reaction conditions, enabling the stereoselective formation of (*E*)-**2** minimizing the formation **3**, has been under our ongoing extensive study.



(1)



(2)

Keywords: Aldimine; Diphenylzinc; Isoprene; Lactol; Multi-component connection; Nickel catalysis.
* Corresponding author. Tel./fax: +81 95 819 2677; e-mail: tamaru@net.nagasaki-u.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.116

In this article, we disclose a full account of phenylative multi-component connection reaction, which provides (*E*)-**1** in good yields and with excellent stereoselectivity for a variety of aldimines prepared in situ from aromatic aldehydes and aromatic amines (R=Ar, Eq. 1). The reaction can be successfully extended to aliphatic aldehyde-*p*-anisidine imines (R=alkyl, Ar=*p*-anisyl, Eq. 1), which is highlighted by the reaction with lactamines, generated in situ from lactols (cyclic hemiacetals) and aromatic amines (Eq. 3). This might be a great achievement, not only because two important building blocks, isoprene and aldimines, are incorporated in the products, but also because tri-substituted (*E*)-homoallylamines **1** and (*E*)-homoallylamino alcohols **4** and **5** are produced with a single operation in one flask in the yields of a synthetically useful level under nickel catalysis. These products may be of great concern for synthetic organic chemists and also for life science researchers.

2. Results and discussion

2.1. Ni-catalyzed four-component connection reaction of Ph_2Zn, isoprene, aldehydes, and aromatic amines

The reaction of benzaldehyde-*p*-anisidine imine under the identical conditions established for the multi-component connection reaction of aldehydes[3] was quite disappointing and provided the expected product **1a** (**1**, R=Ph, Ar=*p*-anisyl, Eq. 1) in as low as 14% yield among many other intractable products (*Experiment* 1). Use of 1 equiv *p*-anisidine as an additive turned out very effective to increase the yield of **1a** (63%, 30 °C for 2 h, *Experiment* 2). Remarkable improvement in the yield was brought about when the reaction was conducted using the aldimine formed in situ from benzaldehyde and *p*-anisidine (2 equiv), where **1a** was obtained in 80% yield (run 1, Table 1, *Experiment* 3). *Experiments* 2 and 3 only differ in the absence or presence of water (1 equiv), respectively. *Experiment* 4, which was undertaken under the identical conditions to those of *Experiment* 1 in the presence of 1 equiv of water, gave **1a** (24%) in a slightly better yield than *Experiment* 1. All these results combine to indicate that both water and *p*-anisidine, 1 equiv each, are essential to give rise to **1a** in satisfactory yield.

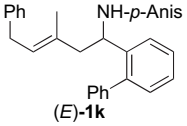
Many precedents point to the success of nucleophilic alkylation of aldimines[6] depending on the steric and electronic effects of both the aldehyde[7] and the nitrogen substituents,[8] and sometimes heteroatoms on these substituents exert tremendous effects on the reaction efficiency.[6,9]

In order to optimize the nitrogen substituents, we examined a wide range of aniline derivatives either bearing an electron-donating or an electron-withdrawing substituent under the conditions established above. The results are summarized in runs 2–9 (Table 1). Except for *o*-chloro- and *o*-bromoanilines (runs 6 and 8), no significant differences in reactivity and yields were observed over a wide range of pK_a of aniline derivatives[10] (e.g., pK_a(*o*-Br)=2.53, pK_a(*p*-OMe)=5.36). In most cases, the reactions were complete within 1–3 h and provided **1** in more than 90% yields. The reactions were monitored with TLC. The sluggishness and the low yields observed for *o*-chloro- and *o*-bromoanilines might be attributed to deactivation of a nickel catalyst rather than steric hindrance of the reaction (vide infra).

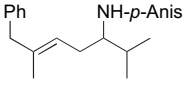
Table 1. Ni-catalyzed four-component connection reaction of Ph_2Zn, isoprene, aldehydes, and amines (Eq. 1)[a]

Run	Aldehyde	Amine	Time (h)	Yield[b]
	R			**3**
1	Ph	*p*-MeOPh	2	(*E*)-**1a**:80
2	Ph	*p*-MePh	1	(*E*)-**1b**:96
3	Ph	Ph	1	(*E*)-**1c**:90
4	Ph	*o*-(F)Ph	3	(*E*)-**1d**:**98**
5	Ph	*p*-(F)Ph	2	(*E*)-**1e**:94
6	Ph	*o*-(Cl)Ph	24	(*E*)-**1f**:30
7	Ph	*p*-(Cl)Ph	2	(*E*)-**1g**:78
8	Ph	*o*-(Br)Ph	24	—[c]
9	Ph	*p*-(Br)Ph	3	(*E*)-**1h**:94
10	Ph	*n*-Hexyl	6	—[c]
11	*p*-Tol	*p*-MeOPh	2	(*E*)-**1i**:83
12	*p*-Anis	*p*-MeOPh	6	(*E*)-**1j**:44
13	*o*-(Cl)Ph	*p*-MeOPh	6	(*E*)-**1k**:87[d]
14	*p*-(Cl)Ph	*p*-MeOPh	1	(*E*)-**1l**:61
15	*o*-(F)Ph	*p*-MeOPh	2	(*E*)-**1m**:94
16	*p*-(F)Ph	*p*-MeOPh	1	(*E*)-**1n**:96
17	2-Furyl	*p*-MeOPh	1	(*E*)-**1o**:98
18	2-Furyl	*p*-(Cl)Ph	1	(*E*)-**1p**:81
19	n-C_7H_{15}	*p*-MeOPh	6	(*E*)-**1q**:76
20	*i*-Pr	*p*-MeOPh	6	(*E*)-**1r**:57[e]

[a] Reaction conditions: an aldehyde (1 mmol) and an amine (2 mmol) in THF (2mL) at 30 °C overnight, and then $Ni(acac)_2$ (0.1 mmol in 3 mL of THF), isoprene (4 mmol), and Ph_2Zn (3.6 mmol) at 30 °C.
[b] Yields for the isolated spectroscopically homogeneous materials.
[c] Complex mixture of products.
[d] (*E*)-1-*p*-Anisylamino-3-methyl-5-phenyl-1-[(2-phenyl)phenyl]-3-pentene ((*E*)-**1k**, see below).
[e] A mixture of (*E*)-**1r** and its regioisomer (*E*)-**1r′** (see below) in a ratio of 2:1.



(*E*)-**1k**



(*E*)-**1r'**

Benzaldehyde imines of alkyl amines, e.g., *n*-hexylamine, on the other hand, showed completely different reactivity and gave intractable mixtures of products (run 10).

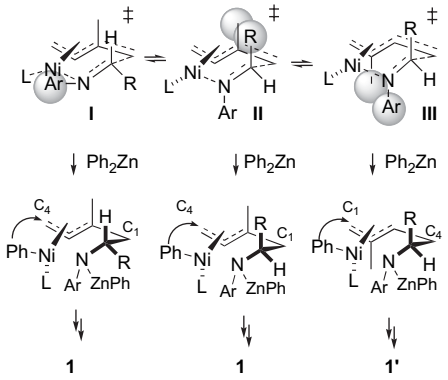
We next examined applicability of the present reaction to other aromatic aldehydes including 2-furaldehyde using *p*-anisidine as an aromatic amine (runs 11–18). Judging from the yields of **1a–h**, *p*-anisidine may not be the best choice of aromatic amines; however, we used it from a practical viewpoint. The *p*-methoxyphenyl group might be regarded as a protecting group of amines; it could be easily removed oxidatively, yielding free primary amines of the product **1** in good yields.[7c,9d,11]

All aromatic aldehydes, irrespective of the steric (*o*- and *p*-) and electronic (electron-donating and electron-withdrawing) nature of the substituents, reacted smoothly at 30 °C and provided the expected products **1** in modest to excellent yields. Interestingly, while the C–Cl bond of the *p*-chloro isomer **1l** remained intact, the C–Cl bond of the *o*-chloro isomer underwent cross-coupling reaction[12] with Ph_2Zn and provided **1k** exclusively in good yield (runs 13 and 14, footnote d, Table 1). The *o*-fluoro counterpart **1m** withstood the cross-coupling reaction (run 15).

The reaction could be extended to aliphatic aldehydes with limited success. Two typical examples, *n*-octanal (a primary

aldehyde) and 2-methylpropanal (a secondary aldehyde), were examined. The results are shown in runs 19 and 20. *n*-Octanal-*p*-anisidine imine provided the expected homoallylamine (*E*)-**1q** as a single isomer in good yield (run 19); however, sterically demanding 2-methylpropanal-*p*-anisidine imine provided an inseparable mixture of two isomers **1r** and **1r′**, the latter arising from incorporation of isoprene in an opposite direction (run 20, see footnote e).

This erosion of regioselectivity might be rationalized on the steric ground as discussed before (Scheme 1);[5c] the reaction would avoid a putative transition state **I** that places both the imine substituents at a di-equatorial position of a cyclic structure, since it suffers from severe gauche repulsion between the ligand on Ni and the aromatic ring on N. Instead, the reaction would proceed through a transition state **II**, where both the aldimine substituents locate in a diaxial position.[13] When R is of great steric bulk, 1,3-quasi-diaxial repulsion between R and the methyl group of isoprene becomes substantial in a transition state **II**, and another transition state **III**, placing isoprene in an opposite direction, would become to contribute to the reaction to a certain extent and would lead to **1′** as a side product.



Scheme 1. Transition states leading to regioisomers **1** and **1′**.

The stereochemical homogeneity of **1** was confirmed with ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectroscopies. The *E* structure of **1** was determined on the basis of NOE experiments. Some representative data are shown in Figure 1. The *E* structure of the regioisomer **1′** was also determined by NOE experiments.

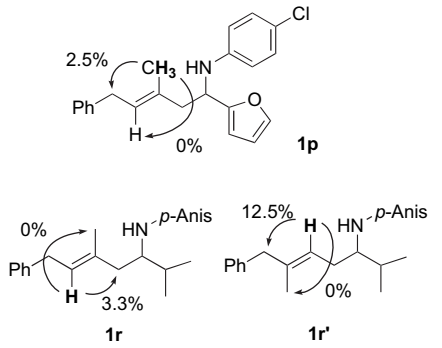
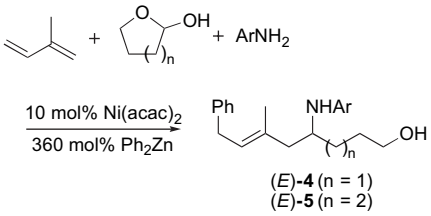


Figure 1. Percent increments of area intensities observed by irradiation at the boldface protons.

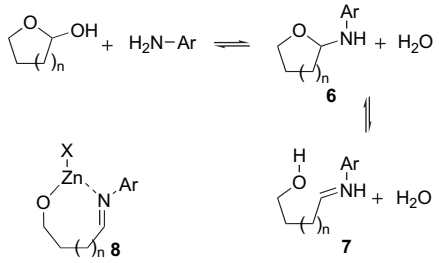
2.2. Ni-catalyzed four-component connection reaction of Ph_2Zn, isoprene, lactols, and aromatic amines

Lactols (2-hydroxy-oxacycloalkanes) share the fundamental skeleton with many carbohydrates, and establishment of methodology for their derivatization, enabling of elongation of carbon chains and especially enabling of introduction of an amino group, is of significant importance in organic synthesis and life science research.[14] The outstanding characteristics of the present methodology, compatibility with water and acceleration of the reaction in the presence of a limited amount of water, encouraged us to examine the multi-component connection reaction with lactols (Eq. 3).



(3)

^{1}H NMR studies revealed that a mixture of 2-hydroxytetrahydrofuran and *p*-anisidine cleanly formed 2-(*p*-anisidyl)-tetrahydrofuran (**6**, *n*=1) (Scheme 2). The mixture did not contain 4-hydroxybutanal-*p*-anisidine imine (**7**, *n*=1) in any detectable amounts. The extremely low concentration of **7** in the equilibrium with **6** suggested us that phenylative multi-component connection reaction using lactols and *p*-anisidine might proceed with difficulty or, if any, very slowly as compared with the reactions of alkyl aldehyde-*p*-anisidine imines.



Scheme 2.

To our pleasant surprise, however, the reaction of 2-hydroxytetrahydrofuran and *p*-anisidine under usual conditions proceeded smoothly, completing within 2 h even at ambient temperature (cf., run 1, Table 2 and runs 19–20, Table 1). The expected product (*E*)-**4a** (Ar=*p*-anisyl) was obtained as a single isomer in remarkably good yield. The parent aniline and *p*-chloroaniline showed almost the same results regarding the reactivity and the product yields (runs 2 and 3, Table 2).

2-Hydroxytetrahydropyran reacted similarly well for variety combinations with aniline derivatives and provided the expected products **5** in modest to good yields (runs 4–13, Table 2). *o*-Chloro- and *o*-bromoaniline gave rise to the expected products **5g** and **5i** about half the yields of the corresponding *p*-isomers, **5h** and **5j** (runs 10–13), respectively. On the other hand, *o*-methoxyaniline gave rise to the expected products

Table 2. Ni-catalyzed four-component connection of Ph_2Zn, isoprene, lactols (n=1 and 2), and anilines (Eq. 3)[a]

Run	n	Anilines	Time (h)	Yield[b] (%)
1	1	*p*-MeO	2	(*E*)-**4a**:83
2	1	H	2	(*E*)-**4b**:84
3	1	*p*-Cl	2	(*E*)-**4c**:88
4	2	*o*-MeO	4	(*E*)-**5a**:68
5	2	*p*-MeO	2	(*E*)-**5b**:76
6	2	H	1	(*E*)-**5c**:81
7	2	*p*-Me	2	(*E*)-**5d**:86
8	2	*o*-F	2	(*E*)-**5e**:45
9	2	*p*-F	3	(*E*)-**5f**:56
10	2	*o*-Cl	2	(*E*)-**5g**:44
11	2	*p*-Cl	2	(*E*)-**5h**:89
12	2	*o*-Br	4	(*E*)-**5i**:34
13	2	*p*-Br	6	(*E*)-**5j**:64

[a] Reaction conditions: a lactol (1 mmol) and an aniline derivative (2 mmol) in THF (2 mL) at room temperature overnight, and then $Ni(acac)_2$ (0.1 mmol in 3 mL of THF), isoprene (4 mmol), and Ph_2Zn (3.6 mmol) at room temperature.

[b] Yields for the isolated and spectroscopically homogeneous materials.

5a in almost the same yield as *p*-methoxyaniline (runs 4 and 5). These results suggest that the decrease in the yields that *o*-bromo- and *o*-chloro-isomers display is not due to steric hindrance but probably due to decomposition of products that might be triggered by oxidative addition of a Ni(0) species upon the *ortho* C-halogen bond followed by elimination of a Ni-amide species. Although the reason is not clear at the moment, the decomposition of **5g** and **5i** is not so serious as that encountered in runs 6 and 8 in Table 1.

The unexpectedly smooth reaction of lactamines might be attributed to an intermediacy of **8**, which is formed by chelation of **7** to zinc(II) through its hydroxy and imine nitrogen (Scheme 2); the C=N→Zn(II) bond would increase the electrophilic reactivity of the imine moiety, hence facilitate the reaction.[6a,15]

3. Conclusion

This paper demonstrates that $Ni(acac)_2$ serves as an efficient catalyst for the four-component connection reaction of diphenylzinc, isoprene, aromatic aldehydes, and aromatic amines and provides (*E*)-1-arylamino-1-aryl-3-methyl-5-phenyl-3-pentenes (**1**) in excellent yields. Aliphatic aldehydes show limited success; primary aldehydes provide (*E*)-1-arylamino-1-alkyl-3-methyl-5-phenyl-3-pentenes (**1**) selectively, while secondary aldehydes provide mixtures of **1** and (*E*)-1-arylamino-1-alkyl-*4-methyl*-5-phenyl-3-pentenes (**1′**), the positional isomers of the isoprene methyl group, as the minor products. Lactamines prepared in situ from five- and six-membered lactols and aromatic amines undergo the multi-component connection reaction smoothly and furnish (*E*)-4-arylamino-6-methyl-8-phenyl-6-octen-1-ols (**4**) and (*E*)-5-arylamino-7-methyl-9-phenyl-7-nonen-1-ols (**5**), respectively, in good yields with excellent *E*-selectivity. The reaction presented here is operationally simple and can be performed with a single flask procedure. The products, tri-substituted (*E*)-homoallylamines **1** and (*E*)-homoallylamino alcohols **4** and **5**, may be of great interest for synthetic organic chemists as synthetic intermediates and for life science researchers as probes in their studies.

4. Experimental

4.1. General

Reactions employed oven-dried glassware unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator (Merck, Silica gel 60F254). Flash chromatography columns were packed with 230–400 mesh silica gel as a slurry in *n*-hexane. Gradient flash chromatography was conducted eluting with a continuous gradient from *n*-hexane to the indicated solvent. Proton and carbon NMR data were obtained with a JEOL-GX400 with tetramethylsilane as an internal standard. Chemical shift values were given in parts per million downfield from the internal standard. Infrared spectra were recorded with a JASCO A-100 FTIR spectrophotometer. High-resolution mass spectra (HRMS) were measured with a JEOL JMS-DX303. Combustion analyses were performed by the Instrumental Analysis Center of Nagasaki University. Analysis agreed with the calculated values within ±0.4%.

4.2. Solvents and reagents

Tetrahydrofuran was dried and distilled from benzophenone and sodium immediately prior to use under nitrogen atmosphere. $Ni(acac)_2$ (purity 95%, Aldrich), PhMgBr (1.0 M THF solution, KANTO), $ZnCl_2$ (1.0 M ether solution, Aldrich), isoprene (Tokyo Kasei Kogyo Co., Ltd), aniline, *o*-anisidine, *p*-anisidine, *o*-fluoroaniline, *p*-fluoroaniline, *o*-chloroaniline, *p*-chloroaniline, *o*-bromoaniline, and *p*-bromoaniline were purchased and used as received. The following aldehydes were purchased and distilled prior to use by Kugelrohr apparatus: benzaldehyde, *o*-tolualdehyde, *p*-tolualdehyde, *o*-anisaldehyde, *p*-anisaldehyde, *o*-fluorobenzaldehyde, *p*-fluorobenzaldehyde, *o*-chlorobenzaldehyde, *p*-chlorobenzaldehyde, 2-furaldehyde, 1-octanal, and 2-methylpropanal.

4.2.1. Preparation of Ph_2Zn. Into a N_2 purged Schlenk flask, were introduced dry THF (10 mL) and $ZnCl_2$ (10 mL, 1 M ether solution; 10 mmol) via syringe. PhMgBr (20 mL, 1 M THF solution; 20 mmol) was successively added to the solution, and then the mixture was stirred at ambient temperature for 3 h. This stock solution was used as 0.25 M Ph_2Zn.

4.2.2. Preparation of hemiacetals. 3,4-Dihydro-2*H*-pyran (8.3 g, 100 mmol) was added into 2 M HCl (20 mL) at 0 °C over 30 min. The mixture was allowed to warm to room temperature, stirred for an additional 1 h, neutralized with satd $NaHCO_3$, and then extracted with dichloromethane (2×20 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by means of Kugelrohr distillation (85 °C/2 mmHg) to give 2-hydroxytetrahydropyran in 93% yield. 2-Hydroxytetrahydrofuran was prepared from 2,3-dihydrofuran as described above (67%, 75 °C/2 mmHg).

4.3. New compounds listed in Table 1

4.3.1. A typical procedure for the Ni-catalyzed four-component connection reaction of Ph_2Zn, isoprene, an aldehyde and an aromatic amine (run 17, Table 1). Into

a N_2 purged two-necked round-bottomed flask containing *p*-anisidine (246 mg, 2.0 mmol), were added dry THF (2.0 mL) and 2-furaldehyde (96 mg, 1.0 mmol) via syringe. The mixture was stirred at 30 °C overnight to form aldimine, which was detected by TLC (R_f=0.59, *n*-hexane/ethyl acetate = 2:1, v/v). A solution of $Ni(acac)_2$ (25.7 mg, 0.1 mmol) in THF (3.0 mL) was introduced into the aldimine solution via a cannula. Isoprene (400 μl, 4.0 mmol) and a Ph_2Zn solution (14.4 mL, 0.25 M, 3.6 mmol) were successively introduced via syringe and the homogeneous mixture was stirred for 1 h. After completion of reaction (TLC), the mixture was poured into ice-water (20 mL) and extracted with ethyl acetate (30 mL). The water phase was extracted with ethyl acetate (2×20 mL). Combined organic extracts were washed with 2 M HCl (20 mL) and satd $NaHCO_3$ (25 mL), and then dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to column chromatography over silica gel (eluent: *n*-hexane/ethyl acetate = 100:1, v/v) to provide **1o** (R_f=0.74, *n*-hexane/ethyl acetate = 2:1, v/v) in 98% as a single isomer.

4.3.1.1. (*E*)-*N*-(1-(Furan-2-yl)-3-methyl-5-phenylpent-3-enyl)-4-methoxybenzenamine (1o). IR (neat) 3396 (w), 2831 (w), 1603 (w), 1514 (s), 1238 (m), 1037 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 3H), 2.52 (dd, *J*=13.4, 8.5 Hz, 1H), 2.65 (dd, *J*=13.4, 5.9 Hz, 1H), 3.33 (dd, *J*=15.1, 7.3 Hz, 1H), 3.39 (dd, *J*=15.1, 7.3 Hz, 1H), 3.71 (s, 3H), 4.47 (dd, *J*=8.5, 5.9 Hz, 1H), 5.47 (t, *J*=7.2 Hz, 1H), 6.13 (d, *J*=3.2 Hz, 1H), 6.26 (dd, *J*=3.2, 1.7 Hz, 1H), 6.48 (d, *J*=8.9 Hz, 2H), 6.71 (d, *J*=8.9 Hz, 2H), 7.12 (d, *J*=7.3 Hz, 2H), 7.18 (t, *J*=7.3 Hz, 1H), 7.26 (t, *J*=3.3 Hz, 2H), 7.32 (d, *J*=1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8, 34.3, 45.7, 51.3, 55.7, 105.7, 110.0, 114.6, 114.8, 125.7, 127.4, 128.1, 128.3, 132.3, 141.0, 141.1, 141.4, 152.2, 156.5; HRMS calcd for $C_{23}H_{25}NO_2$: 347.4501; Found *m*/*z* (relative intensity): 347.1869 (M^+, 100).

4.3.1.2. (*E*)-4-Methoxy-*N*-(3-methyl-1,5-diphenylpent-3-enyl)benzenamine (1a). IR (neat) 3387 (w), 2831 (w), 1605 (w), 1512 (s), 1242 (s), 1034 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.76 (s, 3H), 2.34 (dd, *J*=13.7, 10.1 Hz, 1H), 2.52 (dd, *J*=13.7, 4.5 Hz, 1H), 3.34 (dd, *J*=15.4, 7.4 Hz, 1H), 3.44 (dd, *J*=15.4, 7.4 Hz, 1H), 3.67 (s, 3H), 3.87 (br s, 1H), 4.30 (dd, *J*=10.1, 4.5 Hz, 2H), 5.53 (t, *J*=7.4 Hz, 1H), 6.34 (d, *J*=8.9 Hz, 2H), 6.64 (d, *J*=8.9 Hz, 2H), 7.12–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.3, 50.0, 55.7, 56.5, 114.4, 114.6, 125.8, 126.0, 126.7, 127.6, 128.2, 128.4, 132.9, 141.0, 141.9, 144.6, 151.8; HRMS calcd for $C_{25}H_{27}NO$: 357.2093; Found *m*/*z* (relative intensity): 357.2100 (M^+, 100).

4.3.1.3. (*E*)-4-Methyl-*N*-(3-methyl-1,5-diphenylpent-3-enyl)benzenamine (1b). IR (neat) 3395 (w), 3024 (m), 2916 (m), 1620 (m), 1520 (s), 1450 (m), 1304 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.76 (s, 3H), 2.17 (s, 3H), 2.42 (dd, *J*=13.7, 10.2 Hz, 1H), 2.54 (dd, *J*=13.7, 4.6 Hz, 1H), 3.33 (dd, *J*=15.4, 7.3 Hz, 1H), 3.44 (dd, *J*=15.4, 7.3 Hz, 1H), 3.99 (br s, 1H), 4.34 (dd, *J*=10.2, 4.6 Hz, 1H), 5.51 (t, *J*=7.3 Hz, 1H), 6.32 (d, *J*=8.5 Hz, 1H), 6.86 (d, *J*=8.5 Hz, 1H), 7.13–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 20.4, 34.4, 50.1, 56.0, 113.5, 125.9, 126.1, 126.4, 126.7, 127.6, 128.2, 128.47, 128.51, 129.4, 133.0, 141.1, 144.6, 145.4; HRMS calcd for $C_{25}H_{27}N$: 341.2143; Found *m*/*z* (relative intensity): 341.2131 (M^+, 100).

4.3.1.4. (*E*)-*N*-(3-Methyl-1,5-diphenylpent-3-enyl)-benzenamine (1c). IR (neat) 3402 (w), 3024 (w), 1605 (s), 1504 (s), 748 (s) 694 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.76 (s, 3H), 2.34 (dd, *J*=13.7, 10.2 Hz, 1H), 2.55 (dd, *J*=13.7, 4.3 Hz, 1H), 3.33 (dd, *J*=15.2, 7.5 Hz, 1H), 3.39 (dd, *J*=15.2, 7.5 Hz, 1H), 4.37 (dd, *J*=10.2, 4.3 Hz, 1H), 5.51 (t, *J*=7.5 Hz, 1H), 6.39 (d, *J*=7.4 Hz, 2H), 6.62 (t, *J*=7.4 Hz, 1H), 7.02–7.37 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.3, 50.0, 55.7, 113.3, 117.2, 125.8, 125.9, 126.7, 128.1, 128.4, 128.5, 128.8, 132.8, 141.0, 144.3, 147.5; HRMS calcd for $C_{24}H_{25}N$: 327.1987; Found *m*/*z* (relative intensity): 327.1967 (M^+, 100).

4.3.1.5. (*E*)-2-Fluoro-*N*-(3-methyl-1,5-diphenylpent-3-enyl)benzenamine (1d). Mp 71.1–71.6 °C (*n*-hexane); IR (KBr disk) 3425 (m), 3024 (w), 2909 (w), 1620 (m), 1520 (s), 1450 (m), 1335 (m), 1188 (m), 741(s), 702 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H), 2.44 (dd, *J*=13.8, 9.3 Hz, 1H), 2.58 (dd, *J*=13.8, 4.6 Hz, 1H), 3.36 (dd, *J*=15.9, 7.3 Hz, 1H), 3.43 (dd, *J*=15.9, 7.3 Hz, 1H), 4.42 (dd, *J*=9.3, 4.6 Hz, 1H), 4.44 (br s, 1H), 5.51 (t, *J*=7.3 Hz, 1H), 6.35 (t, *J*=7.8 Hz, 1H), 6.51–6.57 (m, 1H), 6.77 (t, *J*=7.8 Hz, 1H), 6.94 (dd, *J*=12.0, 7.8 Hz, 1H), 7.12–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.2, 49.8, 55.6, 113.1, 113.2, 113.9, 114.1, 116.37, 116.44, 124.2, 124.2, 125.7, 125.9, 126.9, 127.6, 128.1, 128.3, 128.5, 132.5, 135.9, 136.0, 140.8, 143.8; HRMS calcd for $C_{24}H_{24}FN$: 345.1893; Found *m*/*z* (relative intensity): 345.1895 (M^+, 22), 278 (21), 277 (100). Anal. Calcd for $C_{24}H_{24}FN$: C, 83.44; H, 7.00; F, 5.55; N, 4.05. Found: C, 83.20; H, 7.20; N, 4.08.

4.3.1.6. (*E*)-4-Fluoro-*N*-(3-methyl-1,5-diphenylpent-3-enyl)benzenamine (1e). IR (neat) 3402 (w), 3024 (w), 2916 (w), 1605 (w), 1512 (s), 1219 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.76 (s, 3H), 2.34 (dd, *J*=13.8, 10.1 Hz, 1H), 2.54 (dd, *J*=13.8, 4.6 Hz, 1H), 3.34 (dd, *J*=15.4, 7.4 Hz, 1H), 3.44 (dd, *J*=15.4, 7.4 Hz, 1H), 3.99 (br s, 1H), 4.30 (dd, *J*=10.1, 4.6 Hz, 1H), 5.51 (br t, *J*=7.4 Hz, 1H), 6.29 (d, *J*=8.9 Hz, 1H), 6.30 (d, *J*=8.9 Hz, 1H), 6.74 (t, *J*=8.9 Hz, 2H), 7.13–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.3, 50.0, 56.3, 114.0, 114.1, 115.1, 115.3, 125.8, 126.0, 127.7, 128.1, 128.4, 128.5, 132.7, 141.0, 143.9, 154.4, 156.7; HRMS calcd for $C_{24}H_{24}FN$: 345.1893; Found *m*/*z* (relative intensity): 345.1894 (M^+, 100).

4.3.1.7. (*E*)-2-Chloro-*N*-(3-methyl-1,5-diphenylpent-3-enyl)benzenamine (1f). IR (neat) 3395 (w), 3024 (w), 2924 (w), 1597 (s), 1504 (s), 1450 (m), 1319 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.74 (s, 3H), 2.46 (dd, *J*=13.7, 9.8 Hz, 1H), 2.60 (dd, *J*=13.7, 4.6 Hz, 1H), 3.40 (d, *J*=6.9 Hz, 2H), 4.44 (dt, *J*=9.8, 4.6 Hz, 1H), 4.88 (d, *J*=2.9 Hz, 1H), 5.55 (br t, *J*=6.9 Hz, 1H), 6.32 (d, *J*=7.8 Hz, 1H), 6.54 (t, *J*=7.8 Hz, 1H), 6.90 (t, *J*=7.8 Hz, 1H), 7.14–7.36 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8, 34.4, 50.0, 55.8, 112.6, 117.1, 119.4, 125.8, 126.0,

127.0, 127.4, 127.9, 128.3, 128.4, 128.7, 128.8, 132.5, 140.8, 143.3, 143.7; HRMS calcd for $C_{24}H_{24}ClN$: 361.1597; Found *m*/*z* (relative intensity): 361.1581 (M^+, 100).

4.3.1.8. (*E*)-4-Chloro-*N*-(3-methyl-1,5-diphenylpent-3-enyl)benzenamine (1g). IR (neat) 3402 (w), 3024 (w), 2916 (w), 1597 (s), 1497 (s), 1312 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.76 (s, 3H), 2.33 (dd, *J*=13.7, 10.1 Hz, 1H), 2.55 (dd, *J*=13.7, 4.3 Hz, 1H), 3.35 (dd, *J*=15.4, 7.4 Hz, 1H), 3.44 (dd, *J*=15.4, 7.4 Hz, 1H), 4.10 (br s, 1H), 4.33 (m, 1H), 5.51 (br t, *J*=7.4 Hz, 1H), 6.29 (d, *J*=8.9 Hz, 1H), 6.97 (d, *J*=8.9 Hz, 1H), 7.12–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.4, 49.9, 55.9, 114.5, 118.1, 118.8, 121.5, 121.9, 126.0, 127.0, 127.98, 128.2, 128.5, 128.6, 128.7, 129.2, 129.4, 132.7, 141.0, 143.8, 146.1; HRMS calcd for $C_{24}H_{24}ClN$: 361.1597; Found *m*/*z* (relative intensity): 361.1590 (M^+, 100).

4.3.1.9. (*E*)-4-Bromo-*N*-(3-methyl-1,5-diphenylpent-3-enyl)benzenamine (1h). IR (neat) 3402 (w), 3024 (w), 2916 (w), 1597 (m), 1497 (s), 1312 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H), 2.33 (dd, *J*=13.7, 10.2 Hz, 1H), 2.55 (dd, *J*=13.7, 4.1 Hz, 1H), 3.33 (dd, *J*=15.2, 7.4 Hz, 1H), 3.44 (dd, *J*=15.4, 7.4 Hz, 1H), 4.11 (br s, 1H), 4.32 (m, 1H), 5.51 (br t, *J*=7.4 Hz, 1H), 6.24 (d, *J*=8.8 Hz, 1H), 7.10 (d, *J*=8.8 Hz, 1H), 7.13 (d, *J*=7.6 Hz, 2H) 7.18–7.33 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6, 34.3, 49.8, 55.7, 114.9, 125.9, 126.9, 127.9, 128.1, 128.4, 128.6, 131.5, 132.6, 140.9, 143.6, 146.4; HRMS calcd for $C_{24}H_{24}BrN$: 405.1092; Found *m*/*z* (relative intensity): 405.1094 (M^+, 100).

4.3.1.10. (*E*)-4-Methoxy-*N*-(3-methyl-5-phenyl-1-*p*-tolylpent-3-enyl)benzenamine (1i). IR (neat) 3386 (w), 2831 (m), 1605 (w), 1512 (s), 1242 (s), 1034 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H), 2.32 (s, 3H), 2.33 (dd, *J*=13.5, 10.1 Hz, 1H), 2.50 (dd, *J*=13.5, 4.7 Hz, 1H), 3.34 (dd, *J*=15.4, 7.5 Hz, 1H), 3.43 (dd, *J*=15.4, 7.5 Hz, 1H), 3.68 (s, 3H), 4.27 (dd, *J*=10.1, 4.7 Hz, 1H), 5.50 (br t, *J*=7.5 Hz, 1H), 6.35 (d, *J*=8.8 Hz, 2H), 6.64 (d, *J*=8.8 Hz, 2H), 7.09–7.30 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.3, 50.1, 55.7, 56.2, 114.4, 114.6, 125.8, 125.9, 127.4, 128.2, 128.4, 129.1, 133.0, 136.1, 141.0, 141.6, 142.0, 151.8; HRMS calcd for $C_{26}H_{30}NO$: 371.2249; Found *m*/*z* (relative intensity): 371.2259 (M^+, 100).

4.3.1.11. (*E*)-4-Methoxy-*N*-(1-(4-methoxyphenyl)-3-methyl-5-phenylpent-3-enyl)benzenamine (1j). IR (neat) 3384 (w), 2833–3026 (m), 1610 (w), 1512 (s), 1240 (s), 1035 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H), 2.33 (dd, *J*=13.5, 9.9 Hz, 1H), 2.49 (dd, *J*=13.5, 4.7 Hz, 1H), 3.34 (dd, *J*=15.4, 7.4 Hz, 1H), 3.43 (dd, *J*=15.4, 7.4 Hz, 1H), 3.68 (s, 3H), 3.78 (s, 3H), 3.85 (br s, 1H), 4.26 (dd, *J*=9.9, 4.7 Hz, 1H), 5.49 (br t, *J*=7.4 Hz, 1H), 6.35 (d, *J*=9.0 Hz, 2H), 6.50 (d, *J*=9.0 Hz, 2H), 6.50 (d, *J*=9.0 Hz, 2H), 6.83 (d, *J*=8.8 Hz, 1H), 7.14 (d, *J*=7.2 Hz, 2H), 7.20 (t, *J*=7.2 Hz, 1H), 7.27 (d, *J*=8.8 Hz, 2H), 7.28 (t, *J*=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.3, 50.1, 55.2, 55.7, 56.0, 113.9, 114.5, 114.6, 125.8, 127.1, 127.4, 128.2, 128.4, 133.0, 136.6, 141.0, 142.0, 151.8, 158.3; HRMS calcd for $C_{26}H_{29}NO_2$: 387.2198; Found *m*/*z* (relative intensity): 387.2195 (M^+, 100).

4.3.1.12. (*E*)-1-*p*-Anisylamino-3-methyl-5-phenyl-1-[(2-phenyl)phenyl]-3-pentene (1k). IR (neat) 3387 (w), 3024 (m), 2909 (m), 1597 (w), 1512 (s), 1242 (s), 1042 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 3H), 2.12 (dd, *J*=13.7, 10.6 Hz, 1H), 2.41 (br d, 1H), 3.24 (dd, *J*=15.3, 7.3 Hz, 1H), 3.36 (dd, *J*=15.3, 7.3 Hz, 1H), 3.69 (s, 3H), 3.74 (br s, 1H), 4.47 (dd, *J*=10.6, 3.4 Hz, 1H), 5.43 (br t, *J*=7.3 Hz, 1H), 6.31 (d, *J*=8.8 Hz, 2H), 6.65 (d, *J*=8.8 Hz, 2H), 7.09 (d, *J*=7.1 Hz, 2H), 7.16–7.44 (m, 11H), 7.58 (d, *J*=7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.3, 50.1, 55.2, 55.7, 56.0, 113.9, 114.5, 114.6, 125.8, 127.1, 127.4, 128.2, 128.4, 133.0, 136.6, 141.0, 142.0, 151.8, 158.3; HRMS calcd for $C_{31}H_{31}NO$: 433.2406; Found *m*/*z* (relative intensity): 433.2413 (M^+, 100), 432 (6).

4.3.1.13. (*E*)-*N*-(1-(4-Chlorophenyl)-3-methyl-5-phenylpent-3-enyl)-4-methoxybenzenamine (1l). IR (neat) 3384 (w), 2831–3026 (w), 1601 (w), 1512 (s), 1238 (m), 1038 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.74 (s, 3H), 2.32 (dd, *J*=13.5, 9.8 Hz, 1H), 2.48 (dd, *J*=13.5, 4.7 Hz, 1H), 3.33 (dd, *J*=15.3, 7.4 Hz, 1H), 3.42 (dd, *J*=15.3, 7.4 Hz, 1H), 3.67 (s, 3H), 4.27 (dd, *J*=9.8, 4.7 Hz, 1H), 5.48 (t, *J*=7.4 Hz, 1H), 6.33 (d, *J*=8.8 Hz, 2H), 6.65 (d, *J*=8.8 Hz, 2H), 7.12 (d, *J*=7.5 Hz, 2H), 7.20 (t, *J*=7.5 Hz, 1H), 7.27 (d, *J*=8.0 Hz, 4H), 7.28 (t, *J*=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.3, 49.8, 55.6, 55.7, 56.1, 56.2, 114.6, 125.8, 127.5, 127.9, 128.0, 128.4, 128.6, 132.3, 132.4, 140.9, 141.3, 143.0, 152.1; HRMS calcd for $C_{25}H_{26}ClNO$: 391.1703; Found *m*/*z* (relative intensity): 391.1738 (M^+, 10), 282 (3), 249 (10), 248 (66), 247 (32), 246 (100).

4.3.1.14. (*E*)-*N*-(1-(2-Fluorophenyl)-3-methyl-5-phenylpent-3-enyl)-4-methoxybenzenamine (1m). IR (neat) 3387 (w), 3024 (m), 2909 (m), 1589 (w), 1512 (s), 1242 (s), 1042 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.77 (s, 3H), 2.33 (dd, *J*=13.5, 9.7 Hz, 1H), 2.62 (dd, *J*=13.5, 4.8 Hz, 1H), 3.33 (dd, *J*=15.4, 7.5 Hz, 1H), 3.42 (dd, *J*=15.4, 7.5 Hz, 1H), 3.68 (s, 3H), 3.82 (br s, 1H), 4.70 (dd, *J*=9.7, 4.8 Hz, 1H), 5.47 (br t, *J*=7.5 Hz, 1H), 6.37 (d, *J*=9.0 Hz, 2H), 6.66 (d, *J*=9.0 Hz, 2H), 6.68–7.41 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6, 34.3, 47.7, 50.1, 55.2, 55.7, 56.0, 114.3, 114.6, 115.1, 115.3, 124.2, 124.3, 125.8, 127.5, 127.6, 127.7, 128.07, 128.13, 128.4, 130.9, 131.0, 132.8, 141.0, 141.4, 152.0, 159.0, 161.5; HRMS calcd for $C_{25}H_{26}FNO$: 375.1998; Found *m*/*z* (relative intensity): 375.1976 (M^+, 100).

4.3.1.15. (*E*)-*N*-(1-(4-Fluorophenyl)-3-methyl-5-phenylpent-3-enyl)-4-methoxybenzenamine (1n). IR (neat) 3387 (w), 2924 (m), 1605 (w), 1512 (s), 1234 (s), 1034 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H), 2.32 (dd, *J*=13.8, 9.9 Hz, 1H), 2.48 (dd, *J*=13.8, 4.9 Hz, 1H), 3.34 (dd, *J*=15.4, 7.4 Hz, 1H), 3.43 (dd, *J*=15.4, 7.4 Hz, 1H), 3.68 (s, 3H), 3.86 (br s, 1H), 4.28 (dd, *J*=9.9, 4.9 Hz, 1H), 5.49 (br t, *J*=7.4 Hz, 1H), 6.32 (d, *J*=9.0 Hz, 2H), 6.65 (d, *J*=9.0 Hz, 2H), 6.97 (t, *J*=8.6 Hz, 2H), 7.13 (d, *J*=8.6 Hz, 2H), 7.19–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8, 34.4, 50.2, 55.8, 56.0, 114.6, 114.7,

115.2, 115.5, 125.9, 127.50, 127.53, 127.6, 127.8, 127.9, 128.2, 128.5, 132.7, 140.25, 140.27, 141.0, 141.8, 152.0, 160.5, 162.9; HRMS calcd for $C_{25}H_{26}FNO$: 375.1998; Found *m/z* (relative intensity): 375.1988 (M^+, 100).

4.3.1.16. (*E*)-4-Chloro-*N*-(1-(furan-2-yl)-3-methyl-5-phenylpent-3-enyl)benzenamine (1p). IR (neat) 3408 (w), 3026–2853 (w), 1601 (m), 1499 (s), 1313 (s), 1005 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 3H), 2.51 (dd, J=13.6, 8.7 Hz, 1H), 2.67 (dd, J=13.6, 5.7 Hz, 1H), 3.33 (dd, J=15.7, 7.7 Hz, 1H), 3.39 (dd, J=15.7, 7.7 Hz, 1H), 3.93 (br s, 1H), 4.50 (dd, J=8.7, 5.7 Hz, 1H), 5.48 (br t, J=7.7 Hz, 1H), 6.12 (d, J=3.3 Hz, 1H), 6.27 (dd, J=3.3, 1.8 Hz, 1H), 6.42 (d, J=8.8 Hz, 2H), 7.05 (d, J=8.8 Hz, 2H), 7.13 (d, J=7.5 Hz, 2H), 7.19 (t, J=7.5 Hz, 1H), 7.26 (d, J=7.5 Hz, 2H), 7.32 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.3, 45.6, 50.4, 106.0, 110.2, 114.5, 122.4, 126.0, 127.9, 128.3, 128.6, 128.9, 132.1, 141.1, 141.5, 146.0, 155.9; HRMS calcd for $C_{22}H_{22}ClNO$: 351.139; Found *m/z* (relative intensity): 351.13850 (M^+, 100).

4.3.1.17. (*E*)-4-Methoxy-*N*-(3-methyl-1-phenyldodec-2-en-5-yl)benzenamine (1q). IR (neat) 3395 (w), 2924 (s), 1604 (w), 1512 (s), 1242 (m), 1041 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, a major isomer is assigned) δ 0.87 (t, J=6.9 Hz, 3H), 1.26–1.51 (m, 12H), 1.71 (s, 3H), 2.22 (d, J=5.9 Hz, 2H), 3.35 (d, J=7.3 Hz, 3H), 3.74 (br s, 1H), 5.40 (t, J=7.3 Hz, 1H), 6.51 (d, J=8.8 Hz, 2H), 6.75 (d, J=8.8 Hz, 2H), 7.13–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 16.3, 22.6, 25.8, 29.3, 29.8, 31.8, 34.3, 34.9, 45.3, 46.4, 52.3, 55.8, 114.5, 125.6, 126.1, 128.2, 128.3, 133.5, 141.3; HRMS calcd for $C_{26}H_{37}NO$: 379.2875; Found *m/z* (relative intensity): 379.2799 (M^+, 100).

4.3.1.18. (*E*)-*N*-(2,5-Dimethyl-7-phenylhept-5-en-3-yl)-4-methoxybenzenamine (1r). A mixture of **1r** and **1r′** in a ratio of 2:1; IR (neat) 3402 (w), 2955 (m), 1605 (w), 1512 (s), 1234 (m), 1041 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (d, J=6.9 Hz, 3H), 0.95 (d, J=6.9 Hz, 3H), 1.67 (s, 3H), 1.96 (br hept, J=6.9 Hz, 1H), 2.05 (dd, J=13.7, 9.5 Hz, 1H), 2.27 (dd, J=13.7, 4.6 Hz, 1H), 3.29 (ddm, J=9.5, 4.6 Hz, 1H), 3.30 (m, 1H, coalescing to d, J=15.0 Hz by irradiation at 5.40), 3.35 (m, 1H, coalescing to d, J=15.0 Hz by irradiation at 5.40), 3.74 (s, 3H), 5.40 (t, J=7.6 Hz, 1H), 6.49 (d, J=8.8 Hz, 2H), 6.74 (d, J=8.8 Hz, 2H), 7.09–7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 18.07, 18.15, 30.7, 34.4, 41.5, 55.9, 56.9, 114.1, 114.9, 125.7, 126.0, 128.2, 128.3, 133.9, 136.3, 140.2, 141.3, 142.9, 151.4.

4.3.1.19. (*E*)-*N*-(2,6-Dimethyl-7-phenylhept-5-en-3-yl)-4-methoxybenzenamine (1r′). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, J=6.8 Hz, 3H), 0.97 (d, J=6.8 Hz, 3H), 1.51 (s, 3H), 1.89 (dhept, J=4.9, 6.8 Hz, 1H), 2.15 (dt, J=14.5, 7.3 Hz, 1H), 2.27 (dm, J=14.5 Hz, 1H), 3.15 (dt, J=7.3, 4.9 Hz, 1H), 3.26 (s, 2H), 3.74 (s, 3H), 5.30 (t, J=7.3 Hz, 1H), 6.52 (d, J=8.9 Hz, 2H), 6.75 (d, J=8.9 Hz, 2H), 7.09–7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 18.5, 18.9, 30.1, 31.1, 46.5, 59.8, 114.3, 114.9, 123.3, 125.9, 128.1, 128.7, 133.9, 140.2, 141.3, 142.9, 151.4; HRMS calcd for $C_{22}H_{29}NO$: 323.2249; Found *m/z* (relative intensity): 323.2233 (M^+, 100).

4.4. New compounds listed in Table 2

4.4.1. A typical procedure for the four-component connection reaction of Ph_2Zn, isoprene, tetrahydro-*2H*-pyran-2-ol, and *p*-anisidine (run 5, Table 2). Into a N_2 purged two-necked round-bottomed flask containing *p*-anisidine (246 mg, 2.0 mmol), were added dry THF (2.0 mL) and 2-hydroxytetrahydropyran (102 mg, 1.0 mmol) via syringe. The mixture was stirred at room temperature. 2-*p*-Anisidyltetrahydropyran was detected by TLC (R_f=0.56, *n*-hexane/ethyl acetate = 2:1, v/v). A solution of $Ni(acac)_2$ (25.7 mg, 0.1 mmol) in THF (3.0 mL) was introduced into the lactamine solution via a cannula. Isoprene (400 μl, 4.0 mmol) and a Ph_2Zn solution (14.4 mL, 0.25 M, 3.6 mmol) were successively introduced via syringe and the homogeneous mixture was stirred for 2 h at room temperature. The reaction mixture was poured into ice-water (20 mL) and extracted with 30 mL of ethyl acetate. The water phase was extracted with ethyl acetate (2×20 mL). The combined organic extracts were washed with 2 M HCl (20 mL) and with satd $NaHCO_3$ (25 mL), and then dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to column chromatography over silica gel (eluent: *n*-hexane/ethyl acetate = 8:1, v/v) to give **5b** (R_f=0.66, *n*-hexane/ethyl acetate = 2:1, v/v) in 76% yield as a single isomer.

4.4.1.1. (*E*)-5-(4-Methoxyphenylamino)-7-methyl-9-phenylnon-7-en-1-ol (5b). IR (neat) 3387 (m), 2932 (s), 1736 (m), 1512 (s), 1450 (m), 1242 (s), 1042 (m), 818 (m), 741 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24–1.59 (m, 7H), 1.71 (s, 3H), 2.23 (d, J=6.2 Hz, 2H), 3.35 (d, J=7.4 Hz, 2H), 3.39 (t, J=6.2 Hz, 1H), 3.60 (t, J=6.3 Hz, 2H), 3.74 (s, 3H), 5.40 (t, J=7.4 Hz, 1H), 6.50 (d, J=8.9 Hz, 2H), 6.75 (d, J=8.9 Hz, 2H), 7.14 (d, J=7.5 Hz, 2H), 7.17 (t, J=7.5 Hz, 1H), 7.26 (t, J=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 22.0, 32.9, 34.4, 34.7, 45.4, 52.1, 55.9, 62.8, 114.4, 115.0, 125.7, 126.3, 128.2, 128.4, 133.5, 141.3, 142.2, 151.7; HRMS calcd for $C_{23}H_{31}NO_2$: 353.2355; Found *m/z* (relative intensity): 353.2350 (M^+, 100).

4.4.1.2. (*E*)-4-(4-Methoxyphenylamino)-6-methyl-8-phenyloct-6-en-1-ol (4a). IR (neat) 3379 (m), 2931 (s), 1604 (m), 1512 (s), 1450 (m), 1234 (w), 740 (s), 702 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44–1.66 (m, 4H), 1.69 (s, 3H), 2.16 (dd, J=6.9, 13.8 Hz, 1H), 2.25 (dd, J=6.9, 13.8 Hz, 1H), 2.79 (s, 1H), 3.34 (d, J=7.1 Hz, 2H), 3.39 (dd, J=4.4, 6.9 Hz, 1H), 3.56 (t, J=6.2 Hz, 2H), 3.71 (s, 3H), 5.39 (t, J=7.1 Hz, 1H), 6.51–7.25 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3, 29.2, 31.6, 34.3, 45.3, 51.5, 55.7, 62.8, 114.8, 115.0, 125.7, 126.4, 128.1, 128.3, 133.2, 141.2, 141.7, 152.0; HRMS calcd for $C_{22}H_{29}NO_2$: 339.2198; Found *m/z* (relative intensity): 339.2178 (M^+, 100).

4.4.1.3. (*E*)-6-Methyl-8-phenyl-4-(phenylamino)oct-6-en-1-ol (4b). IR (neat) 3394 (m), 2931 (s), 1604 (m), 1504 (s), 1434 (m), 1319 (w), 748 (s), 694 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.50–1.70 (m, 4H), 1.72 (s, 3H), 2.22 (dd, J=6.9, 13.5 Hz, 1H), 2.27 (dd, J=6.9, 13.5 Hz, 1H), 3.35 (dd, J=2.4, 7.4 Hz, 2H), 3.53 (dd, J=4.6, 6.9 Hz, 1H), 3.62 (t, J=6.0 Hz, 2H), 5.41 (t, J=7.4 Hz, 1H), 6.54–7.25 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 29.2,

31.4, 34.4, 45.5, 51.2, 63.0, 113.2, 117.1, 125.7, 126.5, 128.2, 128.4, 129.2, 133.2, 141.2, 147.7; HRMS calcd for $C_{21}H_{27}NO$: 309.2093; Found *m/z* (relative intensity): 309.2074 (M^+, 100).

4.4.1.4. (*E*)-4-(4-Chlorophenylamino)-6-methyl-8-phenyloct-6-en-1-ol (4c). IR (neat) 3402 (m), 2931 (s), 1596 (s), 1496 (s), 1450 (w), 1056 (w), 740 (s), 702 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.50–1.68 (m, 4H), 1.71 (s, 3H), 2.21 (d, J=6.8 Hz, 2H), 3.36 (dd, J=6.8, 15.6 Hz, 2H), 3.46 (dd, J=6.8, 10.0 Hz, 1H), 3.62 (t, J=6.0 Hz, 2H), 5.40 (t, J=6.8 Hz, 1H), 6.44–7.23 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3, 29.0, 31.4, 34.4, 45.4, 51.4, 62.9, 114.1, 121.5, 125.8, 126.8, 128.2, 129.0, 133.0, 141.2, 146.4; HRMS calcd for $C_{21}H_{26}ClNO$: 343.1703; Found *m/z* (relative intensity): 343.1696 (M^+, 83), 267 (100).

4.4.1.5. (*E*)-5-(2-Methoxyphenylamino)-7-methyl-9-phenylnon-7-en-1-ol (5a). IR (neat) 3418 (m), 2932 (s), 1597 (m), 1512 (s), 1458 (m), 1227 (m), 1034 (m), 733 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24–1.59 (m, 7H), 1.72 (s, 3H), 2.23 (dd, J=13.6, 6.8 Hz, 1H), 2.30 (dd, J=13.6, 6.8 Hz, 1H), 3.34 (d, J=7.3 Hz, 2H), 3.50 (t, J=6.8 Hz, 1H), 3.59 (t, J=6.1 Hz, 2H), 3.77 (s, 3H), 5.41 (t, J=7.3 Hz, 1H), 6.59 (dd, J=7.7, 1.3 Hz, 1H), 6.61 (dd, J=7.7, 1.3 Hz, 1H), 6.74 (dd, J=7.7, 1.3 Hz, 1H), 6.83 (dt, J=7.7, 1.3 Hz, 1H), 7.12–7.17 (m, 3H), 7.22–7.26 (t, J=7.5, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5, 22.0, 32.9, 34.3, 34.6, 45.4, 50.9, 55.4, 62.9, 109.6, 109.7, 115.6, 121.2, 125.6, 126.0, 128.2, 128.3, 133.4, 137.8, 141.3, 146.7; HRMS calcd for $C_{23}H_{31}NO_2$: 353.2355; Found *m/z* (relative intensity): 353.2356 (M^+, 100).

4.4.1.6. (*E*)-7-Methyl-9-phenyl-5-(phenylamino)non-7-en-1-ol (5c). IR (neat) 3400 (m), 2934 (s), 1601 (s), 1504 (s), 1452 (w), 1431 (w), 1072 (w), 746 (s), 694 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40–1.61 (m, 7H), 1.72 (s, 3H), 2.24 (d, J=6.1 Hz, 2H), 3.35 (d, J=7.3 Hz, 2H), 3.50 (t, J=6.1 Hz, 1H), 3.60 (t, J=6.2 Hz, 2H), 5.41 (t, J=7.3 Hz, 1H), 6.53 (d, J=8.1 Hz, 2H), 6.65 (t, J=7.3 Hz, 1H), 7.12–7.15 (m, 5H), 7.24–7.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3, 21.9, 32.8, 34.3, 34.6, 45.3, 51.0, 62.8, 112.8, 116.7, 125.7, 126.3, 128.2, 128.3, 129.1, 133.3, 141.2, 147.8; HRMS calcd for $C_{22}H_{29}NO$: 323.2249; Found *m/z* (relative intensity): 324.2247 (M^+, 22), 323 (46).

4.4.1.7. (*E*)-4-(*p*-Tolylamino)-6-methyl-8-phenyloct-6-en-1-ol (5d). IR (neat) 3394 (m), 2931 (s), 1620 (m), 1519 (s), 1450 (m), 1319 (w), 732 (s), 702 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.57–1.63 (m, 6H), 1.81 (s, 3H), 2.32 (d, J=7.8 Hz, 2H), 2.32 (s, 3H), 3.44 (dd, J=2.8, 7.3 Hz, 2H), 3.55 (dd, J=7.8, 11.7 Hz, 1H), 3.65 (t, J=6.3 Hz, 2H), 5.49 (t, J=7.3 Hz, 1H), 6.54–7.25 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 20.0, 21.6, 32.4, 34.0, 45.0, 50.1, 62.3, 112.7, 125.3, 125.5, 125.9, 127.8, 127.9, 129.3, 133.0, 140.9, 145.2; HRMS calcd for $C_{23}H_{31}NO$: 337.2406; Found *m/z* (relative intensity); 337.2391 (M^+, 9), 64.17 (1), 192.14 (100).

4.4.1.8. (*E*)-5-(2-Fluorophenylamino)-7-methyl-9-phenylnon-7-en-1-ol (5e). IR (neat) 3418 (m), 2932 (s), 1620 (m), 1520 (s), 1450 (m), 1335 (m), 740 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26–1.64 (m, 7H), 1.71 (s, 3H), 2.26 (d, J=6.3 Hz, 2H), 3.34 (d, J=7.3 Hz, 2H), 3.52 (t, J=6.3 Hz, 1H), 5.41 (t, J=7.3 Hz, 2H), 6.56 (q, J=7.6 Hz, 1H), 6.67 (t, J=8.5 Hz, 1H), 6.92 (d, J=8.5 Hz, 1H), 6.95 (t, J=7.3 Hz, 1H), 7.12 (d, J=7.3 Hz, 2H), 7.16 (t, J=7.3 Hz, 1H), 7.25 (t, J=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3, 22.0, 32.7, 34.2, 34.7, 45.4, 51.0, 62.7, 111.9, 111.94, 114.3, 114.5, 115.7, 115.8, 124.36, 124.39, 125.6, 126.4, 128.1, 128.2, 132.9, 136.2, 136.4, 141.1, 150.2, 152.6; HRMS calcd for $C_{22}H_{28}FNO$: 341.2155; Found *m/z* (relative intensity): 341.2141 (M^+, 100).

4.4.1.9. (*E*)-5-(4-Fluorophenylamino)-7-methyl-9-phenylnon-7-en-1-ol (5f). IR (neat) 3395 (s), 2932 (s), 1647 (w), 1512 (s), 1450 (w), 1219 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26–1.57 (m, 6H), 1.70 (s, 3H), 2.21 (t, J=6.2 Hz, 2H), 3.34 (d, J=7.1 Hz, 2H), 3.39 (t, J=6.2 Hz, 1H), 3.57 (t, J=6.3 Hz, 2H), 5.39 (t, J=7.1 Hz, 1H), 6.43 (dd, J=8.8, 4.4 Hz, 2H), 6.83 (t, J=8.8 Hz, 2H), 7.12 (d, J=7.3 Hz, 2H), 7.16 (t, J=7.3 Hz, 1H), 7.24 (t, J=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3, 22.0, 32.7, 34.3, 34.7, 45.3, 51.9, 62.6, 113.6, 113.7, 115.4, 115.6, 125.7, 126.4, 128.1, 128.3, 133.2, 141.2, 144.24, 144.26, 154.1, 156.5; HRMS calcd for $C_{22}H_{28}FNO$: 341.2155; Found *m/z* (relative intensity): 341.2146 (M^+, 100).

4.4.1.10. (*E*)-5-(2-Chlorophenylamino)-7-methyl-9-phenylnon-7-en-1-ol (5g). IR (neat) 3410 (s), 2932 (s), 1597 (s), 1512 (s), 1458 (m), 1327 (m), 1034 (m), 741 (s), 694 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22–1.67 (m, 7H), 1.72 (s, 3H), 2.29 (d, J=6.3 Hz), 3.34 (d, J=7.3 Hz, 2H), 3.55 (q, J=6.3 Hz, 1H), 3.61 (t, J=5.7 Hz, 2H), 4.15 (d, J=7.3 Hz, 1H), 5.43 (t, J=7.3 Hz, 1H), 6.57 (t, J=7.6 Hz, 1H), 6.63 (d, J=7.6 Hz, 1H) 7.07–7.18 (m, 3H), 7.21–7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 22.0, 32.8, 34.4, 34.6, 45.3, 51.2, 62.8, 111.1, 116.5, 119.1, 125.7, 126.6, 128.2, 128.3, 129.2, 132.9, 141.2, 143.6; HRMS calcd for $C_{22}H_{28}ClNO$: 357.1859; Found *m/z* (relative intensity): 357.1848 (M^+, 100).

4.4.1.11. (*E*)-5-(4-Chlorophenylamino)-7-methyl-9-phenylnon-7-en-1-ol (5h). IR (neat) 3404 (m), 2936 (s), 1599 (s), 1497 (s) 1319 (m), 814 (m), 743 (m), 698 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39–1.58 (m, 6H), 1.71 (s, 3H), 2.19 (d, J=13.7, 7.6 Hz, 1H), 2.26 (dd, J=13.7, 6.0 Hz, 1H), 3.34 (dd, J=7.3 Hz, 2H), 3.43 (dd, J=7.6, 6.0 Hz, 1H), 3.60 (t, J=6.3 Hz, 2H), 5.40 (t, J=7.3 Hz, 1H), 6.43 (d, J=8.8 Hz, 2H), 7.06 (d, J=8.8 Hz, 2H), 7.12 (d, J=7.3 Hz, 2H), 7.17 (t, J=7.3 Hz, 1H), 7.25 (t, J=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3, 22.0, 32.8, 34.4, 34.7, 45.3, 51.4, 62.8, 113.9, 121.2, 125.8, 126.6, 128.2, 128.4, 129.0, 133.1, 141.2, 146.5; HRMS calcd for $C_{22}H_{28}ClNO$: 357.1859; Found *m/z* (relative intensity): 357.1844 (M^+, 100).

4.4.1.12. (*E*)-5-(2-Bromophenylamino)-7-methyl-9-phenylnon-7-en-1-ol (5i). IR (neat) 3402 (s), 2932 (m), 1597 (s), 1504 (s), 1458 (m), 1319 (m), 1281 (w), 1018 (w), 741 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43–1.69 (m, 6H), 1.72 (s, 3H), 2.29 (dd, J=6.5, 3.4 Hz, 2H),

3.35 (d, J=7.3 Hz, 2H), 3.56 (quintet, J=6.5 Hz, 1H), 3.61 (t, J=6.5 Hz, 2H), 4.17 (d, J=7.4 Hz, 2H), 5.44 (t, J=7.4 Hz, 1H), 6.50 (t, J=7.6 Hz, 1H), 6.61 (d, J=8.0 Hz, 1H), 7.11–7.18 (m, 4H), 7.24 (t, J=7.3 Hz, 2H), 7.39 (d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5, 22.0, 32.8, 34.4, 34.6, 45.3, 51.4, 62.8, 109.9, 111.3, 117.0, 125.7, 126.7, 128.25, 128.30, 128.32, 132.5, 132.9, 141.1, 144.5; HRMS calcd for $C_{22}H_{28}BrNO$: 401.1354; Found *m/z* (relative intensity): 401.1342 (M^+, 100).

4.4.1.13. (*E*)-5-(4-Bromophenylamino)-7-methyl-9-phenylnon-7-en-1-ol (5j). IR (neat) 3402 (m), 2932 (s), 1597 (m), 1497 (s), 1450 (w), 1319 (w), 1072 (w), 741 (w), 694 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26–1.49 (m, 6H), 1.63 (s, 3H), 2.11 (dd, J=13.1, 7.6 Hz, 1H), 2.19 (dd, J=13.1, 5.9 Hz, 1H), 3.27 (dd, J=6.9 Hz, 4.3 Hz, 2H), 3.37 (br s, 1H), 3.53 (t, J=6.3 Hz, 2H), 5.32 (t, J=6.9 Hz, 1H), 6.31 (d, J=8.8 Hz, 2H), 7.04 (d, J=7.3 Hz, 2H), 7.10 (t, J=7.3 Hz, 1H), 7.12 (d, J=8.8 Hz, 2H), 7.19 (t, J=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3, 22.0, 32.8, 34.4, 34.7, 45.3, 51.3, 62.8, 108.2, 114.3, 125.8, 126.7, 128.2, 128.4, 131.9, 141.2, 146.9; HRMS calcd for $C_{22}H_{28}BrNO$: 401.1354; Found *m/z* (relative intensity): 401.1338 (M^+, 100).

References and notes

1. (a) Tamaru, Y. *Modern Organonickel Chemistry*; Wiley-VHC: Weinheim, 2005; (b) Bellrer, M.; Bolm, C. *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*; Wiley-VCH: Weinheim, 2004; (c) Kurosawa, H.; Yamamoto, A. *Fundamentals of Molecular Catalysis*; Elsevier: Amsterdam, 2003; (d) Tsuji, J. *Transition Metal Reagents and Catalysis*; Wiley: Chichester, UK, 2000.
2. (a) Jeong, Y. C.; Ji, M.; Lee, J. J. S.; Yang, J.-D.; Jin, J.; Bail, W.; Sangho, K. *Tetrahedron* **2004**, *60*, 10181–10185; (b) Hilt, G.; Lueers, S.; Schmidt, F. *Synthesis* **2004**, 634–638; (c) Rozhkov, R. V.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 6314–6320; (d) Kimura, M.; Ezoe, A.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3600–3602; (e) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397–400.
3. (a) Shibata, K.; Kimura, M.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Organomet. Chem.* **2001**, *624*, 348–353; (b) Kimura, M.; Shibata, K.; Koudahashi, Y.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 6789–6793; (c) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386–3388; See also: (d) Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 201–209; (e) Ezoe, A.; Kimura, M.; Inoue, T.; Mori, M.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 2784–2786.
4. Kojima, K.; Kimura, M.; Tamaru, Y. *Chem. Commun.* **2005**, 4717–4719.
5. Transition-metal catalyzed alkylation of imines: (a) Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett.* **2005**, *7*, 637–640; (b) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 10117; (c) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, *126*, 14360–14361; (d) Solin, N.; Kjellgren, J.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026–7033; (e) Sakaguchi, S.; Mizuta, T.; Furuwan, M.; Kubo, T.; Ishii, Y. *Chem. Commun.* **2004**, 1638–1639; (f) Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 590–595; (g) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3941–3944; (h) Sebelius, S.; Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2003**, *5*, 3065–3068; (i) Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133–14139; (j) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364–1367; (k) Kang, S.-K.; Kim, K.-J.; Hong, Y.-T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1584–1586.
6. Reviews: (a) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651–673; (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
7. (a) Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6491–6493; (b) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem.—Eur. J* **2003**, *9*, 2359–2367; (c) Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* **2003**, *125*, 3720–3721; (d) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843.
8. (a) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092–1093; (b) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680–3681; (c) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2004**, 1382–1383; (d) Zhu, X.-F.; Lan, J.; Kwan, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716–4717; (e) Hermanns, N.; Dahmen, S.; Bohm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692–3694; (f) Fujihara, H.; Magai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055–12056.
9. (a) Qu, B.; Collum, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 10820–10821; (b) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734–3735; (c) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409–10410; (d) Friestad, G. K.; Qui, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922–9923; (e) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491–4493; (f) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed* **2001**, *40*, 1896–1898.
10. Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall: New York, NY, 1984.
11. (a) Fustero, S.; Soler, J. G.; Bartolome, A.; Rosello, M. S. *Org. Lett.* **2003**, *5*, 2707–2710; (b) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765–2768.
12. Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376.
13. (a) Shibata, I.; Nose, K.; Sakamoto, K.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2004**, *69*, 2185–2187; (b) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610–6611; (c) Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 9493–9499; (d) Lu, W.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 8589–8594; (e) Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942–6943; (f) Teng, X.; Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 11916–11917.
14. Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2001**, *42*, 1275–1277.
15. Kumar, S.; Kaur, P. *Tetrahedron Lett.* **2004**, *45*, 3413–3416.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 7521–7533

An efficient Negishi cross-coupling reaction catalyzed by nickel(II) and diethyl phosphite

Andrei Gavryushin, Christiane Kofink, Georg Manolikakes and Paul Knochel*

Department Chemie und Biochemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5-13 Haus F, 81377 München, Germany

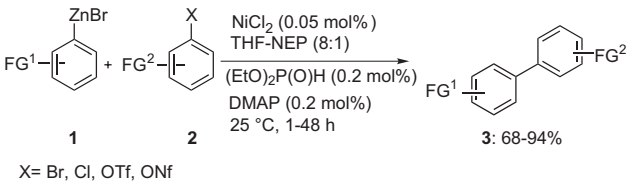
Received 10 January 2005; revised 14 March 2006; accepted 14 March 2006
Available online 21 June 2006

Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry

Abstract—A combination of diethyl phosphite–DMAP and Ni(II) salts forms a very effective catalytic system for the cross-coupling reactions of arylzinc halides with aryl, heteroaryl, and alkenyl bromides, chlorides, triflates, and nonaflates. The choice of solvent is quite important and the mixture of THF–*N*-ethylpyrrolidinone (NEP) (8:1) was found to be optimal. The reaction usually requires only 0.05 mol % of $NiCl_2$ or $Ni(acac)_2$ as catalyst and proceeds at room temperature within 1–48 h.

1. Introduction

The formation of C–C bonds by cross-coupling reactions between aryl organometallics and aryl or alkenyl electrophiles is very important in modern organic chemistry.[1] Organozinc derivatives are attractive partners in this reaction due to their availability and tolerance toward the presence of functional groups.[2] They can be easily prepared from aryl bromides or iodides by a halogen–magnesium exchange,[3] followed by the transmetalation with zinc halides, by a direct zinc insertion[4] or from the corresponding organolithium compounds. Recently, we reported an aryl–aryl cross-coupling reaction of arylzinc halides in the presence of a new catalytic system: nickel chloride–diethyl phosphite–DMAP (Scheme 1).[5] Herein, we wish to report our full results on this highly synthetically attractive process. We found also that alkenyl halides or triflates undergo this reaction as well, although a higher amount of the catalyst is required in these cases.



Scheme 1. Ni-catalyzed cross-coupling reaction of arylzinc bromides with aryl halides and sulfonates.[5]

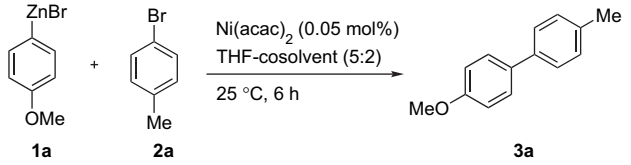
* Corresponding author. Tel.: +49 89 2180 77679; fax: +49 89 2180 77680; e-mail: paul.knochel@cup.uni-muenchen.de

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.123

2. Results and discussion

While studying the cross-coupling reactions of arylzinc compounds, we noticed that the reaction between 4-methoxyphenylzinc bromide, prepared by the transmetalation of 4-methoxyphenylmagnesium bromide with $ZnBr_2$ and some reactive electrophiles like ethyl 4-bromobenzoate in a THF–NMP mixture gave traces of product at room temperature even in the absence of any added catalyst. This could be ascribed to the presence of Pd or Ni traces in commercial $ZnBr_2$. Indeed, no product was formed, when extra pure $ZnBr_2$ (Aldrich, 99.999% purity) was used for the reaction. Further experiments excluded the influence of Pd traces, whereas Ni salts were found to promote the coupling even at the level of 10^{-4} mol % under these conditions, and 0.01 mol % was sufficient to achieve full conversion for some substrates.[6] Other transition metals like Fe or Mn were not active as catalysts under such conditions. Two issues had to be addressed during the reaction optimization: the low reactivity of electron-rich aryl halides and the extensive homocoupling of the organozinc reagent.

For the optimization of the solvent mixture, we chose the test reaction between 4-methoxyphenylzinc bromide (**1a**) and 4-bromotoluene (**2a**) (Scheme 2, 0.05 mol % $Ni(acac)_2$, 1.3 equiv 4-$MeOC_6H_4ZnBr$, THF–cosolvent 5:2, rt, 6 h). The conversion of 4-bromotoluene was determined by GC-analysis with *n*-octadecane as an internal standard. The effect of different cosolvents on the reaction conversion is summarized in Table 1.



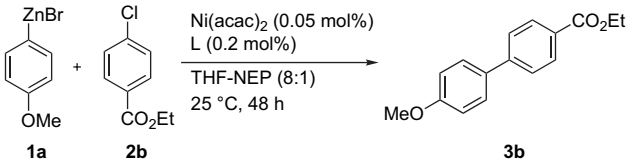
Scheme 2. Ni(acac)$_2$-catalyzed cross-coupling reaction of 4-methoxyphenylzinc bromide (**1a**) and 4-bromotoluene (**2a**).

Table 1. The influence of cosolvents in the Ni-catalyzed Negishi cross-coupling reaction between 4-methoxyphenylzinc bromide (**1a**) and 4-bromotoluene (**2a**)

Solvent	Conversion[a] [%]	Solvent	Conversion[a] [%]
THF	<5	DMF	<5
NMP	44	DMSO	<5
DMAC	<5	Et_3N	11
DMPU	<5	2-Methoxy-ethylpyrrolidinone	68
TMU	<5	*N*-Ethyl-pyrrolidinone (NEP)	88

[a] Substrate conversion was determined by GC-analysis with *n*-octadecane as an internal standard. NMP=*N*-methylpyrrolidinone, DMAC=*N*,*N*-dimethylacetamide, DMPU=*N*,*N*′-dimethylpropyleneurea, TMU=tetramethylurea.

None of the tested solvents afforded the coupling product except *N*-alkylpyrrolidinones,[7] among which *N*-ethylpyrrolidinone (NEP) was the most efficient. The optimal ratio of THF–NEP after further optimization turned out to be 8:1. With higher concentration of NEP in the reaction mixture the final conversion decreased. In most cases, a complete conversion was observed within 1 h and a significant amount of 4,4′-dimethoxybiphenyl as a by-product was formed. To inhibit this side reaction, we have investigated the influence of different ligands on this cross-coupling reaction, using 4-methoxyphenylzinc bromide (**1a**) and ethyl 4-chlorobenzoate (**2b**) as substrates (Scheme 3, 0.05 mol % Ni(acac)$_2$, 0.2 mol % ligand, 1.3 equiv 4-MeOC$_6$H$_4$ZnBr, THF–NEP (8:1), 25 °C, 48 h). The yield of the coupling product (**3b**) was determined by GC-analysis, using *n*-octadecane as an internal standard and by comparing with an authentic sample.

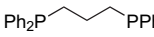
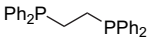
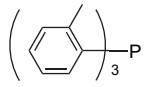
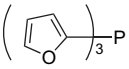
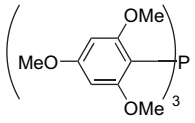
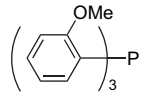
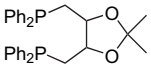
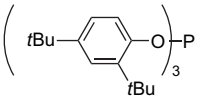
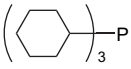
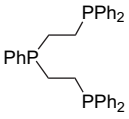
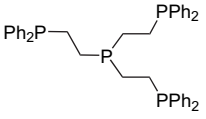
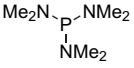
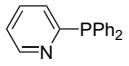
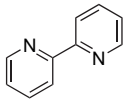
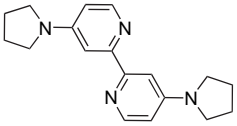
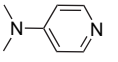
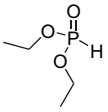


Scheme 3. Ni-catalyzed cross-coupling reaction of 4-methoxyphenylzinc bromide (**1a**) with ethyl 4-chlorobenzoate (**2b**) in presence of a ligand (L).

Without a ligand, this reaction is very sluggish and gives only traces of the desired product **3b**. The results of the ligand screening are shown in Table 2.

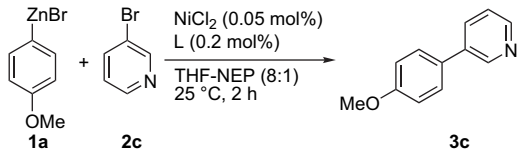
Surprisingly, diethyl phosphite (entry 18) appeared to be the best ligand for the reaction, affording 71% yield of the desired compound along with only a small amount of the homocoupled side product. Among other ligands, dppp (entry 1) and tris-(dimethylamino)phosphine (entry 13) showed good performance. Triphenylphosphine (entry 3)

Table 2. Effect of various ligands in the cross-coupling reaction between 4-methoxyphenylzinc bromide (**1a**) and ethyl 4-chlorobenzoate (**2b**)

Entry	Ligand	Yield [%][a]
1		61
2		51
3		53
4		<5
5		16
6		8
7		27
8		9
9		14
10		47
11		10
12		<5
13		62
14		<5
15		50
16		44
17		18
18		71

[a] Yields are determined by GC-analysis with *n*-octadecane as an internal standard and by comparison with an authentic sample.

was less active and, interestingly, practically did not influence the product yield even in quantities up to 1 mol % (ratio 20:1 for Ni). Noteworthy, the order of reagent mixing significantly influences the reaction rate. The optimal way is the addition of Grignard reagent to the solution of $ZnBr_2$, premixed with NEP. If the Grignard reagent solution is first mixed with $ZnBr_2$, a precipitate forms soon, and the following coupling reaction is much slower. This fact can be explained by the fast formation of oligomers in the arylzinc halide solution, which might possess a lower reactivity. The precomplexation with NEP seems to suppress this process. Some aza-ligands were also found to be active in this process. Thus, 2,2′-bipyridine (entry 15) afforded 50% yield of the product, although along with a large amount of the homocoupling compound. Taking into account that DMAP was also slightly active (entry 17), we prepared 4,4′-bis-(pyrrolidino)-2,2′-bipyridyl[8] (entry 16), an electron-rich *N*,*N*-ligand. However, no improvement was observed for this compound in comparison with 2,2′-bipyridyl (44% yield vs 50% for the latter). Some other aza-ligands were also tested in the reaction between 4-methoxyphenylzinc bromide (**1a**) and 3-bromopyridine (**2c**) (Scheme 4).



Scheme 4. Ni-catalyzed cross-coupling reaction of 4-methoxyphenylzinc bromide (**1a**) with 3-bromopyridine (**2c**).

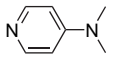
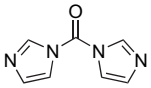
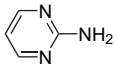
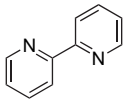
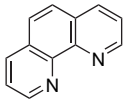
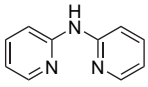
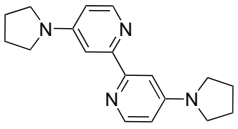
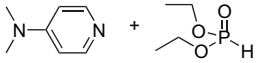
The substrates and the conditions (0.05 mol % $NiCl_2$, 0.2 mol % ligand, 1.3 equiv 4-$MeOC_6H_4ZnBr$, THF–NEP (8:1), rt, 2 h) were changed in order to have a less reactive system for the further catalyst optimization. Since $NiCl_2$ is poorly soluble in THF, it was added as a solution in NEP. The results of aza-ligands screening are given in Table 3.

From all the investigated *N*,*N*-ligands, 2,2′-bipyridine (entry 8) gave the best result with 43% yield of product **3c**. For all aza-ligands tested, the catalytic activity was not superior to diethyl phosphite.

Then we used the same reaction to screen some ligand mixtures. Diethyl phosphite–triphenylphosphine and especially diethyl phosphite–DMAP (1:1) were found superior as additives (entry 12) and yielded 81% of product **3c**. The optimal ratio of Ni–diethyl phosphite turned out to be 1:4. Other phosphites like $(iPrO)_3P$, $(MeO)_2P(O)H$, $(iPrO)_2P(O)H$, $(BuO)_3P$ or $(PhO)_3P$ were found to be by far less active. The results of the aryl–aryl cross-coupling reaction with this optimized catalytic system (0.05 mol % $NiCl_2$, 0.2 mol % $(EtO)_2P(O)H$, and 0.2 mol % DMAP, THF–NEP (8:1), see Scheme 1), are shown in Table 4.

As shown in Table 4, a very broad range of substrates can be involved into this cross-coupling reaction. Electron-rich, electron-poor, and heterocyclic zinc compounds can be coupled with a broad variety of aryl and heteroaryl bromides, chlorides, triflates, and nonaflates. Electron-rich arylzinc halides react with aryl bromides to give the desired products

Table 3. Effect of various *N*-ligands on the cross-coupling reaction between 4-methoxyphenylzinc bromide (**1a**) and 3-bromopyridine (**3c**)

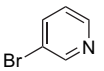
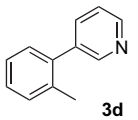
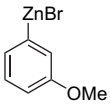
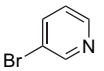
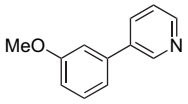
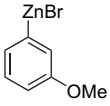
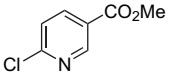
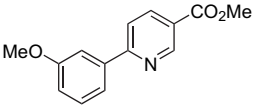
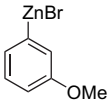
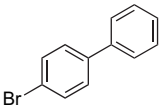
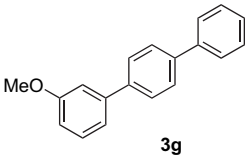
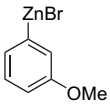
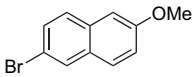
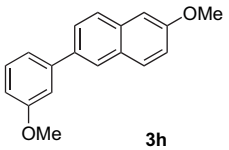
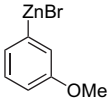
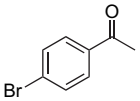
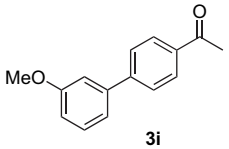
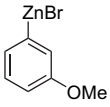
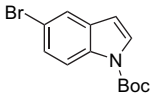
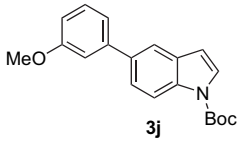
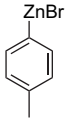
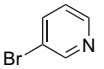
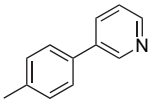
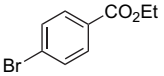
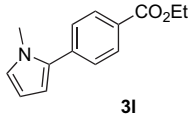
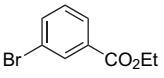
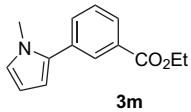
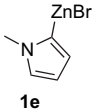
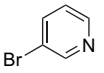
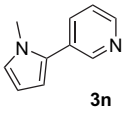
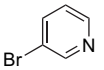
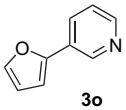
Entry	Ligand	Yield [%][a]
1		35
2		34
3		37
4		36
5		36
6		36
7		38
8		43
9		37
10		32
11		20
12		81

[a] Yields are determined by GC-analysis with *n*-decane as an internal standard and by comparison with an authentic sample.

within few hours at room temperature in good to excellent yields 56–94% (entries 2, 4, 6, 8, 16–20, 22, 29, and 30). With heteroaryl bromides as electrophiles, prolonged reaction time (in most cases about 24 h at room temperature, entries 3, 7, 13, and 15) or elevated temperatures (entries 1 and 14) is required. Aryl and heteroaryl chlorides also react, but compared to bromides the reaction times are longer and the yields decreased (entries 21, 22, 23, and 24). Also the electron-poor zinc bromides, which are often bad substrates for a cross-coupling, could be reacted with various aryl and heteroaryl bromides, affording good yields of the products (entries 25–27).

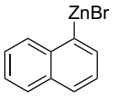
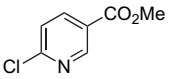
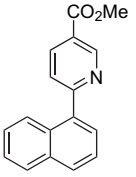
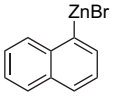
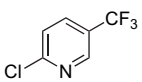
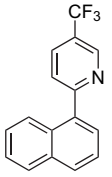
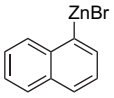
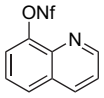
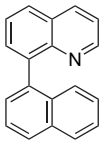
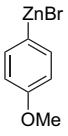
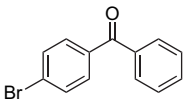
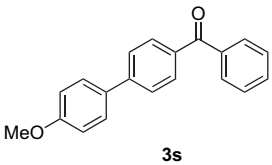
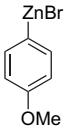
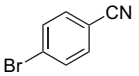
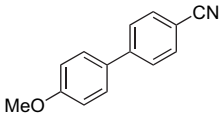
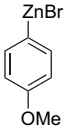
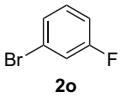
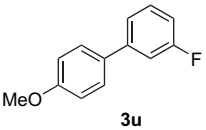
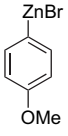
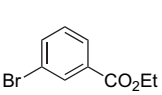
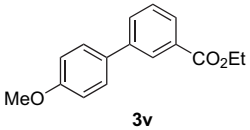
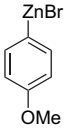
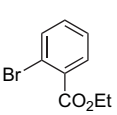
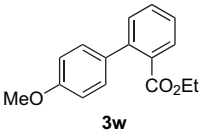
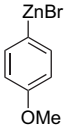
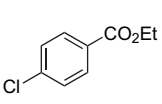
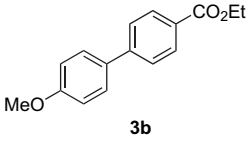
Various heterocyclic zinc compounds like 3-pyridyl-, *N*-methyl-2-pyrrolyl-, and 2-furylzinc bromide could be used. They required elevated temperatures, but lead to the products in satisfactory yields (entries 9–12 and 24). We also attempted to involve some aryl tosylates, mesylates,

Table 4. Ni-catalyzed Negishi cross-coupling between arylzinc compounds and aryl halides in the presence of $(EtO)_2P(O)H$ and DMAP

Entry	Ar^1–ZnX	Ar^2–X	Product	Temperature [°C], reaction time [h]	Yield [%][a]
1	 **1b**	 **2c**	 **3d**	50, 6	47
2	 **1c**	 **2c**	 **3e**	25, 1	66
3	 **1c**	 **2d**	 **3f**	25, 24	74
4	 **1c**	 **2e**	 **3g**	25, 4	77
5	 **1c**	 **2f**	 **3h**	25, 8	86
6	 **1c**	 **2g**	 **3i**	25, 2.5	77
7	 **1c**	 **2h**	 **3j**	25, 24	75
8	 **1d**	 **2c**	 **3k**	25, 1	56
9	 **1e**	 **2i**	 **3l**	70, 22	61
10	 **1e**	 **2j**	 **3m**	70, 22	55
11	 **1e**	 **2c**	 **3n**	70, 22	62
12	 **1f**	 **2c**	 **3o**	110, 22	59

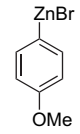
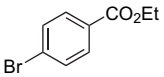
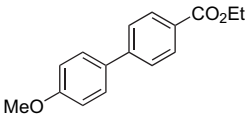
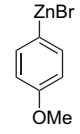
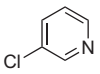
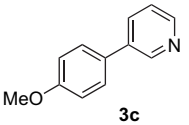
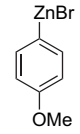
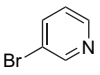
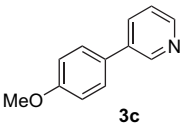
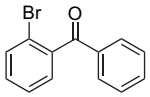
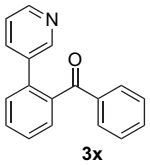
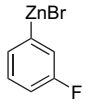
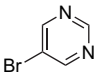
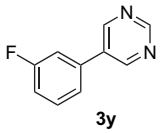
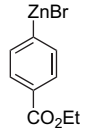
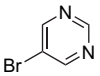
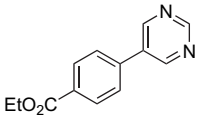
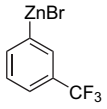
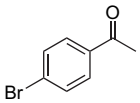
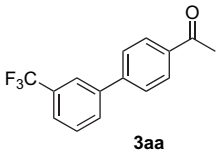
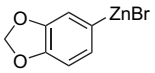
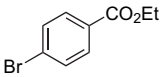
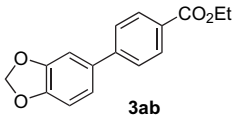
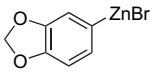
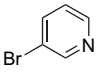
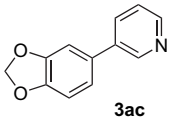
(continued)

Table 4. (*continued*)

Entry	Ar^1–ZnX	Ar^2–X	Product	Temperature [°C], reaction time [h]	Yield [%][a]
13	 **1g**	 **2d**	 **3p**	25, 23	73
14	 **1g**	 **2k**	 **3q**	95, 2	82
15	 **1g**	 **2l**	 **3r**	25, 24	88
16	 **1a**	 **2m**	 **3s**	25, 3	73
17	 **1a**	 **2n**	 **3t**	50, 48	54
18	 **1a**	 **2o**	 **3u**	25, 2	86
19	 **1a**	 **2j**	 **3v**	25, 1	91
20	 **1a**	 **2p**	 **3w**	25, 4	52
21	 **1a**	 **2b**	 **3b**	25, 48	81

(continued)

Table 4. (*continued*)

Entry	Ar^1–ZnX	Ar^2–X	Product	Temperature [°C], reaction time [h]	Yield [%][a]
22	 **1a**	 **2i**	 **3b**	25,1	87
23	 **1a**	 **2q**	 **3c**	25, 12	68
24	 **1a**	 **2c**	 **3c**	25, 2	81
25	 **1h**	 **2r**	 **3x**	50, 3	76
26	 **1i**	 **2s**	 **3y**	25, 1	82
27	 **1j**	 **2s**	 **3z**	50, 24	60
28	 **1k**	 **2g**	 **3aa**	25, 18	68
29	 **1l**	 **2i**	 **3ab**	25, 5	94
30	 **1l**	 **2c**	 **3ac**	25, 5	83

[a] Isolated yield of analytically pure product.

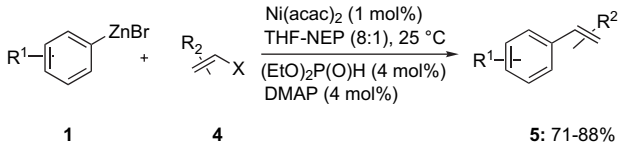
and phosphates into this reaction, but could not achieve acceptable yields of products under our conditions.

The required organozinc reagents were obtained mostly from the corresponding bromides or iodides via halogen–magnesium exchange with *i*-PrMgCl–LiCl,[3a] or by direct insertion of Mg, followed by the transmetalation with 1 equiv of $ZnBr_2$. In the cases of furan and *N*-methylpyrrole, the organometallic species was prepared by direct metalation with *n*-BuLi.[14]

The reaction was found to be rather sensitive to steric hindrance both in the organozinc reagent and aryl electrophile. In the case of *o*-tolylzinc bromide the yield drops significantly (entry 1) and we could not obtain a significant amount of the coupling product from mesitylzinc bromide and

any aryl bromide under our conditions. Functional groups like esters or ketones as well as heteroatoms were perfectly tolerated. Nitriles are less active as substrates probably due to the coordination of the nitrile group with the catalyst species.

Beside aryl–aryl cross-coupling, we have found that arylzinc halides can also react with alkenyl halides and triflates in the presence of our catalytic system, although with a higher amount of catalyst (1 mol % $Ni(acac)_2$, 4 mol % $(EtO)_2P(O)H$, 4 mol % DMAP, 1.3 equiv ArZnBr, THF–NEP (8:1), Scheme 5).

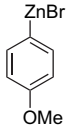
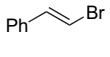
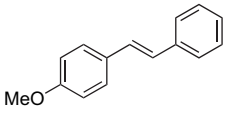
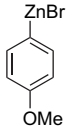
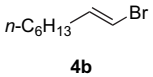
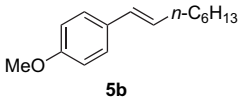
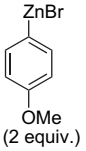
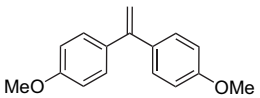
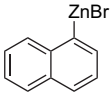
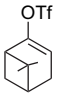
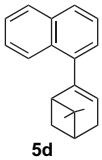
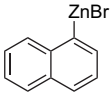
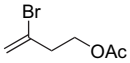
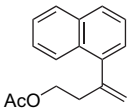
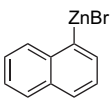
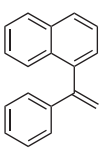


Scheme 5. Ni-catalyzed cross-coupling reaction of arylzinc halides with alkenyl electrophiles.

The reactions were complete at room temperature within a period between 15 min and some hours and gave the desired products **5a**–**5f** in 71–88% yield. The results of the aryl–alkenyl cross-coupling reaction in the presence of a Ni catalyst are summarized in Table 5.

In summary, we have developed a very efficient catalytic system, based on $NiCl_2$, $(EtO)_2P(O)H$, and DMAP for the cross-coupling reaction between arylzinc halides and aryl and alkenyl bromides, triflates, nonaflates, and activated chlorides. A broad range of highly functionalized substrates reacts at room temperature, giving the cross-coupling products in good to excellent yields. An extremely small amount of a transition metal catalyst (0.05 mol % Ni) in comparison with other methods is usually required. In a larger scale, it will hardly pose a problem of waste treatment, or contamination of the products with toxic metals, usually for Ni- and Pd-based cross-coupling processes. The ligands are inexpensive, soluble in water, and therefore easy to remove, and environmentally benign. These are the advantages of this method, which show good perspectives for its future use in industrial processes.

Table 5. Nickel-catalyzed cross-coupling reaction of arylzinc bromides with alkenyl electrophiles

Entry	Arylzinc bromide	Vinyl halide	Product	Temperature [°C], reaction time [h]	Yield [%][a]
1	 **1a**	 **4a**	 **5a**	25, 0.25	85
2	 **1a**	 **4b**	 **5b**	25, 0.5	79
3	 **1a**	 **4c**	 **5c**	25, 6	88
4	 **1g**	 **4d**	 **5d**	25, 12	71
5	 **1g**	 **4e**	 **5e**	25, 12	81
6	 **1g**	 **4f**	 **5f**	25, 6	78

[a] Isolated yield of analytically pure product.

3. Experimental

3.1. General

Unless otherwise indicated, all reactions were carried out with magnetic stirring and in case of air- or moisture-sensitive compounds reactions were carried out in flame-dried glassware under argon. Syringes were used to transfer the reagents and the solvents were purged with argon prior to use. Reactions were monitored by gas chromatography (GC and GC–MS) or thin-layer chromatography. Solutions of organomagnesium compounds were prepared, unless otherwise stated, by the reaction of Mg with aryl bromides in THF, titrated with a standard solution of I_2 in 0.5 M LiCl in THF and diluted with THF to the mentioned concentration. $ZnBr_2$ and $ZnCl_2$ were dried at 140 °C under high vacuum for 30 min and then dissolved in dry THF. Tetrahydrofuran was freshly distilled from Na–benzophenone ketyl. *N*-Ethylpyrrolidinone and other aprotic solvents were dried with CaH_2, distilled in vacuo, and stored under Ar. All new compounds were determined to be with >95% purity by GC and ^{1}H NMR spectroscopy.

3.2. Typical procedure A

The solution of the nickel catalyst A was prepared as follows. In a 25 mL Schlenk tube under argon in dry degassed *N*-ethylpyrrolidinone (NEP, 10.0 mL) were dissolved in anhydrous $NiCl_2$ (8.2 mg, 0.063 mmol), $(EtO)_2P(O)H$ (34.5 mg, 0.25 mmol), and DMAP (30.5 mg, 0.25 mmol).

In a dry argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, the corresponding arylmagnesium reagent in THF (1.30 mmol) was added slowly with cooling to the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF, 1.00 mmol) and NEP (0.17 mL). To this mixture, the electrophile (aryl halide or sulfonate, 1.00 mmol) was added, followed by the catalyst solution A (0.08 mL). The final THF–NEP volume ratio should be about 8:1. The mixture was stirred at the specified temperature until the GC of an aliquot showed the reaction completion, quenched with satd NH_4Cl solution, extracted with ether, and then the product was purified by column chromatography.

3.3. Typical procedure B

The solution of the nickel catalyst B was prepared as follows. In a 25 mL Schlenk tube under argon in dry degassed *N*-ethylpyrrolidinone (10.0 mL) were dissolved in $Ni(acac)_2$ (103 mg, 0.40 mmol), $(EtO)_2P(O)H$ (221 mg, 1.60 mmol), and DMAP (195 mg, 1.60 mmol).

In a dry argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, the corresponding arylmagnesium reagent in THF (1.30 mmol) was added slowly with cooling to the mixture of $ZnBr_2$ solution (0.67 mL, 1.5 M in THF, 1.00 mmol), catalyst solution B (0.25 mL), and electrophile (aryl halide or sulfonate, 1.00 mmol). The final THF–NEP volume ratio should be approximately 8:1. The mixture was stirred at the specified temperature until the GC of an aliquot showed the reaction completion, quenched with satd NH_4Cl solution, extracted with ether, and then the product was purified by column chromatography.

3.3.1. 3-*o*-Tolyl-pyridine (3d). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 2-tolylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 6 h at 50 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3d** (80 mg, 47%) as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.52 (dd, J=4.5, 1.5 Hz, 2H), 7.58 (dd, J=2.2, 1.7 Hz, 1H), 7.30–7.12 (m, 5H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 149.0, 147.1, 137.1, 136.4, 135.4, 134.6, 129.5, 128.8, 127.1, 125.1, 122.0, 19.3. *m/z* (EIMS): 169 (100), 168 (89), 154 (5), 141 (16), 115 (18).

3.3.2. 3-(3-Methoxyphenyl)-pyridine (3e). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 1 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3e** (122 mg, 66%) as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.85 (dd, J=2.3, 0.8 Hz, 1H), 8.59 (dd, J=4.8, 1.7 Hz, 1H), 7.87 (ddd, J=8.0, 2.3, 1.7 Hz, 1H), 7.43–7.33 (m, 2H), 7.17 (ddd, J=7.6, 1.7, 1.0 Hz, 1H), 7.11 (dd, J=2.3, 1.8 Hz, 1H), 6.95 (ddd, J=8.3, 2.7, 1.0 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 159.1, 147.6, 147.4, 138.3, 135.5, 133.4, 129.1, 122.5, 118.6, 112.4, 112.0, 54.3. *m/z* (EIMS): 185 (100), 154 (26), 142 (21), 127 (6), 115 (15).

3.3.3. 6-(3-Methoxyphenyl)-nicotinic acid methyl ester (3f). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL in NEP), and 6-chloronicotinic acid methyl ester **2d** (172 mg, 1.00 mmol). Stirred for 24 h at 25 °C. Standard workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3f** as colorless solid (180 mg, 74%). Mp 89.5–90 °C. IR (KBr): 3059 (w), 3013 (w), 2954 (m), 2925 (m), 1715 (vs), 1596 (vs), 1562 (m), 1480 (s), 1433 (s), 1288 (vs), 1267 (s), 1231 (s), 1117 (s), 1030 (s), 1021 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.24 (d, J=1.9 Hz, 1H), 8.31 (dd, J=8.3, 1.9 Hz, 1H), 7.77 (d, J=8.3 Hz, 1H), 7.63–7.62 (m, 1H), 7.57 (d, J=7.9 Hz, 1H), 7.38 (t, J=8.1 Hz, 1H), 6.99 (dd, J=8.1, 2.4 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 168.0, 162.8, 162.3, 153.1, 141.9, 140.0, 132.0, 126.5, 122.1, 121.8, 118.2, 114.6, 57.6, 54.5. *m/z* (EIMS): 243 (65), 242 (100), 213 (38), 182 (9), 154 (10), 106 (11). HRMS calcd for $C_{14}H_{13}NO_3$: 243.0895, found: 243.0867.

3.3.4. 3-Methoxy-[1,1;4′,1″]terphenyl (3g). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 4-bromobiphenyl **2e** (233 mg, 1.00 mmol). Stirred for 4 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3g** (201 mg, 77%) as colorless solid. Mp 104.5–105 °C. IR (KBr): 3033 (w), 1602

(m), 1578 (s), 1478 (vs), 1217 (s), 761 (vs) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.69–7.65 (m, 6H), 7.49—7.45 (m, 2H), 7.41–7.36 (m, 2H), 7.27–7.24 (m, 1H), 7.20–7.19 (m, 1H), 6.94–6.91 (m, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.4, 172.6, 156.0, 136.2, 134.2, 133.9, 132.2, 131.5, 130.6, 130.2, 129.1, 128.9, 117.3, 110.6. *m/z* (EIMS): 260 (100), 230 (7), 217 (17), 189 (5), 130 (10). HRMS calcd for $C_{19}H_{16}O$: 260.1201, found: 260.1191.

3.3.5. 2-Methoxy-6-(3-methoxyphenyl)-naphthalene (3h). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 2-bromo-6-methoxynaphthalene **2f** (237 mg, 1.00 mmol). Stirred for 8 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3h** (228 mg, 86%) as colorless solid. Mp 85–87.5 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.87 (d, J=1.2 Hz, 1H), 7.69 (dd, J=8.5, 2.0 Hz, 2H), 7.61 (dd, J=8.5, 1.8 Hz, 1H), 7.29 (t, J=7.9 Hz, 1H), 7.22–7.13 (m, 2H), 7.10–7.05 (m, 2H), 6.81 (ddd, J=8.0, 2.5, 0.9 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.0, 157.8, 142.7, 136.2, 133.9, 129.8, 129.7, 129.1, 127.2, 126.0, 125.6, 119.7, 119.1, 112.9, 112.4, 110.6, 55.3. *m/z* (EIMS): 264 (100), 249 (9), 221 (43), 189 (79), 178 (18).

3.3.6. 1-(3′-Methoxybiphenyl-4-yl)-ethanone (3i). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 1-(4-bromophenyl)-ethanone **2g** (199 mg, 1.00 mmol). Stirred for 2.5 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3i** (175 mg, 77%) as yellow solid. Mp 35.2–36.2 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.00 (ddd, J=8.5, 2.9, 1.9 Hz, 2H), 7.65 (ddd, J=8.6, 2.0, 1.9 Hz, 2H), 7.38–7.31 (m, 1H), 7.20–7.17 (m, 1H), 7.13–7.12 (m, 1H), 6.94–6.90 (m, 1H), 3.85 (s, 3H), 2.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.1, 160.4, 146.0, 141.8, 136.4, 130.4, 129.3, 127.7, 120.1, 113.9, 113.5, 55.8, 27.0. *m/z* (EIMS): 226 (56), 211 (100), 168 (14), 152 (11), 139 (21).

3.3.7. 5-(3-Methoxy-phenyl)-indole-1-carboxylic acid *tert*-butyl ester (3j). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL) and 5-bromoindole-1-carboxylic acid *tert*-butyl ester **2h** (296 mg, 1.00 mmol). Stirred for 24 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3j** (242 mg, 75%) as yellow solid. Mp 109.5–110 °C. IR (KBr): 3006 (w), 2968 (w), 1721 (vs), 1607 (m), 1471 (s), 1369 (vs), 1164 (s), 781 (m), 713 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.11 (d, J=8.6 Hz, 1H), 7.69 (d, J=1.4 Hz, 1H), 7.55 (d, J=3.6 Hz, 1H), 7.48 (dd, J=8.6, 1.8 Hz, 1H), 7.31–7.25 (m, 1H), 7.18–7.10 (m, 2H), 6.81 (ddd, J=8.2, 2.5, 0.8 Hz, 1H), 6.54 (d, J=3.7 Hz, 1H), 3.80 (s, 3H), 1.62 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.9, 149.7, 143.2, 135.9, 134.7, 131.0, 129.7, 126.5, 123.7, 119.9, 119.4, 115.3, 113.1, 112.3, 107.5, 83.8, 55.3, 28.2. *m/z* (EIMS): 223 (100), 180 (30), 152 (16), 111 (8), 77 (7). HRMS calcd for $C_{20}H_{21}NO_3$: 323.1521, found: 323.1512.

3.3.8. 3-*p*-Tolyl-pyridine (3k). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-tolylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 1 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3k** (95 mg, 56%) as colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.85 (s, 1H), 8.57 (d, J=4.2 Hz, 1H), 7.93–7.89 (m, 1H), 7.49 (d, J=8.1 Hz, 2H), 7.41–7.37 (m, 1H), 7.30 (d, J=8.1 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.5, 147.4, 138.3, 136.9, 134.8, 134.6, 129.9, 127.0, 123.8, 21.3. *m/z* (EIMS): 169 (100), 154 (6), 141 (7), 115 (14), 91 (6).

3.3.9. 4-(1-Methyl-1*H*-pyrrol-2-yl)-benzoic acid ethyl ester (3l). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-methyl-1*H*-pyrryllithium[14] (2.40 mL, 0.50 M in THF), then the catalyst A solution (0.08 mL), and ethyl 4-bromobenzoate **2i** (229 mg, 1.00 mmol). Stirred for 22 h at 70 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3l** (141 mg, 61%) as yellow solid. Mp 65.1–65.9 °C. IR (KBr): 3104 (w), 2986 (w), 1710 (vs), 1608 (vs), 1478 (m), 1365(m), 1310 (s), 1291 (vs), 1181 (s), 1109 (s), 740 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.09–8.03 (m, 2H), 7.49–7.43 (m, 2H), 6.77–6.74 (m, 1H), 6.34–6.30 (m, 1H), 6.23–6.20 (m, 1H), 4.39 (q, J=7.1 Hz, 2H), 3.71 (s, 3H), 1.41 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 137.6, 133.6, 129.7, 128.3, 127.9, 125.0, 110.0, 108.2, 60.0, 35.4, 14.4. *m/z* (EIMS): 229 (100), 201 (64), 184 (45), 156 (16), 128 (11). HRMS calcd for $C_{14}H_{15}NO$: 229.1103, found: 229.1080.

3.3.10. 3-(1-Methyl-1*H*-pyrrol-2-yl)-benzoic acid ethyl ester (3m). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-methyl-1*H*-pyrryllithium (2.40 mL, 0.50 M in THF), then the catalyst A solution (0.08 mL), and ethyl 3-bromobenzoate **2j** (229 mg, 1.00 mmol). Stirred for 22 h at 70 °C. The usual workup and purification by flash chromatography (pentane–ether 4:1) yielded **3m** (125 mg, 55%) as colorless oil. IR (neat): 3102 (w), 2988 (m), 1717 (vs), 1607 (m), 1468 (m), 1367 (m), 1310 (s), 1270 (vs), 1236 (vs) 1109 (s), 756 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.10 (td, J=1.8, 0.5 Hz, 1H), 7.99–7.96 (m, 1H), 7.59 (ddd, J=7.7, 1.8, 1.3 Hz, 1H), 7.46 (td, J=7.7, 0.5 Hz, 1H), 6.75–6.73 (m, 1H), 6.29–6.28 (m, 1H), 6.23–6.21 (m, 1H), 4.40 (q, J=7.1 Hz, 2H), 3.68 (s, 3H), 1.40 (t, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 133.6, 133.5, 132.8, 130.7, 129.5, 128.4, 127.7, 124.1, 109.2, 107.9, 61.0, 35.1, 14.3. *m/z* (EIMS): 229 (100), 201 (68), 184 (17), 156 (16), 128 (10). HRMS calcd for $C_{14}H_{15}NO$: 229.1103, found: 229.1095.

3.3.11. 3-(1-Methyl-1*H*-pyrrol-2-yl)-pyridine (β-nicotyrine, 3n). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were

added dropwise 1-methyl-1*H*-pyrryllithium[14] (2.40 mL, 0.50 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 22 h at 70 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3n** (98 mg, 62%) as yellow oil.[9] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.66 (d, J=1.8 Hz, 1H), 8.50 (dd, J=4.8, 1.6 Hz, 1H), 7.70 (ddd, J=7.9, 1.8, 1.6 Hz, 1H), 7.31 (ddd, J=7.9, 4.8, 0.8 Hz, 1H), 6.74 (dd, J=2.5, 1.9 Hz, 1H), 6.27 (dd, J=3.6, 1.9 Hz, 1H), 6.20 (dd, J=3.6, 2.8 Hz, 1H), 3.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.3, 147.8, 136.1, 131.1, 129.8, 125.2, 123.7, 110.3, 108.7, 35.5. *m/z* (EIMS): 158 (100), 143 (7), 130 (19), 116 (6), 89 (5).

3.3.12. 3-Furan-2-yl-pyridine (3o). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-furyllithium[14] (2.40 mL, 0.50 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 22 h at 110 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3o** (78 mg, 59%) as yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.93 (d, J=1.5 Hz, 1H), 8.49 (dd, J=4.9, 1.5 Hz, 1H), 7.95 (ddd, J=8.0, 2.2, 1.8 Hz, 1H), 7.52 (dd, J=1.8, 0.7 Hz, 1H), 7.32 (ddd, J=8.0, 4.9, 0.9 Hz, 1H), 6.75 (dd, J=3.4, 0.7 Hz, 1H), 6.52–6.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.9, 147.9, 145.1, 143.1, 131.0, 126.9, 123.6, 111.8, 106.5. *m/z* (EIMS): 145 (100), 116 (36), 89 (23), 63 (14), 51 (3).

3.3.13. 6-Naphthalen-1-yl-nicotinic acid methyl ester (3p). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 6-chloronicotinic acid methyl ester **2d** (172 mg, 1.00 mmol). Stirred for 23 h at 25 °C. The usual workup and purification by flash chromatography (pentane–ether 2:1) yielded **3p** (191 mg, 73%) as colorless solid. Mp 90.5–92.5 °C. IR (KBr): 3044 (w), 2953 (w), 1729 (vs), 1596 (vs), 1440 (s), 1376 (s), 1314 (vs), 1198 (m), 1131 (vs) 1024 (m), 782 (vs) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.40 (dd, J=2.2, 0.8 Hz, 1H), 8.44 (dd, J=8.2, 2.2 Hz, 1H), 8.10–8.07 (m, 1H), 7.97–7.91 (m, 2H), 7.72–7.47 (m, 5H), 4.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.8, 163.0, 150.6, 137.6, 137.3, 133.9, 130.8, 129.7, 128.5, 127.9, 126.8, 126.1, 125.2, 125.1, 124.7, 124.3, 52.4. *m/z* (EIMS): 262 (100), 248 (5), 202 (13), 176 (7), 127 (4). HRMS calcd for $C_{17}H_{13}NO_2$: 263.0946, found: 263.0936.

3.3.14. 2-Naphthalen-1-yl-5-trifluoromethyl-pyridine (3q). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 2-chloro-5-trifluoromethylpyridine **2k** (182 mg, 1.00 mmol). Stirred for 2 h at 95 °C. The usual workup and purification by flash chromatography (pentane–ether 4:1) yielded **3q** (225 mg, 82%) as colorless solid. Mp 67–68 °C. IR (KBr): 3055 (w), 1605 (s), 1566 (m), 1331 (vs), 1161 (s), 1128 (vs), 1016 (s), 804 (s), 784 (vs) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.08–9.07 (m, 1H), 8.10–8.04 (m, 2H), 7.99–7.92 (m, 2H), 7.53 (d, J=8.2 Hz, 1H), 7.65–7.48 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.8, 146.4, 146.3, 137.0, 133.9, 133.7, 133.6, 130.8, 129.8, 128.5, 127.9, 126.9, 126.2, 125.3, 125.1, 124.7. *m/z* (EIMS): 273 (41), 272 (100), 252 (6), 203 (6), 176 (4), 136 (5). HRMS calcd for $C_{16}H_{10}NF_3$: 273.0765, found: 273.0726.

3.3.15. 8-(1-Naphthyl)-quinoline (3r). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 8-quinolyl nonaflate[5] **2l** (427 mg, 1.00 mmol). Stirred for 24 h at 25 °C. The standard workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3r** as a white solid (224 mg, 88%). Mp 163–164 °C. IR (KBr): 3042 (w), 1593 (w), 1492 (s), 829 (s), 797 (vs), 782 (vs), 773 (vs) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.76–8.74 (m, 1H), 8.16–8.13 (m, 1H), 7.89–7.82 (m, 3H), 7.69–7.66 (m, 1H), 7.60–7.46 (m, 3H), 7.41–7.18 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.9, 147.7, 140.6, 138.5, 136.6, 134.1, 133.3, 132.0, 128.9, 128.7, 128.5, 128.4, 128.3, 127.1, 126.6, 126.1, 126.0, 125.8, 121.5. *m/z* (EIMS): 127 (9), 226 (9), 252 (14), 254 (100), 255 (47). HRMS calcd for $C_{19}H_{13}N$: 255.1048, found: 255.1020.

3.3.16. (4′-Methoxy-[1,1′-biphenyl]-4-yl)-(phenyl)-methanone (3s). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 4-bromobenzophenone **2m** (261 mg, 1.00 mmol). Stirred for 3 h at 25 °C. The usual workup and purification by flash chromatography (pentane–ether 19:1) yielded **3s** as a white solid (210 mg, 73%). Mp 167–168 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.87 (d, J=8.1 Hz, 2H), 7.83 (d, J=8.3 Hz, 2H), 7.66 (d, J=8.3 Hz, 2H), 7.60–7.57 (m, 3H), 7.49 (t, J=7.6 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 Hz): δ 196.3, 159.9, 144.8, 137.9, 135.6, 132.4, 132.2, 130.8, 129.9, 128.4, 128.3, 126.4, 114.4, 55.4. *m/z* (EIMS): 288 (100), 211 (76), 183 (6), 168 (8), 139 (8), 105 (11), 77 (10), 51 (1).

3.3.17. 4′-Methoxy[1,1′-biphenyl]-4-carbonitrile (3t). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL), were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 4-bromobenzonitrile **2n** (182 mg, 1.00 mmol). Stirred for 48 h at 50 °C. The standard workup and purification by flash chromatography (pentane–ether 9:1) yielded **3t** as white solid (113 mg, 54%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69–7.61 (m, 4H), 7.53 (d, J=8.9 Hz, 2H), 7.00 (d, J=8.9 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.17, 145.15, 132.50, 131.43, 128.29, 127.04, 119.02, 114.51, 110.05, 55.34. *m/z* (EIMS): 209 (100, M^+), 194 (25), 166 (31), 140 (13), 113 (2), 63 (2).

3.3.18. 3-Fluoro-4′-methoxy-1,1'-biphenyl (3u). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added

dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 3-bromofluorobenzene **2o** (175 mg, 1.00 mmol). Stirred for 2 h at 25 °C. The usual workup and purification by flash chromatography (pentane–ether 19:1) yielded **3u** as white solid (174 mg, 86%). Mp 67.0–67.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39 (d, J=8.9 Hz, 2H), 7.28–7.11 (m, 3H), 6.90–6.84 (m, 3H), 3.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.2 (q, ^1J (C, F)=245 Hz), 159.5, 143.1 (q, ^3J (C, F)=7.6 Hz), 132.4 (q, ^4J (C, F)=2.1 Hz), 130.1 (q, ^3J (C, F)=8.2 Hz), 128.1, 122.2 (q, ^4J (C, F)=2.6 Hz), 114.5, 113.5 (q, ^2J (C, F)=21.7 Hz), 113.3 (q, ^2J (C, F)=21.1 Hz), 55.3. *m/z* (EIMS): 209 (100), 187 (50), 159 (54), 133 (24), 107 (10), 77 (13).

3.3.19. Ethyl 4′-methoxy[1,1′-biphenyl]-3-carboxylate (3v). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and ethyl 3-bromobenzoate **2j** (229 mg, 1.00 mmol). Stirred for 1 h at 25 °C. The standard workup and purification by flash chromatography (pentane–ether 9:1) yielded **3v** as a colorless oil (234 mg, 91%). IR (KBr): 2981 (w), 1717 (vs), 1610 (m), 1518 (s), 1439 (m), 1367 (w), 1300 (s), 1249 (vs), 1182 (m), 1109 (s), 1049 (m), 1030 (m), 834 (m), 758 (s), 574 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (s, 1H), 8.00–7.97 (m, 1H), 7.73–7.70 (m, 1H), 7.56 (d, J=8.8 Hz, 2H), 7.46 (t, J=7.7 Hz, 1H), 6.99 (d, J=8.7 Hz, 2H), 4.41 (q, J=7.1 Hz, 2H), 3.83 (s, 3H), 1.41 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 159.4, 140.9, 132.5, 130.9, 130.8, 128.6, 128.1, 127.6, 127.1, 114.2, 60.9, 55.2, 14.2. *m/z* (EIMS): 256 (100), 241 (9), 228 (11), 211 (20), 183 (10), 168 (6), 139 (12), 105 (3).

3.3.20. Ethyl 4′-methoxybiphenyl-2-carboxylate (3w). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and ethyl 2-bromobenzoate **2p** (229 mg, 1.00 mmol). The mixture was stirred for 4 h at 25 °C. The standard workup and purification by flash chromatography (pentane–ether 9:1) yielded **3w** as colorless oil (134 mg, 52%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71–7.68 (m, 1H), 7.42–7.37 (m, 1H), 7.30–7.25 (m, 2H), 7.16 (d, J=8.8 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 4.03 (q, J=7.1 Hz, 2H), 3.74 (s, 3H), 0.97 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.97, 158.97, 141.92, 133.82, 131.34, 130.98, 130.60, 129.59, 129.49, 126.75, 113.47, 60.85, 55.26, 13.79. *m/z* (EIMS): 256 (100), 241 (9), 228 (12), 211 (93), 183 (8), 168 (21), 139 (18), 105 (5), 77 (4), 43 (5).

3.3.21. Ethyl 4′-methoxy-biphenyl-4-carboxylate (3b). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and ethyl 4-bromobenzoate **2i** (229 mg, 1.00 mmol) or ethyl 4-chlorobenzoate **2b** (184 mg, 1.00 mmol). The mixture was stirred for 1 h at 25 °C (48 h for ethyl 4-chlorobenzoate). The usual workup and purification by flash chromatography (pentane–ether 9:1) yielded **3b** as white solid (224 mg, 87% for ethyl 4-bromobenzoate, 209 mg, 81% for ethyl 4-chlorobenzoate). Mp 100.5–101 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09 (d, J=8.7 Hz, 2H), 7.62–7.55 (m, 4H), 6.99 (d, J=8.7 Hz, 2H), 4.39 (q, J=7.1 Hz, 2H), 3.84 (s, 3H), 1.41 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 159.8, 145.0, 132.4, 130.0, 128.6, 128.3, 126.4, 114.3, 60.8, 55.3, 14.3.

3.3.22. 3-(4-Methoxyphenyl)-pyridine (3c). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (159 mg, 1.00 mmol) or 3-chloropyridine **2q** (114 mg, 1.00 mmol). Stirred for 2 h at 25 °C (12 h for 3-chloropyridine). The usual workup and purification by flash chromatography (pentane–ether 1:1) yielded **3c** as a white solid (150 mg, 81% for 3-bromopyridine and 126 mg, 68% for 3-chloropyridine). The same reaction with 3-bromopyridine, performed in 20 mmol scale, gave 82% yield. Mp 62–63 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.81–8.80 (m, 1H), 8.53 (dd, J=4.8, 1.6 Hz, 1H), 7.84–7.80 (m, 1H), 7.52 (d, J=8.8 Hz, 2H), 7.34–7.30 (m, 1H), 7.01 (d, J=8.8 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 159.7, 148.0, 147.9, 136.3, 133.8, 130.3, 128.2, 123.5, 114.6, 55.4. *m/z* (EIMS): 185 (100, M$^+$), 170 (44), 142 (46), 115 (17), 89 (11), 63 (8).

3.3.23. 2-(3-Pyridino)-benzophenone (3x). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-pyridylmagnesium bromide[3a] (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 2-bromobenzophenone **2r** (270 mg, 1.00 mmol). Stirred for 3 h at 50 °C. The standard workup and purification by flash chromatography (pentane–CH_2Cl_2 1:1) yielded **3x** as a white solid (197 mg, 76%). Mp 106–106.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.56–8.52 (m, 1H), 8.44–8.40 (m, 1H), 7.72–7.10 (m, 11H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.3, 149.8, 148.8, 139.5, 137.9, 137.6, 136.6, 136.3, 133.6, 131.1, 130.6, 130.3, 129.5, 128.7, 128.2, 123.3. *m/z* (EIMS): 77 (27), 105 (25), 127 (20), 182 (36), 230 (100), 231 (26), 259 (19).

3.3.24. 5-(3-Fluorophenyl)-pyrimidine (3y). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-fluoro-phenylmagnesium bromide[3a] (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 5-bromopyrimidine **2s** (159 mg, 1.00 mmol). Stirred for 1 h at 25 °C. The standard workup and purification by flash chromatography (pentane–ether) yielded **3y** as a white solid (143 mg, 82%). Mp 63–63.5 °C. IR (KBr): 2239 (w), 1591 (s), 1416 (s), 909 (vs), 734 (vs) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.13 (s, 1H), 8.85 (s, 2H), 7.44–7.23 (m, 1H), 7.29–7.26 (m, 1H), 7.22–7.17 (m, 1H), 7.10–7.03 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.7 (d, J=248 Hz), 158.3, 155.2, 136.8 (d, J=7.9 Hz), 133.5, 131.5 (d, J=8.5 Hz), 123.0, 116.3 (d, J=21.1 Hz), 114.3 (d, J=21.1 Hz). *m/z* (EIMS): (12), 105 (25), 120 (100), 173

(21), 174 (96). HRMS calcd for $C_{10}H_7N_2F$: 174.0593, found: 174.0577.

3.3.25. 4-Pyrimidin-5-yl-benzoic acid ethyl ester (3z). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-(ethoxycarbonyl)-phenylmagnesium bromide[3a] (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 5-bromopyrimidine **2s** (159 mg, 1.00 mmol). Stirred for 24 h at 50 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3z** (130 mg, 60%) as colorless solid. Mp 64–65.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.25 (s, 1H), 8.99 (s, 2H), 8.19 (m, 2H), 7.66 (m, 2H), 4.42 (q, J=7.2 Hz, 2H), 1.43 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.9, 157.2, 157.0, 154.1, 154.0, 137.5, 132.4, 130.0, 129.6, 125.9, 60.3, 13.3. *m/z* (EIMS): 228 (21), 200 (33), 183 (100), 128 (40), 101 (32).

3.3.26. 1-(3′-Trifluoromethyl-biphenyl-4-yl)-ethanone (3aa). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-(trifluoromethyl)phenylmagnesium bromide[3a] (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 1-(4-bromo-phenyl)-ethanone **2g** (199 mg, 1.00 mmol). Stirred for 18 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3aa** (180 mg, 68%) as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (ddd, J=8.6, 2.4, 2.0 Hz, 2H), 7.87–7.78 (m, 2H), 7.73–7.57 (m, 4H), 2.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.9, 144.6, 141.1, 136.9, 132.2, 132.0, 131.6, 130.9, 130.2, 129.9, 129.5, 127.4, 125.3, 124.4, 27.1. *m/z* (EIMS): 264 (35), 249 (100), 221 (6), 201 (34), 152 (21).

3.3.27. Ethyl 4-(1,3-benzodioxol-5-yl)-benzoate (3ab). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1,3-benzodioxol-5-yl-magnesium bromide[3a] (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and ethyl 4-bromobenzoate **2i** (229 mg, 1.00 mmol). Stirred for 5 h at 25 °C. The usual workup and purification by flash chromatography (pentane–ether 1:1) yielded **3ab** as white solid (253 mg, 94%). Mp 92.5–93.5 °C. IR (KBr): 2904 (w), 1707 (vs), 1606 (m), 1522 (w), 1503 (m), 1486 (s), 1410 (s), 1274 (vs), 1256 (s), 1235 (m), 1182 (s), 1107 (s), 1036 (s), 932 (m), 858 (m), 772 (s), 702 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, J=8.7 Hz, 2H), 7.56 (d, J=8.7 Hz, 2H), 7.11–7.07 (m, 2H), 6.89 (d, J=8.6 Hz, 1H), 5.00 (s, 2H), 4.39 (q, J=7.1 Hz, 2H), 1.40 (d, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 148.3, 147.7, 145.1, 134.3, 130.0, 128.8, 126.6, 121.0, 108.6, 107.6, 101.3, 60.9, 14.3. *m/z* (EIMS): 270 (100), 242 (32), 225 (70), 139 (40), 112 (5), 63 (2). HRMS calcd for $C_{16}H_{14}O_4$: 270.0892, found: 270.0888.

3.3.28. 3-(1,3-benzodioxol-5-yl)-pyridine (3ac). Prepared according to Section 3.2. To the $ZnBr_2$ solution (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1,3-benzodioxol-5-yl-magnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst solution (0.08 mL in NEP), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 5 h at 25 °C. The standard workup and purification by flash chromatography yielded **3ac** as a white solid (165 mg, 83%). Mp 91.5–92.5 °C. IR (KBr): 2912 (w), 1512 (s), 1479 (vs), 1420 (s), 1294 (w), 1266 (m), 1238 (s), 1111 (w), 1037 (s), 931 (m), 806 (s), 706 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.76 (d, J=1.9 Hz, 1H), 8.54–8.51 (m, 1H), 7.78–7.74 (m, 1H), 7.32–7.27 (m, 1H), 7.04–7.00 (m, 2H), 6.90–6.87 (m, 1H), 5.99 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.4, 148.1, 148.0, 147.7, 136.3, 133.9, 131.9, 123.4, 120.8, 108.8, 107.5, 101.3. *m/z* (EIMS): 199 (100), 140 (10), 114 (11), 88 (4), 63 (3). HRMS calcd for $C_{12}H_9NO_2$: 199.0633, found: 199.0602.

3.3.29. 4-Methoxy-stilbene (5a). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and α-bromostyrene **4a** (183 mg, 1.00 mmol) was added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 15 min at 25 °C. The standard workup and purification by flash chromatography yielded **5a** as a white solid (179 mg, 85%). The analytical data corresponded to those obtained from an authentic sample.

3.3.30. 1-(4-Methoxyphenyl)-octene (5b). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and 1-bromo-1-octene[15] **4b** (191 mg, 1.00 mmol) was added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 30 min at 25 °C. The standard workup and purification by flash chromatography yielded **5b** as a colorless oil (172 mg, 79%). The analytical data are in accordance with those reported in the literature.[10]

3.3.31. 1,1-Bis-(*p*-methoxyphenyl)-ethylene (5c). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and 1,1-dichloroethylene **4c** (49 mg, 0.50 mmol) was added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 6 h at 25 °C. The standard workup and purification by flash chromatography yielded **5c** as a white solid (106 mg, 88%). The analytical data are in accordance with those reported in the literature.[11]

3.3.32. 6,6-Dimethyl-2-(1-naphthalenyl)-bicyclo[3.1.1]-hept-2-ene (5d). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and 6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl triflate **4d** (prepared from nopinone,[16] 270 mg, 1.00 mmol) was added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 12 h at 25 °C. The standard workup and purification by flash chromatography yielded **5d** as a white solid (176 mg, 71%). The analytical data are in accordance with those reported in the literature.[12]

3.3.33. γ-Methylene-2-naphthalene-propyl acetate (5e). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and 3-bromo-3-buten-1-yl acetate **4e** (193 mg, 1.00 mmol) was added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 12 h at 25 °C. The standard workup and purification by flash

chromatography yielded **5e** as a colorless oil (195 mg, 81%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (dd, J_1=9.5 Hz, J_2=3.6 Hz, 1H), 7.70 (dd, J_1=9.5 Hz, J_2=3.6 Hz, 1H), 7.62 (d, J=8.3 Hz, 1H), 7.34–7.25 (m, 3H), 7.11 (t, J=8.0 Hz, 1H), 5.32 (s, 1H), 5.04 (s, 1H), 3.97 (t, J=6.7 Hz, 2H), 2.70 (t, J=6.7 Hz, 2H), 1.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 144.7, 140.1, 133.7, 131.1, 128.3, 127.5, 125.9–125.1 (m), 117.6, 62.7, 37.4, 20.8. *m/z* (EIMS): 240 (11, M^+), 180 (46), 179 (52), 167 (19), 165 (100), 153 (20), 152 (37). HRMS calcd for $C_{16}H_{16}O_2$: 240.1150, found: 240.1127.

3.3.34. 1-(1-Phenylethenyl)-naphthalene (5f). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and α-bromostyrene **4f** (183 mg, 1.00 mmol) was added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 6 h at 25 °C. The standard workup and purification by flash chromatography yielded **5f** as a white solid (179 mg, 78%). The analytical data are in accordance with those reported in the literature.[13]

3.3.35. 4,4′-Bis-(*N*-pyrrolidino)-2,2′-bipyridyl. 4,4′-Dichloro-2,2′-bipyridyl-*N*,*N*′-dioxide[17] (386 mg, 1.50 mmol) was dissolved in the mixture of pyrrolidine (4 mL) and H_2O (2 mL). The solution was heated in a sealed tube at 140 °C for 20 h. The mixture was cooled down and the volatiles were removed in vacuo. The solid residue was dissolved in $CHCl_3$ (40 mL) and PCl_3 (4 mL, 46 mmol) was added. The mixture was refluxed under Ar for 3.5 h and poured on ice (150 g). The organic phase was extracted with H_2O (50 mL) and the combined water phases were evaporated in vacuo. To the residue, 30% KOH was added. The precipitate was filtered off and redissolved in CH_2Cl_2. After the addition of Et_2O, the precipitate was filtered and dried in vacuo. Yield 160 mg (35%). Mp 255–256 °C (decomp.) IR (KBr): 2966 (w), 2851 (w), 1586 (vs), 1538 (m), 1478 (s), 1378 (m), 1262 (w), 992 (s), 802 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (d, J=5.8 Hz, 2H), 7.52 (d, J=2.5 Hz, 2H), 6.36 (dd, J_1=5.8 Hz, J_2=2.5 Hz, 2H), 3.40 (t, J=6.6 Hz, 8H), 2.00 (m, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.8, 152.6, 148.9, 106.6, 103.9, 47.1, 25.3. *m/z* (EIMS): 294 (48, M^+), 265 (100), 239 (13), 225 (29), 146 (12). HRMS calcd for $C_{18}H_{22}N_4$: 294.1844, found: 294.1828.

References and notes

1. (a) *Metal-Catalyzed Cross-coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; (b) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, UK, 1995; (c) *Top. Curr. Chem.* **2002**, 219; (d) *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998.
2. (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298; (b) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223; (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340; (d) Tamaru, J.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955; (e) Qian, M.; Negishi, E. *Tetrahedron Lett.* **2005**, *46*, 2927; (f) Zeng, X.; Zeng, F.; Negishi, E. *Org. Lett.* **2004**, *6*, 3245; (g) Zeng, X.; Qian, M.; Hu, Q.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259; (h) Qian, M.; Huang, Z.; Negishi, E. *Org. Lett.* **2004**, *6*, 1531; Shizaki, M.; Osada, S.; Kato, S. *Jpn. Kokai Tokkyo Koho* CAN 112:55007, **1989**, 7 pp; Some important recent contributions in cross-coupling of organozinc compound: (i) Hadei, F.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *J. Org. Chem.* **2005**, *70*, 8503; (j) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028; (k) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482.
3. (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333; (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.
4. (a) Rieke, R. D. *Science* **1989**, *246*, 1260; (b) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674; (c) Lee, J.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428.
5. Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2005**, *7*, 4871.
6. Some examples of the cross-coupling of organozinc compounds in the presence of Ni have been reported: (a) Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819; (b) Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259; (c) Quesnelle, C. A.; Familoni, O. B.; Snieckus, V. *Synlett* **1994**, 349; (d) Tucker, C. E.; de Vries, J. G. *Top. Catal.* **2002**, *19*, 111; (e) Ackermann, L.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2444.
7. An unique influence of *N*-methylpyrrolidinone on the reactivity of organozinc compounds has been described, see, for example: Kneisel, F. F.; Knochel, P. *Synlett* **2002**, 1799 and Refs. therein.
8. 4,4′-Bis-(*N*-pyrrolidino)-2,2′-bipyridyl was prepared from 4,4′-dichloro-2,2′-bipyridyl-*N*,*N*′-dioxide, see Section 3.
9. This compound is a naturally occurring alkaloid (β-nicotyrine), see, for example: Wei, X.; Crooks, P. *Synth. Commun.* **2003**, *33*, 3305 and Refs. therein.
10. Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952.
11. McDonald, E.; Smith, P. *J. Chem. Soc., Perkin Trans. 1* **1980**, 837.
12. Vasconello, M. L.; D'Angelo, L.; Desmaele, D.; Costa, P. R. R.; Potin, D. *Tetrahedron: Asymmetry* **1991**, *2*, 353.
13. Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892.
14. Brittain, J. M.; Jones, R. A.; Arques, J. S.; Saliente, T. A. *Synth. Commun.* **1982**, *12*, 231.
15. Brown, H. C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N. *J. Org. Chem.* **1989**, *54*, 6075.
16. Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941.
17. Wenkert, D.; Woodward, R. B. *J. Org. Chem.* **1983**, *48*, 283.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 62 (2006) 7534–7539
Tetrahedron

Formal hydrochromination of alkynes under nickel catalysis. Regioselective reductive coupling of alkynes and aldehydes leading to allylic alcohols

Kazuhiko Takai,* Shuji Sakamoto, Takahiko Isshiki and Tatsuya Kokumai

Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, Tsushima, Okayama 700-8530, Japan

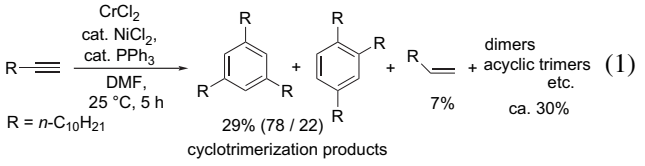
Received 7 November 2005; revised 11 April 2006; accepted 11 April 2006
Available online 15 June 2006

Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry

Abstract—Formal hydrochromation of an alkyne leading to a 1-substituted ethenylchromium reagent is accomplished by addition of the alkyne and water to a mixture of low-valent chromium(II), a catalytic amount of nickel(II), and triphenylphosphine in DMF.

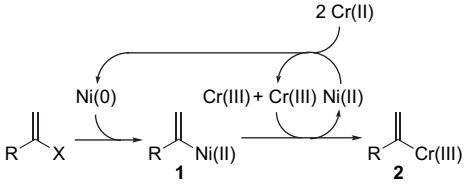
1. Introduction

Treatment of alkynes with a catalytic amount of a low-valent nickel species such as $NiBr_2$-magnesium or -zinc causes cyclotrimerization of the alkynes via nickelacylopropenes and nickelacyclopentadienes to give substituted benzenes.[1] However, when chromium(II) chloride is used as the reductant of a nickel(II) salt, the yield of the cyclotrimerization product decreases.[2] For example, treatment of 1-dodecyne with a mixture of $CrCl_2$, a catalytic amount of $NiCl_2$ and PPh_3 in DMF at 25 °C for 5 h gives the cyclotrimerization product in 29% yield (1,3,5-substituted benzene/1,2,4-substituted benzene = 78/22) and dodecenes in 7% yield (1-dodecene/2-dodecene = 86/14) along with a mixture of olefinic oligomers (dimers, trimers, tetramers, etc.) in ca. 30% combined yields (Eq. 1).



(1)

In separate studies carried out in 1986, we and Kishi reported independently the addition of alkenylchromium reagents to aldehydes to give allylic alcohols under nickel catalysis.[3] At that time, we assumed that the alkenylchromium(III) reagent **2** was generated by transmetallation from the alkenylnickel species **1** (Scheme 1).[3] Later, Hodgson showed that intramolecular insertion of a carbon–carbon triple bond into the generated arylnickel species with $CrCl_2$ and a catalytic amount of $NiCl_2$ occurred before the transmetallation to the alkenylchromium species.[4]



Scheme 1.

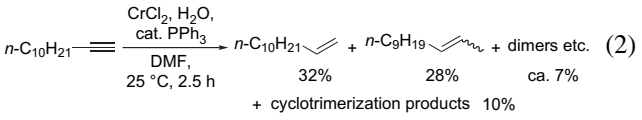
Because the chromium-mediated Barbier-type additions of alkenyl halides to aldehydes proceeded smoothly in the presence of a catalytic amount of a nickel salt, it was suggested that the transmetallation step from nickel to chromium proceeded smoothly under the reaction conditions. If this was the case, the amount of cyclotrimerization products of alkynes would decrease when a catalytic amount of low-valent nickel was generated in the presence of excess amounts of chromium salts because transmetallation from nickel to chromium occurs before formation of nickelacyclopentadienes. A decrease in the amount of cyclotrimerization products and the formation of the olefinic oligomers described in Eq. 1 suggested that the transmetallation from the alkenylnickel species to the corresponding chromium species proceeded in the reaction mixture to some extent.[5]

We then focused on the formation of dodecenes, which may have been derived by hydrolysis of the alkenylchromium species upon addition of water.[6] In order to examine this hypothesis, 8 equiv of water was added to a mixture of

* Corresponding author. E-mail: ktakai@cc.okayama-u.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.04.105

$CrCl_2$, cat. $NiCl_2$, and cat. PPh_3 in DMF before addition of 1-dodecyne. Dodecenes were produced in 60% combined yields (1-dodecene/2-dodecene = 53/47) by stirring the mixture for 2.5 h (Eq. 2). When the reaction was quenched at 30 min, most of 1-dodecyne remained but the ratio of the formed dodecenes was 1-dodecene/2-dodecene = 90/10. Thus, the 2-dodecene was produced by isomerization of 1-dodecene in the reaction mixture.

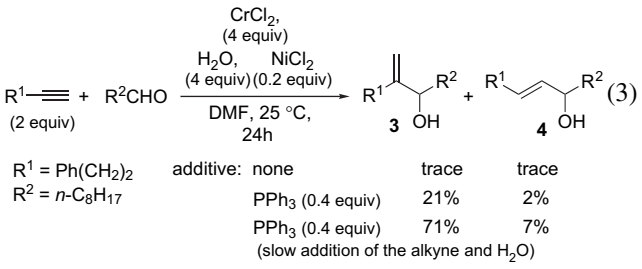


(2)

Nucleophilic carbon–carbon bond formation with organometallic compounds, except organoboron and -indium reagents, is usually conducted under water-free conditions. This is because organometallic compounds hydrolyze with a lot of water. However, the rate of hydrolysis of organochromium compounds is not very fast among the early transition metal compounds.[7] Therefore, the addition of an organochromium reagent can be accomplished without protecting the hydroxyl group of the substrate aldehyde in some cases,[8] and even a nucleophilic organochromium species can be generated by addition of a small aliquot of water.[9] As in Eq. 2, reduction of 1-dodecyne to 1-dodecene proceeded with $CrCl_2$ and water in the presence of a catalytic amount of $NiCl_2$ and PPh_3. If the two hydrogen atoms were introduced to 1-dodecyne with a different timing, i.e., one hydrogen atom was introduced later due to the hydrolysis of a carbon–chromium bond, new carbon–carbon bond formation could be established when the reaction was conducted in the presence of an aldehyde. In order to clarify this hypothesis, we examined the addition of a small amount of water to a mixture of an alkyne, $CrCl_2$, and catalytic amounts of $NiCl_2$ and PPh_3 in the presence of an aldehyde.

2. Results and discussion

To a stirred solution of chromium(II) chloride (4 equiv) and catalytic amounts of nickel(II) chloride (0.2 equiv) and PPh_3 (0.4 equiv) in DMF were added a solution of 4-phenyl-1-butyne (2 equiv) and nonanal (1 equiv) at 25 °C. A 1 M solution of water (2 equiv) in DMF was added slowly to the mixture at 25 °C over 2 h, and the mixture was stirred at the same temperature for an additional 4 h. After usual workup with water, the two desired allylic alcohols, 2-(2-phenylethyl)-1-undecen-3-ol (**3**) and (*E*)-1-phenyl-3-tridecen-5-ol (**4**) were obtained in a 23% combined yields (**3**/**4**=91/9, Eq. 3).[10]

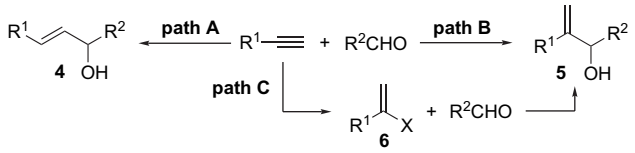


(3)

When the reaction was conducted without addition of PPh_3, a deposition of nickel(0) was observed, and most of the alkyne and the aldehyde were recovered; the two allylic alcohols **3** and **4** were detected after hydrolysis, although the combined yields were less than 3%. Addition of the phosphine ligand to the mixture was indispensable to prevent this deposition. Among those examined, triphenylphosphine was found to accelerate the reaction markedly. Effects of additives on the yields and regioselectivities of the reactions between 4-phenyl-1-butyne and nonanal were as follows: PBu_3, 14% (**3**/**4**=0/100); P(*o*-tolyl)$_3$, 16% (64/36); P(2-franyl)$_3$, 18% (78/22); P[3,5-$(CF_3)_2C_6H_3$]$_3$, 30% (90/10); P[2,6-$(MeO)_2C_6H_3$]$_3$, <5%.

The yield was also improved by slow addition of a mixture of the alkyne and water to a mixture of the aldehyde, chromium(II) chloride, nickel(II) chloride, and triphenylphosphine in DMF. For example, when a mixture of 4-phenyl-1-butyne (2 equiv) and water (2 equiv) in DMF was added at 25 °C over a period of 2 h to a mixture of nonanal (1 equiv), chromium(II) chloride (4 equiv), nickel(II) chloride (0.2 equiv), and triphenylphosphine (0.4 equiv) in DMF, a mixture of the two allylic alcohols was obtained in 78% yield (**3**/**4**= 91/9, Eq. 3). The 2-alkyl-substituted allylic alcohol **3** was produced selectively. Although the addition of water to the mixture was indispensable for the reaction, the yields of allylic alcohols decreased when an excess amount (16 equiv) of water was added.

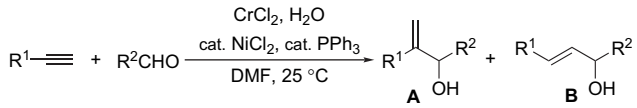
Addition of a metal-hydride species to a terminal alkyne generates two regioisomeric alkenylmetal compounds, which afford the corresponding allylic alcohols upon treatment with an aldehyde. Because hydroboration, -alumination, and -zirconation of a terminal alkyne generate the corresponding (*E*)-alkenylmetal compound, the 3-alkyl-substituted allylic alcohol **4** is produced selectively via these hydrometallation methods (Scheme 2, path A).[11,12] Recent reports on intermolecular coupling reactions promoted with Et_3B and a catalytic amount of nickel also produce the alcohol **4** regioselectively.[13] In contrast, it is not easy to prepare the 2-alkyl-substituted allylic alcohol **5** directly from a terminal alkyne and an aldehyde (path B). A two-step procedure via the 2-halo-1-alkene **6**[14] has been usually employed for this purpose (path C).[15] Therefore, the method using chromium(II) and water under nickel catalysis we report here is a direct approach for the preparation of the 2-substituted allylic alcohol **5** from a terminal alkyne and an aldehyde.

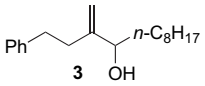
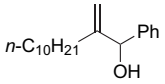
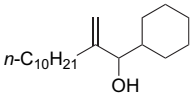
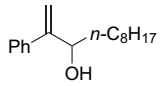
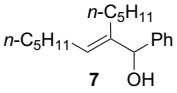
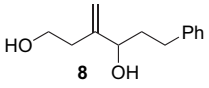
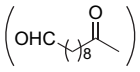
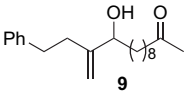
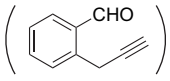
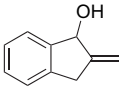


Scheme 2.

The results obtained with several kinds of alkynes and aldehydes are summarized in Table 1. Cyclotrimerization of the alkynes was also observed as a side reaction, thus, 2–3 equiv of the alkyne was employed to obtain good yields. Some additional interesting features are as follows: 2-substituted allylic alcohols were obtained in a selective manner except in the case of phenyl acetylene (entry 5). An internal alkyne, 6-dodecyne, also reacted with an aldehyde to give the corresponding allylic alcohol **7** in 60% yield although the reaction

Table 1. Coupling reactions between terminal alkynes and aldehydes[a]

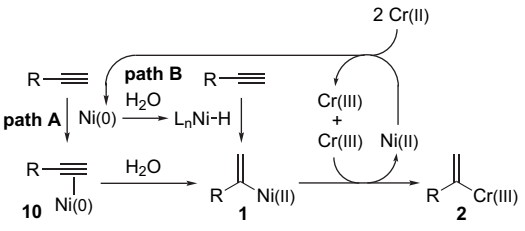


Entry	R^1	R^2	Time (h)	Major product	Yield (%)	**A/B**
1	$Ph(CH_2)_2$	n-C_8H_{17}	8	 **3**	82	95/5
2	$Ph(CH_2)_2$	n-C_8H_{17}	8	**3**	99[b]	95/5
3	n-$C_{10}H_{21}$	Ph	8		80[b]	94/6
4	n-$C_{10}H_{21}$	c-C_6H_{11}	8		79	90/10
5	Ph	n-C_8H_{17}	8		74	55/45
6	(6-Dodecyne)	Ph	24	 **7**	60[b]	
7	$HO(CH_2)_2$	$Ph(CH_2)_2$	8	 **8**	83[c]	>99/<1
8	$Ph(CH_2)_2$		8	 **9**	81	95/5
9			3		64	>99/<1

[a] Reaction was conducted on a 1.0 mmol scale. See typical procedure.
[b] Three mol of an alkyne, 6 mol of $CrCl_2$, 0.3 mol of $NiCl_2$, 0.6 mol of PPh_3, and 6 mol of water were used for per mole of an aldehyde. $E/Z = 98/2$.
[c] Three mol of water was used for per mole of an aldehyde.

proceeded slowly (entry 6). The alcohol **7** was produced almost exclusively, and the stereochemistry of the double bond of **7** proved to be the *E* configuration.[16] Since the coupling reaction is insensitive to a proton source, carbon–carbon bond formation could be accomplished without protecting the hydroxyl group (entry 7). In this case, one regioisomer **8** was produced exclusively, probably due to the coordination of the hydroxyl group to the nickel. A typical feature of the nucleophilic additions of organochromium reagents is their selective addition to aldehydes prior to ketone carbonyl groups.[7c,17] This was also observed in the reaction with a keto aldehyde (entry 8). An intramolecular reaction of 2-propargylbenzaldehyde proceeded under the similar reaction conditions to give 2-methyleneinden-1-ol in 64% yield selectively (entry 9).

There are two possibilities for the formation of the alkenylnickel species **1** from terminal alkynes (Scheme 3). In path A, a terminal alkyne coordinates to nickel(0) generated by the reduction of nickel(II) with 2 equiv of chromium(II), and a nickel–alkyne complex **10** is produced. A reaction of the complex **10** with water gives the alkenylnickel species **1**,[18] which transmetallates to yield the alkenylchromium reagent **2**. In path B, nickel(0) reacts immediately with water to give a nickel-hydride species. Addition of the nickel-hydride species to the terminal alkyne gives the alkenylnickel species **1**.[19]



Scheme 3.

Water is a typical proton source, but in this case it acts formally as a hydride anion source by reaction with low-valent metals.[20]

3. Experimental

3.1. General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Dry, oxygen-free dimethylformamide (DMF) was purchased from Kanto Chemicals, Co. Column chromatography was performed with silica gel (200 mesh). Distillation of small amounts of products was performed with a Büchi Kugelrohr, and boiling points are indicated by an air bath temperature without correction. Preparative HPLC was performed on a Japan Analytical Industry LC-908 with JAI gel using toluene as an eluent. FTIR spectra were obtained on a Nicolet Protégé 460 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA400 instrument. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane using the δ scale. Low and high resolution of EI mass spectra were obtained with a capillary GC interfaced JEOL JMS-GCmate and JMS-700 MStation spectrometers, respectively. Elemental analyses were performed by the staff at the Elemental Analyses Center of Kyoto University.

3.2. Reaction of 1-dodecyne with $CrCl_2$ and water in the presence of a catalytic amount of $NiCl_2$ and PPh_3 (Eq. 2)

A mixture of $CrCl_2$ (0.37 g, 3.0 mmol) and a catalytic amount of $NiCl_2$ (19 mg, 0.15 mmol) and triphenylphosphine (0.77 g, 0.30 mmol) in DMF (4 mL) was stirred at 25 °C for 30 min. To the mixture was added a solution of water (0.22 g, 12 mmol) in DMF (2 mL) and the mixture was stirred for 15 min. To the greenish-yellow suspension was added a solution of 1-dodecyne (0.25 g, 1.5 mmol) in DMF (2 mL) over a period of 2 h, and the resulting mixture was stirred for an additional 30 min. The reaction mixture was poured into water (30 mL). The mixture was extracted with hexane (3×20 mL), and organic extracts were dried over anhydrous magnesium sulfate and concentrated. Purification by column chromatography on silica gel and preparative HPLC afforded dodecenes in 60% combined yields (0.15 g, 1-dodecene/2-dodecene = 53/47), trisubstituted benzenes in 10% combined yields (0.023 g, 1,3,5-substituted benzene/1,2,4-substituted benzene = 85/15), and a mixture of olefinic products containing 2,3-didecyl-1,3-butadiene and 2-decyl-1,3-tetradecadiene in ca. 7% yields.

3.3. Reductive coupling of alkynes and aldehydes. A general procedure (Table 1)

To a mixture of $CrCl_2$ (0.61 g, 5.0 mmol) and catalytic amounts of $NiCl_2$ (32 mg, 0.25 mmol) and triphenylphosphine (0.13 g, 0.50 mmol) in DMF (6 mL) was added a solution of an aldehyde (1.0 mmol) in DMF (4 mL) at 25 °C and the mixture was stirred for 10 min. A solution of a terminal alkyne (2.5 mmol) and water (72 μL) in DMF (10 mL) was added at 25 °C to the mixture over a period of 4 h. After stirring at 25 °C for an additional 4 h, the reaction mixture was poured into brine (30 mL). The mixture was extracted with ether (3×20 mL), and organic extracts were dried over anhydrous magnesium sulfate and concentrated. Purification by column chromatography on silica gel gave the desired coupling product.

3.3.1. 2-(2-Phenylethyl)-1-undecen-3-ol (3). Bp 145 °C (bath temp, 0.46 Torr); IR (neat): 3355, 3085, 3027, 2927, 2855, 1646, 1604, 1496, 1455, 1076, 1031, 901, 746, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J=6.9 Hz, 3H), 1.22–1.33 (m, 12H), 1.38–1.43 (m, 1H), 1.49–1.61 (m, 2H), 2.29 (dt, J=15.3, 8.0 Hz, 1H), 2.42 (dt, J=15.6, 8.0 Hz, 1H), 2.81 (t, J=8.1 Hz, 2H), 4.07 (s, 1H), 4.91 (d, J=1.2 Hz, 1H), 5.06 (s, 1H), 7.15–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 25.7, 29.3, 29.5, 29.6, 31.9, 32.9, 34.5, 35.5, 75.7, 109.9, 125.9, 128.3, 128.3, 142.0, 151.5. Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.31; H, 11.27.

3.3.2. (*E*)-1-Phenyl-3-tridecen-5-ol (4).[21] IR (neat): 3337, 3108, 3086, 3027, 2954, 2855, 1604, 1496, 1454, 1377, 1304, 1131, 1030, 969, 746, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J=6.9 Hz, 3H), 1.23–1.31 (m, 12H), 1.34–1.37 (m, 1H), 1.41–1.53 (m, 2H), 2.36 (dt, J=7.8, 7.1 Hz, 2H), 2.70 (t, J=7.6 Hz, 2H), 4.00–4.05 (m, 1H), 5.47 (ddt, J=15.3, 7.1, 1.2 Hz, 1H), 5.67 (dt, J=15.3, 7.1 Hz, 1H), 7.17–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 25.4, 29.3, 29.5, 29.5, 31.9, 33.9, 35.6, 37.3, 73.1, 125.8, 128.3, 128.4, 130.9, 133.8, 141.7.

3.3.3. 2-Decyl-1-phenyl-2-propen-1-ol.[3a] IR (neat): 3364, 3085, 3063, 3029, 2925, 2853, 1648, 1603, 1493, 1454, 1377, 1190, 1025, 902, 842, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J=6.9 Hz, 3H), 1.19–1.31 (m, 14H), 1.34–1.43 (m, 2H), 1.79–1.88 (m, 2H), 1.95 (dt, J=15.6, 7.9 Hz, 1H), 4.98 (s, 1H), 5.16 (d, J=3.3 Hz, 1H), 5.26 (s, 1H), 7.28–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 27.8, 29.3, 29.4, 29.5, 29.55, 29.58, 31.8, 31.9, 77.3, 109.6, 126.7, 127.7, 128.4, 142.2, 151.2.

3.3.4. (*E*)-1-Phenyl-2-tridecen-1-ol.[22] IR (neat): 3347, 3103, 3082, 3060, 2926, 2855, 1599, 1494, 1465, 965, 748, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.86 (t, J=6.8 Hz, 3H), 1.21–1.28 (m, 14H), 1.34–1.41 (m, 2H), 1.90 (s, 1H), 2.03 (dt, J=7.2, 7.0 Hz, 2H), 5.14 (d, J=6.6 Hz, 1H), 5.63 (dd, J=15.3, 6.6 Hz, 1H), 5.74 (dt, J=15.3, 6.6 Hz, 1H), 7.23–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 29.1, 29.2, 29.3, 29.4, 29.6, 29.6, 31.9, 32.2, 75.2, 126.1, 127.4, 128.4, 132.2, 132.9, 143.4.

3.3.5. 1-Cyclohexyl-2-decyl-2-propen-1-ol. Bp 120 °C (bath temp, 0.45 Torr); IR (neat): 3398, 2924, 2852, 1645, 1465, 1450, 1378, 1306, 1261, 1082, 1021, 897, 803, 735, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J=6.8 Hz, 3H), 0.92–1.05 (m, 1H), 1.11–1.29 (m, 18H), 1.41–1.50 (m, 5H), 1.63–1.67 (m, 1H), 1.71–1.79 (m, 2H), 1.88–1.96 (m, 2H), 2.06 (dt, J=15.9, 7.9 Hz, 1H), 3.77 (d, J=6.9 Hz, 1H), 4.88 (d, J=3.0 Hz, 1H), 4.95 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 26.1, 26.3, 26.5, 28.0, 28.1, 29.4, 29.59, 29.63, 29.63, 29.7, 29.9, 31.2, 31.9, 41.0, 80.7, 110.3, 151.0. Anal. Calcd for $C_{19}H_{36}O$: C, 81.36; H, 12.94. Found: C, 81.43; H, 13.08.

3.3.6. (*E*)-1-Cyclohexyl-2-tridecen-1-ol. IR (neat): 3371, 2925, 2853, 1669, 1464, 1450, 1378, 1306, 1261, 1084, 1004, 969, 892, 721, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J=6.7 Hz, 3H), 0.91–1.01 (m, 1H), 1.14–1.43 (m, 21H), 1.64–1.77 (m, 4H), 1.86 (d, J=12.6 Hz, 1H), 2.03 (dt, J=7.2, 7.1 Hz, 2H), 2.17 (s, 1H), 3.76 (t, J=6.9 Hz, 1H), 5.44 (dd, J=15.3, 7.5 Hz, 1H), 5.60 (dt, J=15.3, 7.1 Hz,

1H); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 26.07, 26.15, 26.6, 28.7, 28.8, 29.16, 29.23, 29.3, 29.5, 29.60, 29.61, 31.9, 32.3, 43.7, 77.7, 131.4, 133.1. Anal. Calcd for $C_{19}H_{36}O$: C, 81.36; H, 12.94. Found: C, 81.20; H, 13.12.

3.3.7. 2-Phenyl-1-undecen-3-ol.[23] IR (neat): 3415, 3080, 3056, 2924, 2854, 1630, 1574, 1494, 1465, 1378, 1131, 1064, 1027, 908, 777, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J=6.9 Hz, 3H), 1.19–1.28 (m, 11H), 1.42–1.63 (m, 3H), 1.75 (s, 1H), 4.60–4.64 (m, 1H), 5.30 (s, 1H), 5.35 (s, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.6, 25.6, 29.2, 29.4, 29.5, 31.8, 36.0, 73.9, 112.5, 126.9, 127.5, 128.3, 140.1, 152.2.

3.3.8. (*E*)-1-Phenyl-1-undecen-3-ol.[24] IR (neat): 3347, 3103, 3082, 3026, 2926, 2855, 1599, 1494, 1465, 965, 748, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J=6.6 Hz, 3H), 1.23–1.45 (m, 12H), 1.55–1.71 (m, 3H), 4.27 (dd, J=6.6, 6.3 Hz, 1H), 6.21 (dd, J=15.9, 6.6 Hz, 1H), 6.56 (d, J=15.9 Hz, 1H), 7.21–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.6, 25.4, 29.2, 29.5, 29.6, 31.8, 37.4, 73.1, 126.4, 127.6, 128.5, 130.1, 132.6, 136.8.

3.3.9. (*E*)-2-Pentyl-1-phenyl-2-octen-1-ol (7).[16] IR (neat): 3357, 3089, 3062, 2955, 2927, 2857, 1493, 1455, 1378, 1084, 1008, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.83 (t, J=6.9 Hz, 3H), 0.90 (t, J=6.9 Hz, 3H), 1.14–1.15 (m, 12H), 1.77 (d, J=3.3 Hz, 1H), 1.77–1.86 (m, 1H), 1.93–2.03 (m, 1H), 2.07 (dt, J=7.3, 7.2 Hz, 2H), 5.16 (d, J=2.7 Hz, 1H), 5.61 (t, J=7.2 Hz, 1H), 7.24–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.0, 14.1, 22.4, 22.6, 27.6, 27.7, 29.2, 29.5, 31.7, 32.1, 78.2, 126.5, 127.3, 127.3, 128.2, 141.2, 142.8.

3.3.10. 3-Methylene-6-phenyl-hexane-1,4-diol (8). IR (neat): 3353, 3085, 3026, 2927, 2862, 1645, 1603, 1496, 1454, 1320, 1045, 908, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.84–1.98 (m, 2H), 2.29–2.33 (m, 2H), 2.43 (ddd, J=14.0, 8.1, 6.0 Hz, 1H), 2.64 (ddd, J=13.8, 9.1, 6.8 Hz, 1H), 2.74 (ddd, J=13.9, 9.4, 6.4 Hz, 2H), 3.72 (ddd, J=10.4, 8.0, 4.7 Hz, 1H), 3.82 (dt, J=10.5, 5.4 Hz, 1H), 4.13 (t, J=5.4 Hz, 1H), 4.98 (d, J=1.2 Hz, 1H), 5.12 (s, 1H), 7.17–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 32.0, 34.8, 37.1, 62.4, 74.9, 113.7, 125.9, 128.41, 128.43, 141.8, 148.8. Elemental analysis was conducted with a trimethylsilyl ether of **8** [bp 60 °C (bath temp, 1.3 Torr)]. Anal. Calcd for $C_{19}H_{34}O_2Si_2$: C, 65.08; H, 9.77. Found: C, 65.04; H, 9.85.

3.3.11. 11-Hydroxy-12-(2-phenylethyl)-12-tridecen-2-one (9). IR (neat): 3428, 3063, 3027, 2929, 2855, 1713, 1646, 1604, 1496, 1454, 1360, 1167, 900, 748, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.24–1.28 (m, 12H), 1.51–1.58 (m, 3H), 2.13 (s, 3H), 2.29 (dt, J=15.3, 7.9 Hz, 1H), 2.41 (t, J=7.3 Hz, 2H), 2.42 (dt, J=15.3, 8.0 Hz, 1H), 2.80 (t, J=8.2 Hz, 2H), 4.05–4.09 (m, 1H), 4.92 (d, J=1.2 Hz, 1H), 5.07 (s, 1H), 7.17–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 23.8, 25.7, 29.1, 29.3, 29.4, 29.5, 29.8, 32.9, 34.5, 35.5, 43.8, 75.6, 109.9, 125.9, 128.3, 128.3, 142.0, 151.5, 209.3. Elemental analysis was conducted with a trimethylsilyl ether of **9** [bp 155 °C (bath temp, 0.34 Torr)]. Anal. Calcd for $C_{24}H_{40}O_2Si$: C, 74.17; H, 10.37. Found: C, 74.06; H, 10.56.

3.3.12. (*E*)-11-Hydroxy-15-phenyl-12-pentadecen-2-one. IR (neat): 3409, 3026, 2928, 2854, 1715, 1496, 1454, 1361, 969, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.20–1.31 (m, 12H), 1.43–1.58 (m, 3H), 2.13 (s, 3H), 2.36 (dt, J=7.7, 7.8 Hz, 2H), 2.41 (t, J=7.5 Hz, 2H), 2.70 (dd, J=8.1, 7.2 Hz, 2H), 4.01 (dt, J=6.6, 6.6 Hz, 1H), 5.46 (dd, J=15.3, 6.9 Hz, 1H), 5.66 (dt, J=15.3, 6.6 Hz, 1H), 7.16–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 23.8, 25.3, 29.1, 29.30, 29.35, 29.4, 29.8, 33.9, 35.6, 37.2, 43.8, 73.0, 125.8, 128.3, 128.4, 130.9, 133.9, 141.7, 209.3. Elemental analysis was conducted with a trimethylsilyl ether of (*E*)-11-hydroxy-15-phenyl-12-pentadecen-2-one [bp 150 °C (bath temp, 0.3 Torr)]. Anal. Calcd for $C_{24}H_{40}O_2Si$: C, 74.17; H, 10.37. Found: C, 74.29; H, 10.42.

3.3.13. 2-Methyleneindan-2-ol. IR (nujol): 3306, 3072, 1662, 1610, 1586, 1317, 1250, 1204, 1174, 1037, 895, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.81 (d, J=9.0 Hz, 1H), 3.62 (d, J=20.0 Hz, 1H), 3.70 (d, J=20.1 Hz, 1H), 5.29 (dd, J=4.1, 1.9 Hz, 1H), 5.49 (d, J=9.0 Hz, 1H), 5.50 (dd, J=4.1, 2.1 Hz, 1H), 7.24–7.51 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 36.5, 76.5, 110.4, 124.7, 124.9, 127.1, 128.6, 140.8, 144.0, 152.8; EI MS m/z (%): 146 (M^+, 100), 145 (61), 131 (66), 118 (28), 115 (47), 91 (25). HRMS (EI) m/z calcd for (M^+) $C_{10}H_{10}O$ 146.0732, found 146.0732.

Acknowledgements

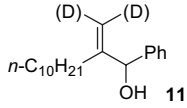
This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and by the Nagase Science and Technology Foundation.

References and notes

1. (a) Saito, S. *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH: Weinheim, 2005; pp 171–204; (b) Reppe, W.; Schweckendiek, W. J. *Justus Liebigs Ann. Chem.* **1948**, *560*, 104–116; (c) Alphonse, P.; Moyen, F.; Mazerolles, P. *J. Organomet. Chem.* **1988**, *345*, 209–216.
2. Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268–5270.
3. (a) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050; (b) Jin, H.; Uenishi, J.-i.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646.
4. Hodgson, D. M.; Wells, C. *Tetrahedron Lett.* **1994**, *35*, 1601–1604.
5. For transmetallation from zirconium to chromium, see: Takahashi, T.; Liu, Y.; Chaki, S.; Nakajima, K.; Kanno, K.-i. *J. Am. Chem. Soc.* **2005**, *127*, 11928–11929.
6. There is a possibility of hydrolysis with a trace amount of water in the reaction mixture.
7. (a) Hanson, J. R.; Premuzic, E. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 247–252; (b) Espenson, J. H. *Acc. Chem. Res.* **1992**, *25*, 222–227; (c) Wessjohann, L. A. *Synthesis* **1999**, 1–36.
8. Kauffmann, T.; Abeln, R.; Wingbermühle, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 729–730.
9. Takai, K.; Toratsu, C. *J. Org. Chem.* **1998**, *63*, 6450–6451; See also a review on water-accelerated organic transformations: Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299–307.
10. Takai, K.; Sakamoto, S.; Isshiki, T. *Org. Lett.* **2003**, *5*, 653–655.
11. For representative examples using hydrozirconation, see: (a) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K.

Tetrahedron Lett. **1992**, *33*, 5965–5968; (b) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197–5200.

12. The reactivity of the alkenylboron and -aluminum species towards carbonyl compounds is low even when they are converted to the corresponding ate complexes. Thus, the alkenylboron and -aluminum species are usually converted to the corresponding halides with electrophilic sources of halides (iodine or *N*-bromosuccinimide), and metallated. (a) Brown, H. C.; Bowman, D. H.; Misumi, S.; Unni, M. K. *J. Am. Chem. Soc.* **1967**, *89*, 4531–4532; (b) Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2753–2754.
13. (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc*. **1997**, *119*, 9065–9066; (b) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221–4223.
14. Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675–676; See also: Takai, K.; Sakogawa, K.; Kataoka, Y.; Oshima, K.; Utimoto, K. *Org. Synth.* **1995**, *72*, 180–188.
15. For representative examples, see: Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735–2737; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391–10392; Taylor, R. E.; Chen, Y. *Org. Lett.* **2001**, *3*, 2221–2224.
16. Takai, K.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 1707–1708; Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333–4339.
17. For reviews on organochromium reagents, see: (a) Takai, K.; Utimoto, K. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 66–77; (b) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1046; (c) Takai, K. *Org. React.* **2004**, *64*, 253–612. see also Ref. 7c.
18. Bennett, M. A.; Castro, J.; Edwards, A. J.; Kopp, M. R.; Wenger, E.; Willis, A. C. *Organometallics* **2001**, *20*, 980–989.
19. In order to obtain more information for the reaction, we used a deuterated terminal allylic alcohol **11** for the coupling reaction. Deuterium was incorporated in both cis and trans positions in a 1:1 ratio.



11

20. (a) Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 6777–6784; (b) Trost, B. M. *Chem.—Eur. J.* **1998**, 2405–2412.
21. Inomata, K.; Igarashi, S.; Mohri, M.; Yamamoto, T.; Kinoshita, H.; Kotake, H. *Chem. Lett.* **1987**, 707–710.
22. Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481–2483.
23. Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281–5284.
24. Vettel, S.; Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 7473–7481.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7540–7546
Tetrahedron

Two-carbon ring expansion of cyclobutanone skeletons by nickel-catalyzed intermolecular alkyne insertion

Masahiro Murakami,* Shinji Ashida and Takanori Matsuda

Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Katsura, Kyoto 615-8510, Japan

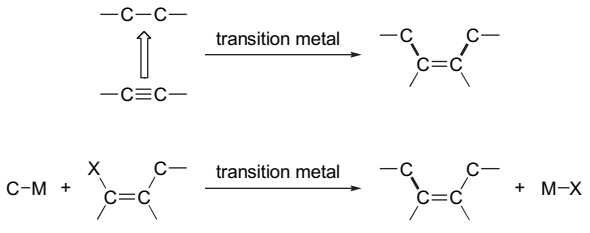
Received 30 November 2005; revised 8 March 2006; accepted 8 March 2006
Available online 12 June 2006

Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry as the pioneer

Abstract—The reaction of cyclobutanone with an alkyne in the presence of a nickel(0) catalyst formally achieves intermolecular alkyne insertion between the carbonyl carbon and the α-carbon of a cyclobutanone, providing a six-membered carbocyclic skeleton.

1. Introduction

A variety of transformations of organic compounds are currently available for synthetic chemists. The introduction of transition metals in organic synthesis has greatly expanded the repertoire of organic reactions to such an extent to include those, which are otherwise difficult to achieve.[1] We discovered that the carbon–carbon bond between the carbonyl carbon and the α-carbon of cyclobutanones was catalytically cleaved by rhodium in 1994.[2] Since then, we have pursued our studies to develop various kinds of carbon–carbon bond cleavage reactions.[3] Those investigations led us to think that it would be a potentially useful protocol of considerable novelty if a carbon–carbon single bond is cleaved by inserting an unsaturated organic functionality[4] like a carbon–carbon triple bond. Two carbon–carbon single bonds are newly formed in one chemical operation without wasting any unwanted material. Such an insertion reaction is highly atom-economical, making a sharp contrast to cross-coupling reactions, for example, which produce a stoichiometric amount of an unnecessary metal salt (Scheme 1).



Scheme 1.

As a result of our intensive studies along this line, we have achieved intramolecular olefin insertion into cyclobutanones,[5] which proceeds through insertion of rhodium(I) between the carbonyl carbon and the α-carbon of cyclobutanone, subsequent intramolecular migratory insertion of an olefin into the resulting Rh–C linkage, and reductive elimination. We attempted to realize analogous olefin insertion also in intermolecular reactions. However, the reactions examined have all failed so far. Then, another idea to achieve intermolecular insertion reactions occurred to us, which exploits a different elementary step for carbon–carbon bond cleavage, that is, β-carbon elimination.[6] A number of reactions are known in which the four-membered carbocycle of a cyclobutylmethyl- or (cyclobutyloxy)metal is opened through β-carbon elimination.[7] On the other hand, there have recently appeared several reports on the nickel-catalyzed carbon–carbon bond forming reactions of carbonyl compounds with other unsaturated bonds like carbon–carbon double and triple bonds.[8,9] In the initial step, nickel(0) acts as a template to promote oxidative cyclization of a carbonyl group with an unsaturated bond on it.[10] We envisaged that an intermolecular insertion of alkynes into cyclobutanones would be achieved by combining a process of oxidative cyclization with a process of β-carbon elimination. A five-membered oxanickelacyclopentene resulting from oxidative cyclization of a cyclobutanone and an alkyne contains a nickel cyclobutanolate skeleton as a spiro appendant. The five- and four-membered rings can be merged into a seven-membered ring nickelacycle through β-carbon elimination. The following reductive elimination completes a formal alkyne insertion. We herein describe the details of our studies on the nickel-catalyzed intermolecular alkyne insertion reaction into cyclobutanones, which expands the four-membered ring skeleton by two carbons to six-membered ring skeletons.[11,12]

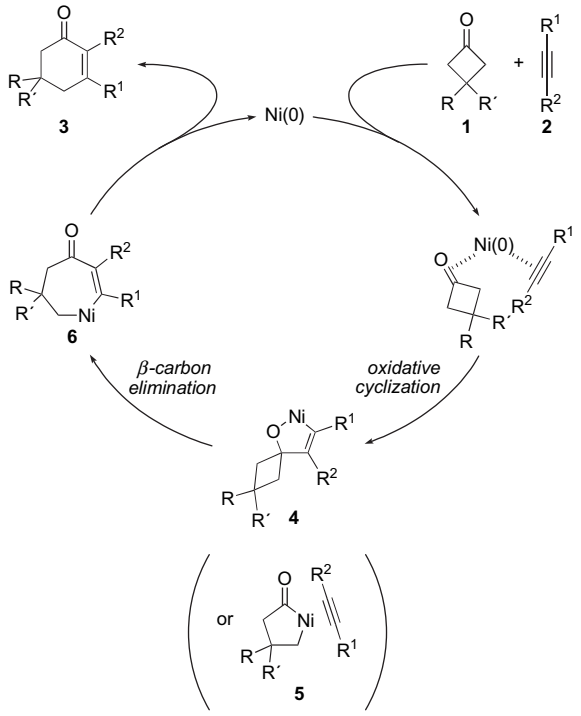
Keywords: Alkyne; β-Carbon elimination; Cyclobutanone; Nickel; Oxidative cyclization; Ring expansion.
* Corresponding author. Tel.: +81 75 383 2747; fax: +81 75 383 2748; e-mail: murakami@sbchem.kyoto-u.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.118

2. Results and discussion

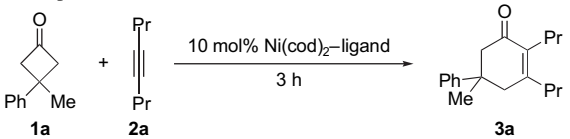
Various ligands of nickel(0) were examined for the formal insertion of an alkyne into cyclobutanone. A mixture of 3-methyl-3-phenylcyclobutanone (**1a**) and 4-octyne (**2a**, 1.5 equiv) was heated in the presence of a nickel catalyst prepared in situ from bis(1,5-cyclooctadiene)nickel(0) (10 mol %) and an additional ligand (Table 1). Whereas no reaction occurred without any additional ligand (entry 1), an intermolecular alkyne insertion reaction took place to produce six-membered ring ketone **3a** when a phosphine ligand was added to $Ni(cod)_2$. Especially, tricyclohexylphosphine showed excellent reactivity (entries 2–5). The best yield of **3a** was obtained when the reaction was carried out in toluene at 100 °C for 3 h using 2 equiv of P(*c*-Hex)$_3$ to nickel (entry 2). Similar ligands such as tricyclopentylphosphine and triisopropylphosphine worked equally well to give **3a** in 92% and 94% yields, respectively (entries 6 and 7). Use of tri-*n*-butylphosphine resulted in incomplete conversion and afforded an inseparable mixture of **3a** (82%) and **1a** (13%) (entry 8). Triphenylphosphine and tri-*tert*-butylphosphine gave only a trace amount of **3a** (entries 9 and 10).

We assumed the catalytic cycle shown in Scheme 2 for this insertion reaction on the basis of the mechanism proposed for the nickel-catalyzed reactions of aldehydes with alkynes.[7a,b,d] Oxanickelacyclopentene **4** having a four-membered ring spiro appendant is initially formed by oxidative cyclization of the carbonyl group of cyclobutanone **1** and alkyne **2** on nickel(0). The four-membered ring is then opened by β-carbon elimination, resulting in ring expansion to form seven-membered ring nickelacycle **6**. Finally, reductive elimination gives the product **3** with nickel(0) regenerated. Although oxidative cyclization of an alkyne with a ketonic carbonyl group on nickel(0) is more difficult to occur than the one with an aldehydic carbonyl group in general, the ketonic carbonyl group of **1** possesses a relatively high reactivity presumably due to its ring strain. Upon oxidative cyclization, the carbonyl sp^2 carbon, whose ideal angle is approximately 120°, changes to a sp^3 carbon, whose ideal angle is 108°, thereby diminishing the ring strain of the four-membered carbocycle. Another mechanistic pathway leading to intermediate **4** through insertion of nickel(0) between the carbonyl carbon and the α-carbon is also conceivable. In this case, seven-membered nickelacycle **6** is formed by migratory insertion of an alkyne into the Ni–C bond of intermediate **5**.



Scheme 2.

Table 1. Optimization of reaction conditions



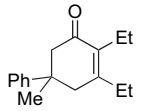
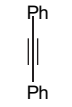
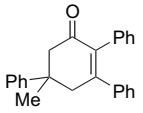
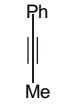
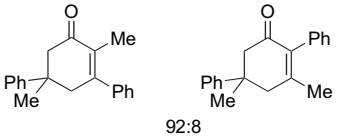
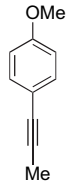
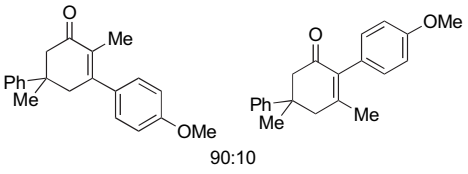
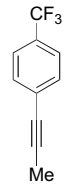
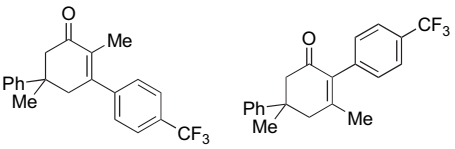
Entry	Ligand[a] (mol %)	Solvent	Temp/°C	%Yield[b]
1	None	Toluene	100	0
2	P(*c*-Hex)$_3$ (20)	Toluene	100	95
3	P(*c*-Hex)$_3$ (10)	Toluene	100	70[c]
4	P(*c*-Hex)$_3$ (20)	Toluene	80	50[c]
5	P(*c*-Hex)$_3$ (20)	1,4-Dioxane	100	39[c]
6	P(*c*-Pent)$_3$ (20)	Toluene	100	92
7	P(*i*-Pr)$_3$ (20)	Toluene	100	94
8	P(*n*-Bu)$_3$ (20)	Toluene	100	82[c]
9	PPh_3 (20)	Toluene	100	Trace
10	P(*t*-Bu)$_3$ (20)	Toluene	100	Trace

[a] P(*c*-Hex)$_3$: tricyclohexylphosphine; P(*c*-Pent)$_3$: tricyclopentylphosphine.
[b] Isolated yield.
[c] Obtained as an inseparable mixture of **1a** and **3a**. The yields of **3a** were calculated by ^{1}H NMR.

Next, various alkynes were subjected to the insertion reaction into **1a** under the optimized reaction conditions (Table 2). Symmetrical internal alkynes, such as 3-hexyne (**2b**) and diphenylacetylene (**2c**), reacted with cyclobutanone **1a** to give cyclohexenones **3b** and **3c**, respectively, in good yield (entries 1 and 2). With unsymmetrical 1-phenyl-1-propyne (**2d**), fairly regioselective alkyne insertion (92:8) was observed under the standard conditions. The methyl group was located α to the carbonyl group in the major product (entry 3). In order to see if any electronic effect impacts the regioselectivity, alkynes **2e** and **2f** having electron-donating and -withdrawing substituents at the *para*-positions of the phenyl group were subjected to the insertion reaction (entries 4 and 5). The regioisomeric ratios hardly changed depending on the electronic nature of the substituents. These results suggest that a steric factor rather than an electronic one dominates in determining the regioselectivity of this insertion reaction. In the case of aryl-substituted alkynes **2c–f**, which otherwise underwent rapid self-oligomerization on nickel(0), slow addition of 3.0 equiv of the alkyne to the reaction mixture was required to attain a high product yield.

Terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reaction due to rapid self-oligomerization of the alkynes (Fig. 1). Internal silylalkynes as

Table 2. Reaction of 3-methyl-3-phenylcyclobutanone (**1a**) and alkynes **2b–f**[a]

Entry	**2** (equiv)	Product **3** (%Yield[b])
1	 **2b** (1.5)	 **3b** (97)
2	 **2c** (3.0)	 **3c** (84)
3	 **2d** (3.0)	 **3d**[c] (78) 92:8
4	 **2e** (3.0)	 **3e**[c] (58) 90:10
5	 **2f** (3.0)	 **3f**[c] (65) 91:9

[a] Cyclobutanone **1**, alkyne **2** (1.5–3.0 equiv to **1**), $Ni(cod)_2$ (10 mol %), and P(*c*-Hex)$_3$ (20 mol %) were heated in toluene at 90–110 °C for 3–6 h.
[b] Isolated yield.
[c] Regioisomeric ratios were determined by ^{1}H NMR.

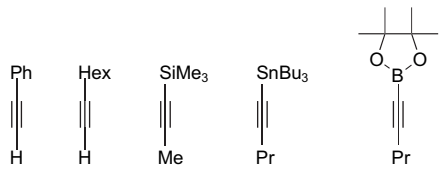


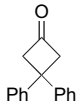
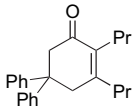
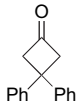
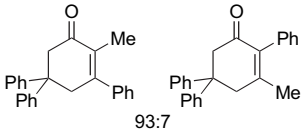
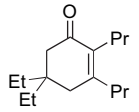
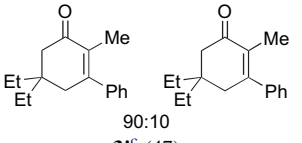
Figure 1.

a surrogate of terminal alkynes also failed to join, probably due to steric reasons. Other internal functionalized alkynes, including borylalkynes and stannylalkynes, were not suitable coupling partners either.

Cyclobutanone **1b** possessing two phenyl groups at the 3-position showed reactivity similar to that of **1a** and reacted with **2a** and **2d** to afford the corresponding six-membered ring products in 91% and 69% yields, respectively (Table 3, entries 1 and 2). The reaction of 3,3-diethylcyclobutanone (**1c**) required 20 mol % of the nickel catalyst to gain an acceptable yield due to its lower reactivity than the phenyl-substituted **1a** and **1b** (entries 3 and 4).

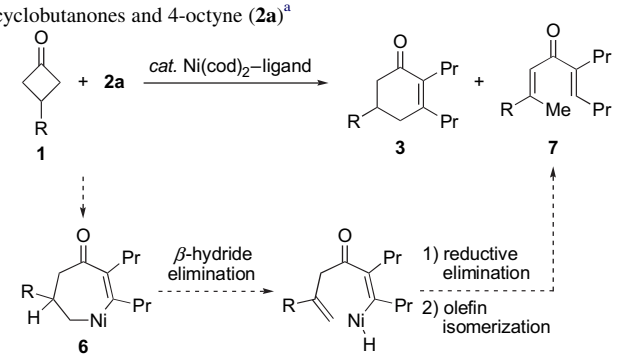
The reaction pathway with a cyclobutanone having a hydrogen at the 3-position turned out to be somewhat different (Table 4). The reaction of 3-octylcyclobutanone **1d** in the presence of the nickel(0)–P(*c*-Hex)$_3$ catalyst afforded

Table 3. Nickel-catalyzed reaction of **1** and **2** forming cyclohexenone **3**[a]

Entry	**1**	**2** (equiv)	Mol % Ni	**3** (%Yield[b])
1	 **1b**	 **2a** (1.5)	10	 **3g** (91)
2	 **1b**	 **2d** (3.0)	10	 **3h**[c] (69) 93:7
3	 **1c**	 **2a** (1.5)	20	 **3i** (91)
4	 **1c**	 **2d** (3.0)	20	 **3j**[c] (47) 90:10

[a] Cyclobutanone **1**, alkyne **2** (1.5–3.0 equiv to **1**), $Ni(cod)_2$, and P(*c*-Hex)$_3$ (2 equiv to Ni) were heated in toluene at 90–110 °C for 3–6 h.
[b] Isolated yield.
[c] Regioisomeric ratios were determined by ^{1}H NMR.

Table 4. Reaction of 3-monosubstituted cyclobutanones and 4-octyne (**2a**)[a]



Entry	**1** (R)	Mol % Ni	Ligand (mol %)	Toluene/mL	Conditions	**3** (%Yield[b])	**7** (%Yield[b])
1	**1d** (n-C_8H_{17})	10	P(c-Hex)$_3$ (20)	1.0	100 °C, 3 h	**3k** (37)	**7a**[c] (37)
2	**1e** (Ph)	10	P(c-Hex)$_3$ (20)	1.0	100 °C, 3 h	**3l** (41)	**7b** (54)
3	**1e** (Ph)	10	PPh_3 (20)	1.0	100 °C, 3 h	**3l** (37)	**7b** (26)
4	**1e** (Ph)	10	IPr[d] (20)	2.0	110 °C, 18 h	**3l** (59)	—
5	**1e** (Ph)	10	IPr (10)	2.0	110 °C, 18 h	**3l** (61)	—
6	**1e** (Ph)	20	IPr (20)	4.0	110 °C, 15 h	**3l** (79)	—
7	**1f** (2-naphthyl)	10	IPr (10)	2.0	110 °C, 15 h	**3m** (32)	—

[a] Cyclobutanone **1** (0.20 mmol), alkyne **2a** (0.30 mmol), and nickel catalyst were heated in toluene.
[b] Isolated yield.
[c] A mixture of *Z*- and *E*-isomers with respect to the 2-methyldec-1-enyl moiety was obtained.
[d] IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

a mixture of the desired product **3k** (37%) and linear unsaturated ketone **7a** (37%) (entry 1). Similar results were obtained for the reaction of 3-phenylcyclobutanone (**1e**), affording two products **3l** and **7b** (entries 2 and 3). The formation of the linear ketones **7** is explained by assuming that the hydrogen at the 3-position of cyclobutanone undergoes β-hydride elimination from intermediate **6**. The following reductive elimination and subsequent olefin isomerization give **7**.[13] Ligands of nickel(0) were again screened to improve the product selectivity in favor of **3**. To our delight, the use of a *N*-heterocyclic carbene ligand (IPr) afforded cyclohexenone **3l** selectively without any detectable formation of **7**, although the reaction became slower (entries 4 and 5).[14] Sterically bulkier IPr ligand might hinder an agostic interaction with the hydrogen on the β-carbon, suppressing the formation of **7**. The yield increased to 79% when 20 mol % of the nickel catalyst was employed (entry 6). The reaction of 3-(2-naphtyl)cyclobutanone (**1f**) with **2a** using the Ni–IPr catalyst produced cyclohexenone **3m** also selectively but in lower yield (entry 7).

The reaction failed to take place with cyclobutanones possessing substituents at the 2-position shown in Figure 2, presumably due to steric reasons.

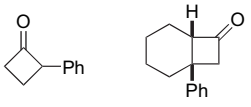


Figure 2.

3. Conclusions

Combining a process of the carbonyl–alkyne oxidative cyclization on nickel(0) with a process of the nickel(II) cyclobutanolate ring opening by β-carbon elimination rendered it possible for alkynes to insert intermolecularly between the carbonyl carbon and the α-carbon of cyclobutanone. This new reaction demonstrated the potential of cyclobutanones as a 1-oxobutane-1,4-diyl unit to build carbocyclic frameworks in a concise and efficient way (Fig. 3).

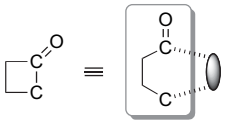


Figure 3.

4. Experimental

4.1. General

All manipulations were carried out in a nitrogen-filled gloved box or with standard Schlenk techniques under a nitrogen atmosphere. Preparative thin-layer chromatography was performed with silica gel 60 PF_{254} (Merck). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (^1H at 300.07 Hz and ^{13}C at 75.46 Hz) spectrometer. All NMR data were obtained in $CDCl_3$. Proton chemical shifts were referenced to the residual proton signal of the solvent at 7.26 ppm. Carbon chemical shifts were referenced to the carbon signal of the solvent at 77.00 ppm. High resolution mass spectra were recorded on a JEOL JMS-SX102A spectrometer. IR spectra were recorded on a Shimadzu FTIR-8100 spectrometer. Cyclobutanones **1** were prepared by [2+2] cycloaddition of the corresponding olefins with dichloroketene and the subsequent dechlorination with zinc dust in acetic acid.[15] 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) was prepared according to the literature procedure.[16] Toluene was distilled over sodium–benzophenone ketyl prior to use. All other commercially available chemical resources were used without further purifications.

4.2. Nickel-catalyzed reactions of cyclobutanones 1 with alkynes 2

4.2.1. 5-Methyl-5-phenyl-2,3-dipropyl-2-cyclohexenone (3a). To a toluene solution (1.0 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol) and P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol) were added **1a** (32.7 mg, 0.20 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 100 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 9:1) to afford **3a** (52.4 mg, 95%): IR (neat) 1663 cm^{-1}; ^1H NMR δ 0.81 (t, J=7.4 Hz, 3H), 0.91 (t, J=7.4 Hz, 3H), 1.19–1.29 (m, 2H), 1.33 (s, 3H), 1.47 (sext, J=7.5 Hz, 2H), 2.12–2.31 (m, 4H), 2.58 (d, J=18.2 Hz, 1H), 2.59 (dd, J=16.2, 1.2 Hz, 1H), 2.80 (d, J=18.2 Hz, 1H), 2.89 (dd, J=16.1, 1.2 Hz, 1H), 7.15–7.20 (m, 1H), 7.27–7.32 (m, 4H); ^{13}C NMR δ 14.1, 14.2, 20.8, 22.6, 26.8, 29.0, 36.9, 39.6, 44.0, 49.9, 125.1, 126.1, 128.3, 135.2, 147.1, 155.7, 198.4; HRMS (EI) calcd for $C_{19}H_{26}O$ (M^+) 270.1984, found 270.1982. Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.55; H, 9.85.

4.2.2. 2,3-Diethyl-5-methyl-5-phenyl-2-cyclohexenone (3b). To a toluene solution (0.5 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol) and P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol) were added **1a** (32.1 mg, 0.20 mmol) and 3-hexyne (**2b**, 24.6 mg, 0.30 mmol). After being stirred for 6 h at 90 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 9:1) to afford **3b** (47.2 mg, 97%): ^1H NMR δ 0.87 (t, J=7.5 Hz, 3H), 1.04 (t, J=7.7 Hz, 3H), 1.33 (s, 3H), 2.17–2.33 (m, 4H), 2.58 (d, J=17.7 Hz, 1H), 2.60 (dd, J=16.1, 1.1 Hz, 1H), 2.79 (d, J=17.7 Hz, 1H), 2.88 (dd, J=16.1, 1.1 Hz, 1H), 7.17–7.21 (m, 1H), 7.27–7.30 (m, 4H); ^{13}C NMR δ 12.0, 14.0, 17.9, 27.7, 28.8, 39.5, 43.6, 49.9, 125.1, 126.1, 128.2, 136.0, 147.1, 156.7, 198.4; HRMS (EI) calcd for $C_{17}H_{22}O$ (M^+) 242.1671, found 242.1670.

4.2.3. 5-Methyl-2,3,5-triphenyl-2-cyclohexenone (3c). A toluene solution (0.3 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1a** (31.6 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.2 mL) of diphenylacetylene (**2c**, 106.9 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 9:1) to afford **3c** (56.0 mg, 84%): ^1H NMR δ 1.57 (s, 3H), 2.91 (dd, J=16.1, 0.6 Hz, 1H), 3.15 (d, J=18.0 Hz, 1H), 3.24 (dd, J=16.1, 1.7 Hz, 1H), 3.35 (dd, J=18.0, 1.7 Hz, 1H), 6.83–6.86 (m, 2H), 6.98–7.03 (m, 2H), 7.11–7.19 (m, 6H) 7.24–7.30 (m, 1H) 7.36–7.45 (m, 4H); ^{13}C NMR δ 29.5, 40.3, 46.3, 50.3, 125.4, 126.4, 126.7, 127.4, 127.7, 127.8, 127.9, 128.5, 130.7, 134.9, 137.4, 140.7, 146.3, 155.2, 197.6; HRMS (EI) calcd for $C_{25}H_{22}O$ (M^+) 338.1671, found 338.1671.

4.2.4. 2,5-Dimethyl-3,5-diphenyl-2-cyclohexenone (3d) and 3,5-dimethyl-2,5-diphenyl-2-cyclohexenone (3′d). A toluene solution (0.4 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1a** (31.7 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-phenyl-1-propyne (**2d**, 69.6 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 9:1) to afford **3d** (39.2 mg, 72%) and **3′d** (3.2 mg, 6%). Compound **3d**: ^1H NMR δ 1.44 (s, 3H), 1.68 (t, J=1.8 Hz, 3H), 2.76 (dd, J=16.1, 1.1 Hz, 1H), 2.92 (ddd, J=17.7, 1.9, 1.2 Hz, 1H), 3.07 (dd, J=16.1, 1.5 Hz, 1H), 3.13 (dt, J=17.7, 1.5 Hz, 1H), 7.14–7.17 (m, 2H), 7.22–7.26 (m, 1H), 7.30–7.43 (m, 7H); ^{13}C NMR δ 12.5, 29.5, 40.3, 46.3, 49.8, 125.2, 126.3, 126.9, 127.8, 128.4, 128.5, 131.6, 141.2, 146.8, 153.8, 199.3; HRMS (EI) calcd for $C_{20}H_{20}O$ (M^+) 276.1514, found 276.1512. Compound **3′d**: ^1H NMR δ 1.45 (s, 3H), 1.82 (s, 3H), 2.76 (d, J=16.8 Hz, 1H+1H), 2.97 (d, J=18.0 Hz, 1H), 3.05 (d, J=15.9 Hz, 1H), 6.93–6.96 (m, 2H), 7.22–7.35 (m, 8H).

4.2.5. Stereochemical assignment of 3d and 3′d. The two regioisomers **3d** and **3′d** were subjected to NOE experiments. No NOE between the methyl protons (δ 1.68) and the C4 and C6 methylene protons (δ 2.76, 2.92, 3.07, and 3.13) was observed for **3d**. On the other hand, a NOE between the methyl protons (δ 1.82) and the C4 methylene protons (δ 2.76 and 2.97) was observed for **3′d**.

4.2.6. 3-(4-Methoxyphenyl)-2,5-dimethyl-5-phenyl-2-cyclohexenone (3e) and 2-(4-methoxyphenyl)-3,5-dimethyl-5-phenyl-2-cyclohexenone (3′e). A toluene solution (0.4 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1a** (31.3 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-(4-methoxyphenyl)-1-propyne (**2e**, 87.7 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 8:1) to afford **3e** (31.1 mg, 52%) and **3′e** (3.5 mg, 6%). Compound **3e**: ^1H NMR δ 1.43 (s, 3H), 1.71 (t, J=1.8 Hz, 3H), 2.74 (dd, J=16.1, 0.8 Hz, 1H), 2.90 (ddd, J=17.9, 1.7, 0.8 Hz, 1H), 3.05 (dd, J=16.1, 1.2 Hz, 1H), 3.12 (dt, J=17.9, 1.6 Hz, 1H), 3.83 (s, 3H), 6.90–6.95 (m, 2H), 7.09–7.14 (m, 2H), 7.19–7.24 (m, 1H), 7.32–7.34 (m, 4H); ^{13}C NMR δ 12.7, 29.5, 40.2, 46.3, 49.8, 55.3, 113.7, 125.2, 126.2, 128.4, 128.6, 131.3, 133.4, 146.8, 153.5, 159.2, 199.3; HRMS (EI) calcd for $C_{21}H_{22}O_2$ (M^+) 306.1620, found 306.1621. Compound **3′e**: ^1H NMR δ 1.44 (s, 3H), 1.84 (s, 3H), 2.75 (d, J=16.5 Hz, 1H+1H), 2.96 (d, J=18.9 Hz, 1H), 3.04 (dd, J=15.9, 1.2 Hz, 1H), 3.80 (s, 3H), 6.83–6.90 (m, 4H), 7.20–7.27 (m, 1H), 7.30–7.35 (m, 4H); HRMS (EI) calcd for $C_{21}H_{22}O_2$ (M^+) 306.1620, found 306.1617.

4.2.7. 2,5-Dimethyl-5-phenyl-3-(4-trifluoromethylphenyl)-2-cyclohexenone (3f) and 3,5-dimethyl-5-phenyl-2-(4-trifluoromethylphenyl)-2-cyclohexenone (3′f). A toluene solution (0.4 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1a** (31.8 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-(4-trifluoromethylphenyl)-1-propyne (**2f**, 110.4 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3f** (40.8 mg, 60%) and **3′f** (3.9 mg, 6%).

Compound **3f**: ^{1}H NMR δ 1.44 (s, 3H), 1.65 (t, J=1.8 Hz, 3H), 2.77 (d, J=15.9 Hz, 1H), 2.90 (dd, J=18.2, 2.0 Hz, 1H), 3.04–3.14 (m, 2H), 7.20–7.28 (m, 3H), 7.30–7.38 (m, 4H), 7.66 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 12.4, 29.6, 40.5, 46.1, 49.7, 123.9 (q, $^1J_{C-F}$=271.5 Hz), 125.2, 125.5 (q, $^3J_{C-F}$=3.8 Hz), 126.4, 127.3, 128.6, 129.9 (q, $^2J_{C-F}$= 32.4 Hz), 132.3, 144.7, 146.4, 151.9, 198.8; HRMS (EI) calcd for $C_{21}H_{19}F_3O$ (M^+) 344.1388, found 344.1386. Compound **3′f**: ^{1}H NMR δ 1.46 (s, 3H), 1.82 (s, 3H), 2.76 (d, J=16.2 Hz, 1H), 2.78 (d, J=18.0 Hz, 1H), 2.99 (d, J=18.0 Hz, 1H), 3.08 (dd, J=16.2, 1.5 Hz, 1H), 7.06 (d, J=8.4 Hz, 2H), 7.21–7.29 (m, 1H), 7.31–7.40 (m, 4H), 7.58 (dd, J=8.4, 0.6 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{19}F_3O$ (M^+) 344.1388, found 344.1385.

4.2.8. 5,5-Diphenyl-2,3-dipropyl-2-cyclohexenone (3g). To a toluene solution (0.5 mL) of Ni(cod)$_2$ (5.5 mg, 0.02 mmol) and P(c-Hex)$_3$ (11.2 mg, 0.04 mmol) were added **1b** (44.5 mg, 0.20 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3g** (60.7 mg, 91%): ^{1}H NMR δ 0.73 (t, J=7.5 Hz, 3H), 0.88 (t, J=7.4 Hz, 3H), 1.11–1.23 (m, 2H), 1.39–1.51 (m, 2H), 2.16–2.22 (m, 2H), 2.24–2.29 (m, 2H), 3.14 (s, 2H), 3.15 (s, 2H), 7.13–7.19 (m, 6H), 7.22–7.28 (m, 4H); ^{13}C NMR δ 14.0, 14.2, 20.7, 22.4, 26.8, 37.1, 42.6, 47.6, 49.9, 126.2, 126.7, 128.2, 136.3, 146.3, 155.4, 197.7; HRMS (EI) calcd for $C_{24}H_{28}O$ (M^+) 332.2140, found 332.2143.

4.2.9. 2-Methyl-3,5,5-triphenyl-2-cyclohexenone (3h) and 3-methyl-2,5,5-triphenyl-2-cyclohexenone (3′h). A toluene solution (0.1 mL) of Ni(cod)$_2$ (5.5 mg, 0.02 mmol), P(c-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1b** (44.5 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-phenyl-1-propyne (**2d**, 69.6 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3h** (43.2 mg, 64%) and **3′h** (3.4 mg, 5%). Compound **3h**: ^{1}H NMR δ 1.66 (s, 3H), 3.34 (s, 2H), 3.46 (s, 2H), 7.12–7.44 (m, 15H); ^{13}C NMR δ 12.5, 45.0, 48.3, 49.7, 126.3, 126.6, 126.9, 128.0, 128.4, 132.6, 141.0, 146.1, 153.4, 198.5 [one carbon signal is missing due to overlapping]; HRMS (EI) calcd for $C_{25}H_{22}O$ (M^+) 338.1671, found 338.1671. Compound **3′h**: ^{1}H NMR δ 1.87 (s, 3H), 3.27 (s, 2H), 3.33 (s, 2H), 6.85–6.88 (m, 2H), 7.20–7.32 (m, 13H).

4.2.10. 5,5-Diethyl-2,3-dipropyl-2-cyclohexenone (3i). To a toluene solution (1 mL) of Ni(cod)$_2$ (11.0 mg, 0.04 mmol) and P(c-Hex)$_3$ (22.4 mg, 0.08 mmol) were added **1c** (24.4 mg, 0.19 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3i** (28.1 mg, 61%): ^{1}H NMR δ 0.77 (t, J=7.4 Hz, 6H), 0.89 (t, J=7.4 Hz, 3H), 0.96 (t, J=7.5 Hz, 3H), 1.25–1.38 (m, 6H), 1.42–1.55 (m, 2H), 2.16–2.25 (m, 8H); ^{13}C NMR δ 7.7, 14.3, 14.4, 21.2, 22.8, 26.9, 28.7, 36.9, 37.8, 40.4, 47.8, 134.6, 155.7, 199.5; HRMS (EI) calcd for $C_{16}H_{28}O$ (M^+) 236.2140, found 236.2143.

4.2.11. 5,5-Diethyl-2-methyl-3-phenyl-2-cyclohexenone (3j) and 5,5-diethyl-3-methyl-2-phenyl-2-cyclohexenone (3′j). A toluene solution (0.4 mL) of Ni(cod)$_2$ (11.0 mg, 0.04 mmol), P(c-Hex)$_3$ (22.4 mg, 0.08 mmol), and **1c** (24.5 mg, 0.19 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-phenyl-1-propyne (**2d**, 69.6 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 20:1) to afford **3j** (20.3 mg, 43%) and **3′j** (2.1 mg, 4%). Compound **3j**: ^{1}H NMR δ 0.83 (t, J=7.4 Hz, 6H), 1.45 (q, J=7.5 Hz, 4H), 1.69 (t, J=2.0 Hz, 3H), 2.39 (s, 2H), 2.49 (d, J=1.8 Hz, 2H), 7.16–7.19 (m, 2H), 7.32–7.42 (m, 3H); ^{13}C NMR δ 7.8, 12.5, 28.8, 38.4, 43.0, 47.5, 127.0, 127.7, 128.3, 130.9, 141.6, 153.9, 200.3; HRMS (EI) calcd for $C_{17}H_{22}O$ (M^+) 242.1671, found 242.1671. Compound **3′j**: ^{1}H NMR δ 0.85 (t, J=7.5 Hz, 6H), 1.46 (q, J=7.4 Hz, 4H), 1.80 (s, 3H), 2.36 (s, 2H), 2.41 (s, 2H), 7.04–7.07 (m, 2H), 7.25–7.38 (m, 3H).

4.2.12. 5-Octyl-2,3-dipropyl-2-cyclohexenone (3k). To a toluene solution (0.5 mL) of Ni(cod)$_2$ (5.5 mg, 0.02 mmol) and P(c-Hex)$_3$ (11.2 mg, 0.04 mmol) were added **1d** (36.3 mg, 0.20 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3k** (21.7 mg, 37%) and **6a** (21.3 mg, 37%): ^{1}H NMR δ 0.85–0.98 (m, 9H), 1.26–1.35 (m, 16H), 1.42–1.54 (m, 2H), 1.96–2.08 (m, 3H), 2.19–2.26 (m, 4H), 2.30–2.37 (m, 1H), 2.47–2.51 (m, 1H); ^{13}C NMR δ 14.1, 14.3, 21.3, 22.7, 22.9, 26.5, 27.1, 29.3, 29.6, 29.7, 31.9, 34.6, 35.9, 37.0, 37.3, 44.5, 135.3, 158.1, 199.6 [one carbon signal is missing due to overlapping]; HRMS (EI) calcd for $C_{20}H_{36}O$ (M^+) 292.2766, found 292.2770.

4.2.13. 5-Phenyl-2,3-dipropyl-2-cyclohexenone (3l). A toluene solution (1.5 mL) of **1e** (29.3 mg, 0.20 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol) was stirred for 10 min at 110 °C. To the stirring solution, a toluene solution (0.5 mL) of Ni(cod)$_2$ (5.5 mg, 0.02 mmol) and IPr (7.8 mg, 0.02 mmol), which was stirred for 6 h at room temperature in glove box, was added. After being stirred for 18 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3l** (31.4 mg, 61%): ^{1}H NMR δ 0.94 (t, J=7.5 Hz, 3H), 0.97 (t, J=7.4 Hz, 3H), 1.32–1.44 (m, 2H), 1.47–1.60 (m, 2H), 2.23–2.36 (m, 4H), 2.52–2.62 (m, 3H), 2.71 (dd, J=16.2, 4.2 Hz, 1H), 3.17–3.28 (m, 1H), 7.22–7.26 (m, 3H), 7.31–7.37 (m, 2H); ^{13}C NMR δ 14.2, 14.3, 21.1, 22.8, 27.1, 36.8, 38.5, 40.4, 44.6, 126.5, 126.7, 128.5, 135.4, 143.6, 157.6, 198.5; HRMS (EI) calcd for $C_{18}H_{24}O$ (M^+) 256.1827, found 256.1829.

4.2.14. (2*E*,5*E*)-2-Phenyl-5-propyl-2,5-nonadien-4-one (7b). The title compound was obtained by the reaction with Ni(cod)$_2$–P(c-Hex)$_3$. ^{1}H NMR δ 0.94 (t, J=7.8 Hz, 3H), 0.96 (t, J=7.8 Hz, 3H), 1.35–1.56 (m, 4H), 2.25 (q, J=7.4 Hz, 2H), 2.33–2.39 (m, 2H), 2.40 (d, J=1.2 Hz, 3H), 6.62 (t, J=7.4 Hz, 1H), 6.78 (d, J=1.2 Hz, 1H), 7.34–7.42 (m, 3H), 7.48–7.52 (m, 2H); ^{13}C NMR δ 14.0, 14.2,

18.4, 22.3, 22.5, 27.8, 31.0, 123.3, 126.2, 128.4, 128.5, 142.8, 143.1, 143.6, 150.5, 194.7; HRMS (EI) calcd for $C_{18}H_{24}O$ (M^+) 256.1827, found 256.1826.

4.2.15. Stereochemical assignment of 7b. Divinylketone **7b** was subjected to NOE experiments. No NOE between the vinyl proton (δ 6.78) and the methyl protons (δ 2.40) was observed. On the other hand, a NOE between the vinyl proton (δ 6.78) and the aromatic *ortho* protons (δ 7.48–7.52) was observed.

4.2.16. 5-(2-Naphthyl)-2,3-dipropyl-2-cyclohexenone (3m). A toluene solution (1.5 mL) of **1f** (39.2 mg, 0.2 mmol) and 4-octyne (**2a**, 33 mg, 0.3 mmol) was stirred for 10 min at 110 °C. To the stirring solution, a toluene solution (0.5 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol) and IPr (7.8 mg, 0.02 mmol), which was stirred for 6 h at room temperature in glove box, was added. After being stirred for 15 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3m** (19.5 mg, 32%): ^{1}H NMR δ 0.95 (t, J=7.2 Hz, 3H), 0.98 (t, J=7.6 Hz, 3H), 1.33–1.46 (m, 2H), 1.48–1.59 (m, 2H), 2.28–2.38 (m, 4H), 2.63–2.73 (m, 3H), 2.80 (dd, J=16.1, 4.1 Hz, 1H), 3.35–3.46 (m, 1H), 7.37–7.40 (m, 1H), 7.43–7.51 (m, 2H), 7.66–7.67 (m, 1H), 7.79–7.84 (m, 3H); ^{13}C NMR δ 14.3, 21.3, 22.9, 27.2, 36.9, 38.5, 40.5, 44.7, 124.9, 125.3, 125.6, 126.2, 127.6, 127.6, 128.3, 132.4, 133.5, 135.5, 141.1, 157.7, 198.6 [one carbon signal is missing due to overlapping]; HRMS (EI) calcd for $C_{22}H_{26}O$ 306.1984, found 306.1985.

Acknowledgements

We thank H. Fujita for his assistance in the structure determination by NMR and H. Ushitora for obtaining the HRMS data. This work was supported by a Grant-in-Aid for Young Scientists (B) (No. 15750085) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. (a) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1999; (b) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: New York, NY, 2000; (c) *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004.
2. (a) Murakami, M.; Amii, H.; Ito, Y. *Nature* **1994**, *370*, 540–541; (b) Murakami, M.; Amii, H.; Shigeto, K.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 8285–8290.
3. (a) Murakami, M.; Takahashi, K.; Amii, H.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9307–9308; (b) Murakami, M.; Itahashi, T.; Amii, H.; Takahashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9949–9950; (c) Murakami, M.; Tsuruta, T.; Ito, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 2484–2486.
4. For recent examples, see: (a) Müller, C.; Lachicotte, R. J.; Jones, W. D. *Organometallics* **2002**, *21*, 1975–1981; (b) Kondo, T.; Taguchi, Y.; Kaneko, Y.; Niimi, M.; Mitsudo, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5369–5372; (c) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904–13905.
5. (a) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976–13977; (b) Matsuda, T.; Fujimoto, A.; Ishibashi, M.; Murakami, M. *Chem. Lett.* **2004**, *33*, 876–877.
6. For recent examples of β-carbon elimination, see: (a) Zhao, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 11618–11619; (b) Siriwardana, A. I.; Kamada, M.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 5932–5937; (c) Funayama, A.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2005**, *127*, 15354–15355 and references therein.
7. Pd: (a) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201–216; (b) Nishimura, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 5342–5347; (c) Satoh, T.; Miura, M. *Palladium in Organic Synthesis*; Tsuji, J., Ed.; Topics in Organometallic Chemistry; Springer: Berlin, 2005; Vol. 14, pp 1–20; Rh: (d) Matsuda, T.; Makino, M.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4608–4611; (e) Matsuda, T.; Makino, M.; Murakami, M. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1528–1533.
8. For recent examples, see: (a) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698–3699; (b) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342–15343; (c) Tekavec, T. N.; Louie, J. *Org. Lett.* **2005**, *7*, 4037–4039; (d) Knapp-Reed, B.; Mahandru, G. M.; Montgomery, J. *J. Am. Chem. Soc.* **2005**, *127*, 13156–13157; (e) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 14194–14195; For a review, see: (f) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908.
9. For related reactions with carbon dioxide, see: (a) Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* **2001**, *3*, 3345–3347; (b) Tekavec, T. N.; Arif, A. M.; Louie, J. *Tetrahedron* **2004**, *60*, 7431–7437 and references therein.
10. For mechanistic studies, see: (a) Hratchian, H. P.; Chowdhury, S. K.; Gutierrez-Garcia, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636–4646; (b) Ogoshi, S.; Oka, M.-a.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802–11803; (c) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810–12811.
11. A part of this work appeared as a preliminary communication: Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932–6933.
12. For related catalytic reactions of cyclobutenones, see: (a) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 8617–8618; (b) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771–2772. Therein, η^4-vinylketene metal complexes are presumably formed as the intermediate from cyclobutenones, which are much more labile thermally as well as catalytically than cyclobutanones.
13. The *E*-isomer is more stable than the *Z*-isomer because the maximum conjugative stabilization is achieved with the O=C–C=C–Ph moiety of the *E*-isomer for which it is easier to take a planar conformation. With the *Z*-isomer, steric interaction of the acyl and the phenyl groups causes deviation of the conjugated moiety from planarity, reducing such stabilization. The more stable *E*-isomer was formed as a result of isomerization under the reaction conditions.
14. 1,3-Dimesitylimidazol-2-ylidene (IMes) and 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene (SIPr) showed even lower reactivities than IPr.
15. Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159–646.
16. Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523–14534.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7547–7551
Tetrahedron

Nickel(0)-mediated [2+2+1] cyclization reaction of chromium carbene complexes and internal alkynes

José Barluenga,* Pablo Barrio, Lorena Riesgo, Luis A. López and Miguel Tomás

Instituto Universitario de Química Organometálica 'Enrique Moles', Unidad Asociada al C.S.I.C., Universidad de Oviedo, Julián Clavería 8, Oviedo 33006, Spain

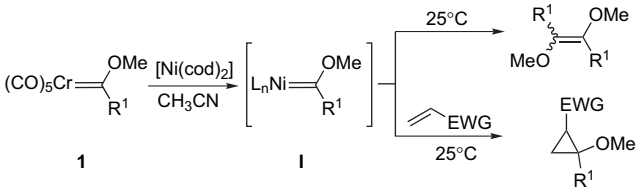
Received 24 November 2005; revised 2 March 2006; accepted 2 March 2006
Available online 5 June 2006

Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry

Abstract—Alkyl, aryl, and heteroaryl chromium Fischer carbene complexes undergo Ni(0)-mediated [2+2+1] cyclization reaction with internal unactivated and electron-poor internal alkynes to yield highly substituted cyclopentadienes with complete regioselectivity in most cases. The intramolecular version of this cyclization has been accomplished with 1,8-diphenyl-1,7-octadiyne to produce indene derivatives. This three-component [2+2+1] cyclization represents a very uncommon process in the chemistry of Fischer carbene complexes.

1. Introduction

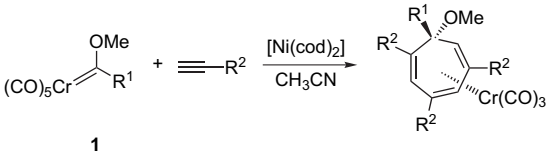
In the last years Fischer carbene complexes have become useful reagents in synthetic organic chemistry.[1] Although these type of carbene complexes are well known for a number of transition metals, only a few nickel(0) carbene complexes have been hitherto reported. Wilke et al.[2] and Pinhas and Simunic[3] described the preparation and characterization of the complexes $[L_2Ni{=}C(NR_2)Ph]$ and $[(CO)_3Ni{=}C(OSiMe_3)Bu]$, respectively.[4] We and others have studied recently the transmetalation reaction[5] as a convenient route to access new carbene complexes of late transition metals, such as Cu(I),[6] Pd(0),[7] and Rh(I) .[8] This methodology proved to be also useful for the generation of nickel(0) alcoxycarbene complexes **I** from the corresponding chromium complexes **1** and $[Ni(cod)_2]$. The existence of the species **I** is validated by (i) the room temperature thermal dimerization of the carbene ligand, and (ii) its capability to cyclopropanate electron-poor alkenes at room temperature (Scheme 1).[9,10]



1 I

Scheme 1.

More importantly, the different nature of chromium and nickel allowed us to discover novel reaction patterns in the transition metal carbene chemistry area.[9,11] Specifically, we found that complexes **1** undergo a very unusual [2+2+2+1] cyclization reaction with terminal alkynes to give selectively chromium cycloheptatriene complexes (Scheme 2).[9]



1

Scheme 2.

This result sharply contrasts with those found previously after extensive studies with the group 6 carbene precursors themselves. In this respect, Figure 1 summarizes the most common cyclization modes of group 6 Fischer carbene complexes toward terminal and internal alkynes. Thus, metal aryl carbenes afford variable mixtures of naphthol, indene, cyclobutenone, and furan derivatives,[12] while chromium alkyl carbenes have been reported to yield substituted cyclopentenones.[13]

We report herein that the reaction of chromium carbene complexes with internal alkynes (Fig. 2) in the presence of $[Ni(cod)_2]$ neither proceeds as outlined in Figure 1 nor via a [2+2+2+1] cyclization as for terminal alkynes (Scheme 2), but a new reaction pathway for Fischer carbene complexes, namely the [2+2+1] cyclization, actually operates.[14] It will be also noted that the mode of assembling of both alkyne units into the resulting cyclopentadiene depends primarily on the electronic demand of the alkyne.

Keywords: Carbene complexes; Chromium(0); Nickel(0); Carbene transfer; Alkynes; Cyclopentadienes; Three-component process.
* Corresponding author. Tel./fax: +34 98 5103450; e-mail: barluenga@uniovi.es

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.117

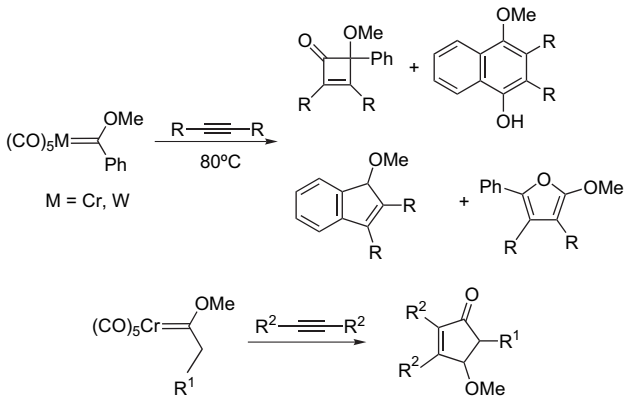


Figure 1.

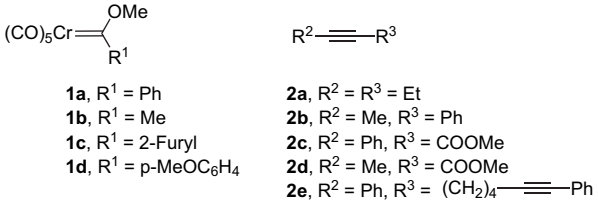
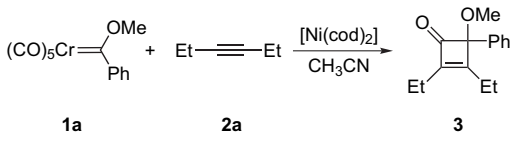


Figure 2.

2. Results and discussion

First we examined the reaction of chromium phenyl carbene complex **1a** with 3-hexyne **2a** and [Ni(cod)$_2$] (molar ratio 1:3:1) in acetonitrile. The reagents were mixed at −10 °C and allowed to reach room temperature during 2 h. The reaction mixture was chromatographed giving rise to the [2+1+1] cycloadduct **3** (25% yield)[12] as the sole isolable reaction product (Scheme 3).[15]

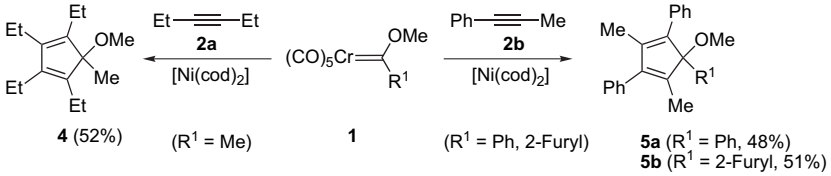


Scheme 3.

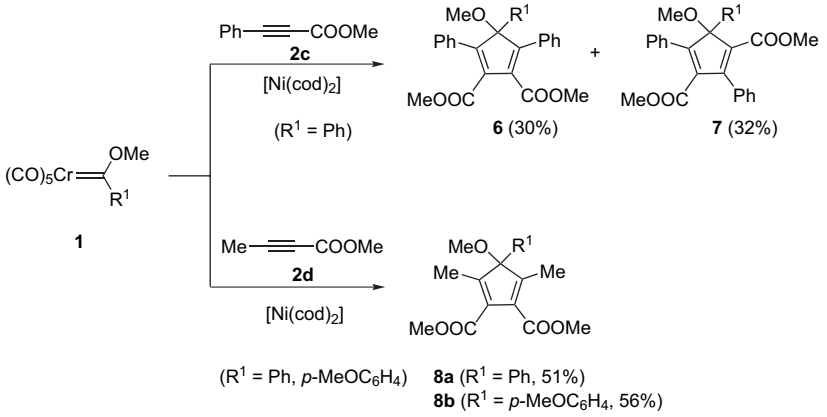
Interestingly, starting from appropriate carbene complex/alkyne combinations resulted in the complete inhibition of cyclobutenone formation in favor of a three-component [2+2+1] cyclization reaction (Scheme 4). Thus, [Ni(cod)$_2$] was added to a solution of 3-hexyne and methylcarbene **1b** (R^1=Me) in acetonitrile at −10 °C (molar ratio 1:2.5:1) and the mixture allowed to reach room temperature. Removal of solvent and alkyne excess followed by column chromatography purification afforded the densely substituted cyclopentadiene **4** in 52% yield.

The regioselectivity of this rare cyclization was then tested with 1-phenyl-1-propyne **2b**. In this case, the reaction of such an alkyne with carbene complexes **1a** (R^1=Ph) and **1c** (R^1=2-furyl) under the above reaction conditions led to unsymmetrical cycloadducts **5a**,**b** (48 and 51% yield) as a sole isomer in each case.

It was delightful to find that alkynes with an electron-withdrawing substituent are productive components in this reaction to provide functionalized cycloadducts (Scheme 5). For instance, the cyclization of the carbene complex **1a** and methyl phenylpropynoate **2c** resulted in the formation of a mixture of symmetrical and unsymmetrical cyclopentadienes **6** and **7**, respectively, in 62% yield (**6**/**7** ratio = 1:1). In contrast, the cyclization between **1a**,**d** and methyl 2-butynoate **2d** resulted in the regioselective formation of the cycloadducts **8a**,**b** in 51–56% yield. The structural assignment of 1,4-diphenyl-1,3-cyclopentadiene **6** and 1,4-dimethyl-1,3-cyclopentadiene **8** over 2,3-diphenyl- and



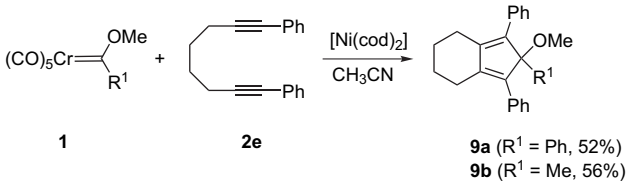
Scheme 4.



Scheme 5.

2,3-dimethylcyclopentadiene regioisomers (not shown) becomes apparent from NMR experiments (including HMQC, HMBC, and NOESY).

The scope of this cyclization could be successfully extended to the intramolecular version, thus allowing to access bicyclic cyclopentadienes (Scheme 6). This task was brought about by reacting carbene complexes **1a**,**b** and 1,8-diphenyl-1,7-octadiyne **2e** under the above reaction conditions to produce tetrahydroindenes **9a**,**b** (52–56% yield).



Scheme 6.

Concerning the reaction pathway, it should be noted that a common mechanism cannot operate in all cases since a divergent regiochemistry is observed depending on the nature of the alkyne (compare cyclopentadienes **5** *vs* **8**). A tentative rationale for the alkynes 1-phenyl-1-propyne **2b** and methyl 2-butynoate **2d** is outlined in Scheme 7. The chromium–nickel exchange to form the nickel carbene species **I** is assumed to be the common initial step. Two consecutive regioselective insertion reactions of 1-phenyl-1-propyne into the nickel–carbon double bond would generate the 1-nickela-1,3,6-hexatriene **II**, which would produce the final cycloadducts **5** upon cyclization to the nickelacycle **III** and Ni(0) reductive elimination (via *A*).[16] On the contrary, the symmetrical structure of cycloadducts **8** makes this mechanism unsatisfactory. On the ground of a recent proposal by Ni and Montgomery involving nonheteroatom stabilized carbene nickel(0) species and dienynes,[17] we propose that the formation of the symmetrical products **8** begins with the oxidative co-cyclization of nickel carbene complex **I** with two alkyne units to form regioselectively the nickelacyclopentadiene **IV** (via *B*).[18] Then, carbene insertion into the nickel–carbon bond would allow production of nickelacyclohexadiene **V**, which would provide **8** by reductive elimination.[19] When phenylpropiolate, instead of methylpropiolate is employed, we suspect that both mechanisms, double insertion (via *A*) and cyclometalation (via *B*), are productive yielding **7** and **6**, respectively.[20,21] We have no further evidences so as to decide the actual mechanism in the case of the intramolecular cyclization. While the single, neutral alkyne would suggest the insertion route, the entropic argument would facilitate the assembling of both reaction components and thus would favor the nickelacyclopentadiene pathway.

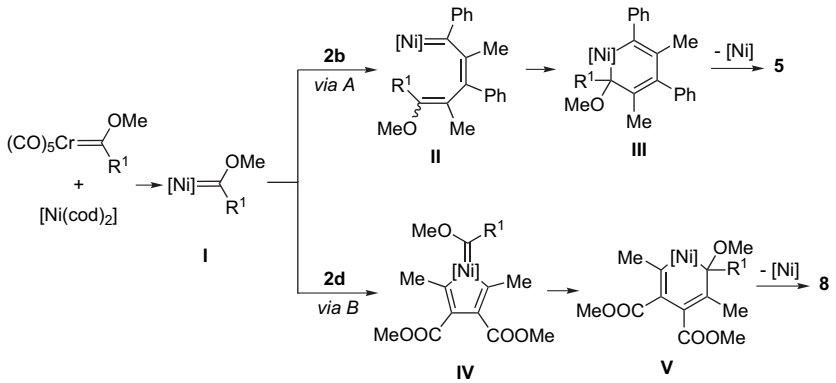
3. Conclusion

In conclusion, we have developed a highly efficient inter- and intramolecular [2+2+1] cyclization of chromium (methoxy)carbene complexes with internal alkynes and diynes in the presence of $[Ni(cod)_2]$. Except for methyl phenylpropiolate, the reaction is completely regioselective in all cases tested. Depending on the electronic nature of the alkyne different reaction pathways are proposed beginning with a nickel(0) Fischer carbene complex, namely carbene/alkyne insertion and alkyne/nickel cyclometalation. This approach provides a convenient entry to highly substituted cyclopentadiene and indene derivatives.[22] Further studies aimed at investigating the scope of this new reaction are currently ongoing in our laboratories.

4. Experimental

4.1. General methods

All reactions were carried out under N_2 using standard Schlenck techniques. Fischer carbene complexes **1a–d**[23] and 1,8-diphenyl-1,7-octadiyne[24] were prepared according to literature procedures. All common reagents were obtained from commercial suppliers and used without further purification unless otherwise indicated. Acetonitrile was distilled from CaH_2. TLC was performed on aluminum-backed plates coated with silica gel 60 with F254 indicator. Flash column chromatography was carried out on silica gel 60 (230–240 mesh). ^1H NMR (300 MHz) and ^{13}C NMR (70.5 MHz) spectra were measured in $CDCl_3$ at room temperature on a Bruker AC-300 instrument, with tetramethylsilane (δ=0.0, ^1H NMR) and $CDCl_3$ (δ=77.0, ^{13}C NMR) as internal standard. Elemental analyses were carried out on Perkin–Elmer 2400 and Carlo Erba 1108 microanalyzers.



Scheme 7.

4.2. General procedure for the nickel(0)-mediated [2+2+1] reaction of Fischer carbene complexes 1 with internal alkynes

To a solution of complex **1** (1.0 equiv) and alkyne (2.5 equiv) or diyne (1.1 equiv) in acetonitrile was added [Ni(cod)$_2$] (1.1 equiv) at −10 °C. The reaction mixture was allowed to reach room temperature during 2 h. The solvent was then removed and the resulting residue was subjected to flash chromatography (SiO_2, mixtures of hexane/ethyl acetate) to give pure cyclopentadiene and indene derivatives.

4.2.1. 1,2,3,4-Tetraethyl-5-methoxy-5-methyl-1,3-cyclopentadiene (4). The general procedure was followed using complex **1b** (125 mg, 0.5 mmol), 3-hexyne (103 mg, 1.25 mmol), and [Ni(cod)$_2$] (151 mg, 0.55 mmol) in acetonitrile (7 ml). Final chromatographic purification using a 10:1 mixture of hexane/ethyl acetate as eluent afforded the *title compound* **4** (58 mg, 52%) as a colorless oil; [Found: C, 81.22; H, 11.70. $C_{15}H_{26}O$ requires C, 81.02; H, 11.79%]; δ_H (300 MHz, $CDCl_3$) 2.84 (3H, s, OMe), 2.29–2.10 (8H, m, CH_2–CH_3), 1.24 (3H, s, Me), 1.10 (6H, t, *J* 7.9 Hz, CH_2–CH_3), 1.06 (6H, t, *J* 7.9 Hz, CH_2–CH_3); δ_C (70.5 MHz, $CDCl_3$) 141.6, 141.4, 89.4, 51.1, 20.4, 18.6, 17.6, 14.8, 13.8.

4.2.2. 5-Methoxy-1,3-dimethyl-2,4,5-triphenyl-1,3-cyclopentadiene (5a). The general procedure was followed using complex **1a** (156 mg, 0.5 mmol), 1-phenyl-1-propyne (145 mg, 1.25 mmol), and [Ni(cod)$_2$] (151 mg, 0.55 mmol) in acetonitrile (7 ml). Final chromatographic purification using a 20:1 mixture of hexane/ethyl acetate as eluent afforded the *title compound* **5a** (84 mg, 48%) as a colorless oil; [Found: C, 88.52; H, 6.94. $C_{26}H_{24}O$ requires C, 88.60; H, 6.86%]; δ_H (300 MHz, $CDCl_3$) 7.37–7.02 (15H, m, Ph), 3.27 (3H, s, OMe), 2.11 (3H, s, Me), 1.58 (3H, s, Me); δ_C (70.5 MHz, $CDCl_3$) 144.2, 142.7, 141.4, 140.3, 140.1, 135.5, 135.3, 129.3, 128.2, 128.1, 128.0, 127.9, 127.0, 126.6, 126.2, 125.3, 94.4, 50.9, 14.3, 10.2.

4.2.3. 5-(2-Furyl)-5-methoxy-1,3-dimethyl-2,4-diphenyl-1,3-cyclopentadiene (5b). The general procedure was followed using complex **1c** (151 mg, 0.5 mmol), 1-phenyl-1-propyne (145 mg, 1.25 mmol), and [Ni(cod)$_2$] (151 mg, 0.55 mmol) in acetonitrile (7 ml). Final chromatographic purification using a 40:1 mixture of hexane/ethyl acetate as eluent afforded the *title compound* **5b** (87 mg, 51%) as a colorless oil; [Found: C, 84.25; H, 6.37. $C_{24}H_{22}O_2$ requires C, 84.18; H, 6.48%]; δ_H (300 MHz, $CDCl_3$) 7.31 (1H, d, *J* 1.7 Hz, Fu), 7.30–7.15 (10H, m, Ph), 6.46 (1H, dd, *J* 3.2 and 1.7 Hz, Fu), 6.34 (1H, dd, *J* 3.2 and 0.6 Hz, Fu), 3.56 (3H, s, OMe), 1.87 (3H, s, Me), 1.79 (3H, s, Me); δ_C (70.5 MHz, $CDCl_3$) 162.5, 153.6, 141.9, 141.4, 139.5, 135.9, 135.8, 129.3, 128.4, 127.9, 127.4, 126.7, 118.8, 110.1, 107.5, 63.7, 60.84, 12.0, 10.8. HRMS (EI) calcd for $C_{24}H_{22}O_2$: 342.1620; found 342.1635 $[M]^+$.

4.2.4. Reaction of complex 1a and methyl phenylpropynoate 2c. The general procedure was followed using complex **1a** (156 mg, 0.5 mmol), methyl phenylpropynoate (200 mg, 1.25 mmol), and [Ni(cod)$_2$] (151 mg, 0.55 mmol) in acetonitrile (7 ml). Final chromatographic purification using a 5:1 mixture of hexane/ethyl acetate as eluent afforded compounds **6** and **7**.

4.2.4.1. 5-Methoxy-2,3-bis(methoxycarbonyl)-1,4,5-triphenyl-1,3-cyclopentadiene (6). The *title compound* **6** was isolated as a yellowish oil (66 mg, 30%); [Found: C, 76.48; H, 5.37. $C_{28}H_{24}O_5$ requires C, 76.35; H, 5.49%]; δ_H (300 MHz, $CDCl_3$) 7.45–7.13 (15H, m, Ph), 3.78 (6H, s, COOMe), 3.34 (3H, s, OMe); δ_C (70.5 MHz, $CDCl_3$) 167.7, 152.3, 138.0, 136.9, 134.5, 128.7, 128.1, 127.9, 127.7, 96.3, 52.3, 51.7.

4.2.4.2. 5-Methoxy-1,3-bis(methoxycarbonyl)-2,4,5-triphenyl-1,3-cyclopentadiene (7). The *title compound* **7** was isolated as a yellowish oil (70 mg, 32%); [Found: C, 76.24; H, 5.52. $C_{28}H_{24}O_5$ requires C, 76.35; H, 5.49%]; δ_H (300 MHz, $CDCl_3$) 7.57–7.22 (15H, m, Ph), 3.56 (3H, s, OMe), 3.44 (3H, s, OMe), 3.42 (3H, s, OMe); δ_C (70.5 MHz, $CDCl_3$) 166.2, 162.7, 154.3, 153.3, 136.6, 135.8, 135.5, 133.6, 131.8, 129.2, 128.6, 128.3, 128.2, 127.8, 127.7, 127.4, 125.1, 94.3, 52.1, 52.0, 51.0.

4.2.5. 5-Methoxy-2,3-bis(methoxycarbonyl)-1,4-dimethyl-5-phenyl-1,3-cyclopentadiene (8a). The general procedure was followed using complex **1a** (156 mg, 0.5 mmol), methyl butynoate (123 mg, 1.25 mmol), and [Ni(cod)$_2$] (151 mg, 0.55 mmol) in acetonitrile (7 ml). Final chromatographic purification using a 5:1 mixture of hexane/ethyl acetate as eluent afforded the *title compound* **8a** (81 mg, 51%) as a yellowish oil; [Found: C, 68.53; H, 6.51. $C_{18}H_{20}O_5$ requires C, 68.34; H, 6.37%]; δ_H (300 MHz, $CDCl_3$) 7.33–7.03 (5H, m, Ph), 3.60 (6H, s, COOCH_3), 3.23 (3H, s, OCH_3), 2.40 (6H, s, C≡C–CH_3); δ_C (70.5 MHz, $CDCl_3$) 163.5, 154.8, 138.2, 137.5, 127.7, 126.7, 124.9, 92.1, 51.6, 51.1, 13.2.

4.2.6. 5-Methoxy-2,3-bis(methoxycarbonyl)-5-(4-methoxyphenyl)-1,4-dimethyl-1,3-cyclopentadiene (8b). The general procedure was followed using complex **1d** (171 mg, 0.5 mmol), methyl butynoate (123 mg, 1.25 mmol), and [Ni(cod)$_2$] (151 mg, 0.55 mmol) in acetonitrile (7 ml). Final chromatographic purification using a 5:1 mixture of hexane/ethyl acetate as eluent afforded the *title compound* **8b** (97 mg, 56%) as a yellowish oil; [Found: C, 65.73; H, 6.29. $C_{19}H_{22}O_6$ requires C, 65.88; H, 6.40%]; δ_H (300 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.9 Hz, Ar), 6.77 (2H, d, *J* 8.9 Hz, Ar), 3.77 (3H, s, $ArOCH_3$), 3.62 (6H, s, COOCH_3), 3.21 (3H, s, OCH_3), 2.38 (6H, s, C≡C–CH_3); δ_C (70.5 MHz, $CDCl_3$) 163.5, 158.3, 154.4, 138.0, 129.2, 126.0, 113.1, 91.8, 55.0, 51.6, 51.1, 13.2. HRMS (EI) calcd for $C_{19}H_{22}O_6$: 346.1416; found 346.1416 $[M]^+$.

4.2.7. 4,5,6,7-Tetrahydro-2-methoxy-1,2,3-triphenyl-2*H*-indene (9a). The general procedure was followed using complex **1a** (156 mg, 0.5 mmol), 1,8-diphenyl-1,7-octadiyne (142 mg, 0.55 mmol), and [Ni(cod)$_2$] (151 mg, 0.55 mmol) in acetonitrile (7 ml). Final purification using a 20:1 mixture of hexane/ethyl acetate afforded the *title compound* **9a** (98 mg, 52%) as a colorless oil; [Found: C, 88.92; H, 6.83. $C_{28}H_{26}O$ requires C, 88.85; H, 6.92%]; δ_H (300 MHz, $CDCl_3$) 7.29–7.12 (15H, m, Ph), 3.21 (3H, s, OMe), 2.88–2.72 (4H, m, C≡C–CH_2–CH_2), 1.84–1.73 (4H, m, C≡C–CH_2–CH_2); δ_C (70.5 MHz, $CDCl_3$) 141.2, 141.1, 140.6, 134.7, 127.9, 126.2, 125.2, 95.3, 51.0, 26.9, 23.6.

4.2.8. 4,5,6,7-Tetrahydro-2-methoxy-2-methyl-1,3-diphenyl-2*H*-indene (9b). The general procedure was

followed using complex **1b** (125 mg, 0.5 mmol), 1,8-diphenyl-1,7-octadiyne (142 mg, 0.55 mmol), and [Ni(cod)$_2$] (151 mg, 0.55 mmol) in acetonitrile (7 ml). Final purification using a 20:1 mixture of hexane/ethyl acetate afforded the *title compound* **9b** (88 mg, 56%) as a colorless oil; [Found: C, 87.42; H, 7.71. $C_{23}H_{24}O$ requires C, 87.30; H, 7.64%]; δ_H (300 MHz, $CDCl_3$) 7.49–7.30 (10H, m, Ph), 3.20 (3H, s, OMe), 2.91–2.75 (4H, m, C═C–CH_2–CH$_2$), 1.84–1.71 (4H, m, C═C–CH$_2$–CH_2), 1.38 (3H, s, Me); δ_C (70.5 MHz, $CDCl_3$) 140.0, 138.6, 135.4, 128.1, 127.8, 126.3, 91.5, 51.2, 26.1, 23.3, 23.1.

Acknowledgements

We are grateful to the Ministerio de Educación y Ciencia (MEC, Project BQU2001-3853), the Principado de Asturias (Project PR-01-GE-9), and the Fundación Ramón Areces for the support of this research. P.B. thanks the Principado de Asturias for a predoctoral fellowship.

References and notes

1. For recent reviews on Fischer carbene complexes, see: (a) Wulff, W. D. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, NY, 1995; Vol. 12, p 469; (b) Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271; (c) Herndon, J. W. *Tetrahedron* **2000**, *56*, 1257; (d) Barluenga, J.; Fañanás, F. J. *Tetrahedron* **2000**, *56*, 4597; (e) Sierra, M. A. *Chem. Rev.* **2000**, *100*, 3591; (f) Aumann, R. *Eur. J. Org. Chem.* **2000**, 17; (g) de Meijere, A.; Schirmer, H.; Duestch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964; (h) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *J. Organomet. Chem.* **2005**, *690*, 539.
2. Gabor, B.; Krüger, C.; Marczinke, B.; Mynott, R.; Wilke, G. *Angew. Chem.* **1991**, *103*, 1711; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1666.
3. (a) Simunic, L.; Pinhas, A. R. *Organometallics* **1987**, *6*, 1358; (b) Simunic, L.; Pinhas, A. R. *Inorg. Chem.* **1989**, *28*, 2400.
4. (a) The preparation of *N*-heterocyclic carbenes of nickel(0) was first reported by Arduengo et al.: Arduengo, A. J., III; Gamper, S. F.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1994**, *116*, 4391; (b) For the preparation and the X-ray structure of a diphenylcarbene complex of nickel(0), see: Mindiola, D. J.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 9976.
5. For a recent review on this field, see: Sierra, M. A.; Mancheño, M. J.; Gómez-Gallego, M. *Acc. Chem. Res.* **2005**, *37*, 44.
6. Barluenga, J.; López, L. A.; Löber, O.; Tomás, M.; García-Granda, S.; Alvarez-Rúa, C.; Borge, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3392.
7. (a) Albeniz, A. C.; Espinet, P.; Manrique, R.; Pérez-Mateo, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2363; (b) Albeniz, A. C.; Espinet, P.; Manrique, R.; Pérez-Mateo, A. *Chem.—Eur. J.* **2005**, *11*, 1565.
8. (a) Göttker-Schnetmann, I.; Aumann, R.; Bergander, K. *Organometallics* **2001**, *20*, 3574; (b) Barluenga, J.; Vicente, R.; López, L. A.; Rubio, E.; Tomás, M.; Alvarez-Rúa, C. *J. Am. Chem. Soc.* **2004**, *126*, 470.
9. Barluenga, J.; Barrio, P.; López, L. A.; Tomás, M.; García-Granda, S.; Alvarez-Rúa, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3008.
10. del Amo, J. C.; Mancheño, M. J.; Gómez-Gallego, M.; Sierra, M. A. *Organometallics* **2004**, *23*, 5021.
11. (a) Barluenga, J.; Vicente, R.; Barrio, P.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2004**, *126*, 5974; (b) Barluenga, J.; Vicente, R.; Barrio, P.; López, L. A.; Tomás, M.; Borge, J. *J. Am. Chem. Soc.* **2004**, *126*, 14354.
12. Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**, *13*, 102.
13. Challener, C. A.; Wulff, W. D.; Anderson, B. A.; Chamberlin, S.; Faron, K. L.; Kim, O. K.; Murray, C. K.; Xu, Y. C.; Yang, D. C.; Darling, S. D. *J. Am. Chem. Soc.* **1993**, *115*, 1359.
14. (a) For an isolated example involving the [2+2+1] cyclization of pentacarbonyl[(*N*,*N*-dimethylamino)methylene]chromium with methyl acrylate and acrylonitrile, see: Sierra, M. A.; Soderberg, B.; Lander, P. A.; Hegedus, L. S. *Organometallics* **1993**, *12*, 3769; (b) For the thermal [2+2+1] cyclization of phenylallene and chromium carbene complexes, see: Aumann, R.; Uphoff, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 357.
15. In terms of comparison, the reaction of **1a** and 3-hexyne has been reported by Wulff et al. to take place at 80 °C producing variable mixtures wherein cyclobutenone **3** constitutes a minor component (0–23% yield, depending on the reaction conditions).
16. In contrast with the results found in the reaction with terminal alkynes (see Ref. 9), no triple insertion of the alkyne was observed in the present case.
17. Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 11162; See also, Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255.
18. (a) The same regioselectivity, based on a nickelacyclopentadiene closely related to intermediate **IV**, was reported to explain the cocyclotrimerization of methyl alkylpropiolates with allenes: Shanmugasundaram, M.; Wu, M.-S.; Cheng, C. H. *Org. Lett.* **2001**, *3*, 4233; (b) A reviewer points that the production of **8** is not inconsistent with the double insertion mechanism. He argues that the initial insertion of an alkyne unit would produce a new carbene that possesses a carboalkoxy substituent, which in turn could induce a second alkyne insertion with the opposite regiochemical sense.
19. The oxidative cyclometalation pathway (via *B*) is abandoned in the case of 1-phenyl-1-propyne as Eisch et al. observed that the nickel(0)-mediated cyclotrimerization product of 1-phenyl-1-propyne arises exclusively from the symmetrical nickelacyclopentadiene species. See, Eisch, J. J.; Damasevitz, G. A. *J. Organomet. Chem.* **1975**, *96*, C19.
20. For studies concerning the regiochemistry of the formation of nickelazacyclopentadione by Ni(0)-catalyzed oxidative co-cyclometalation of 1-phenyl-1-propyne and isocyanates, see: Duong, H. A.; Louie, J. *J. Organomet. Chem.* **2005**, *690*, 5098.
21. The nickel-catalyzed co-cyclotrimerization of methyl phenylpropiolate-allene was suggested to involve a head-to-tail cyclometalation of methyl phenylpropiolate (Ref. 18). In the present study, the participation of the nickel carbene species **I** makes the alkyne–carbene insertion reaction more likely to occur.
22. For the preparation of 5-methoxy-1,2,3,4,5-pentamethyl-1,3-cyclopentadiene from 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene, see: (a) Jutzi, P.; Mix, A. *Chem. Ber.* **1992**, *125*, 951; (b) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136.
23. Fischer, E. O.; Maasböl, A. *Angew. Chem.* **1964**, *76*, 645; *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 580.
24. Crisp, G. T.; Turner, P. D.; Stephens, K. A. *J. Organomet. Chem.* **1998**, *570*, 219.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7552–7559
Tetrahedron

A nickel(0) catalyzed cycloaddition of alkynes and isocyanates that affords pyrimidine-diones

Hung A. Duong and Janis Louie*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, UT 84112-0850, USA

Received 12 January 2006; revised 6 March 2006; accepted 6 March 2006
Available online 15 June 2006

Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry

Abstract—A Ni/*N*-heterocyclic carbene catalyzed cycloaddition of *one alkyne* and *two isocyanates* that affords pyrimidine-dione is described. The key to the success of this protocol is the use of unsymmetrically substituted alkynes that favors the formation of pyrimidine-diones over pyridones. A variety of pyrimidine-diones were prepared. A one-pot cycloaddition and Stille coupling were reported for tributyl(1-propynyl)tin. Competition studies also provide insights into the mechanism of the cycloaddition.

1. Introduction

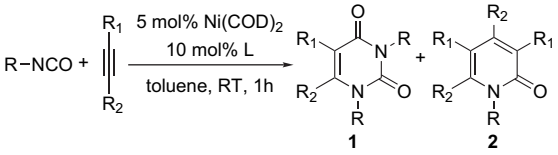
The transition metal catalyzed cycloaddition of unsaturated coupling partners has developed into a powerful and efficient method for the construction of heterocycles.[1] Such reactions generally involve the coupling of two alkynes with a heteroatom-containing substrate. For example, Co,[2] Ru,[3] and Ni[4] based systems catalyze cycloaddition reactions that yield pyrones, pyridones, pyrans, and pyridines. Any other combination of these coupling partners is rare.[5] We report that pyrimidine-diones can be prepared from the Ni-catalyzed cycloaddition of *one alkyne* and *two isocyanates*.

2. Results and discussion

We recently showed that the combination of Ni and IPr (or SIPr)[6] is an effective catalyst system for the cycloaddition of alkynes and isocyanates to afford pyridones in excellent yield.[4c] Included was the cycloaddition of 3-hexyne and phenyl isocyanate, which gave an excellent yield of tetraethylpyridone **2a** (entry 1, Table 1).[4c] During our investigations, we discovered that reactions run in excess of isocyanate led to the formation of a new heterocyclic product, pyrimidine-dione **1a**, in appreciable amounts (entry 2, Table 1).

A mechanism that diverges at a common intermediate and accounts for both pyridone and pyrimidine-dione products is shown in Scheme 1.[7] Initial oxidative coupling between

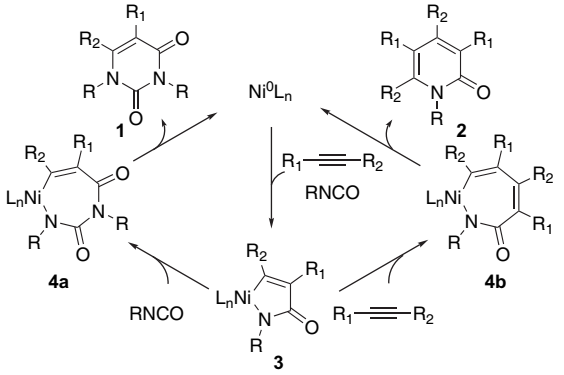
Table 1. Ni-catalyzed cycloaddition of alkynes and isocyanates



(1)

Entry	L	RNCO R	RNCO concn (M)	Alkyne R_1	Alkyne R_2	Alkyne concn (M)	% Alkyne conversion	1 (% Yield)	2 (% Yield)
1	IPr	Ph	0.2	Et	Et	0.1	100	**1a** (0)	**2a** (87)[a]
2	IPr	Ph	0.8	Et	Et	0.1	100	**1a** (30)[a]	**2a** (53)[a]
3	IPr	Ph	0.2	Ph	Ph	0.1	5	**1b** (0)[b]	**2b** (0)[b]
4	IPr	Ph	0.2	TMS	TMS	0.1	0	**1c** (0)[b]	**2c** (0)[b]
5	IPr	Ph	0.8	TMS	Me	0.1	100	**1d** (75)[a]	**2d** (0)[a]
6	None	Ph	0.2	TMS	Me	0.1	7	**1d** (0)[b]	**2d** (0)[b]

[a] Isolated yield.
[b] Determined by GC.



Scheme 1. Proposed mechanisms of the Ni-catalyzed cycloaddition.

* Corresponding author. Tel.: +1 801 581 7309; fax: +1 801 581 8433; e-mail: louie@chem.utah.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.119

an alkyne and the isocyanate leads to nickelacycle **3**. When isocyanate concentrations are high, subsequent reaction with isocyanate, rather than alkyne, occurs and yields pyrimidine-dione products. This mechanism suggests that an increase in steric bulk on alkyne substrates would promote selective insertion of isocyanate rather than alkyne. Indeed, although diphenyl acetylene and bis(trimethylsilyl) acetylene failed to react (entries 3 and 4, Table 1), 1-trimethylsilyl propyne gave excellent yield of the pyrimidine-dione (**1d**) without the need for excess isocyanate concentrations (entry 5). Interestingly, the same reactants afforded only pyridone **2d** when Ni/PEt_3 was used as the catalyst.[4e] Thus, the steric hindrance of the IPr ligand may help to encourage isocyanate insertion over the insertion of another hindered alkyne. No cycloaddition occurred when $Ni(COD)_2$ was used in the absence of IPr ligand (entry 6).

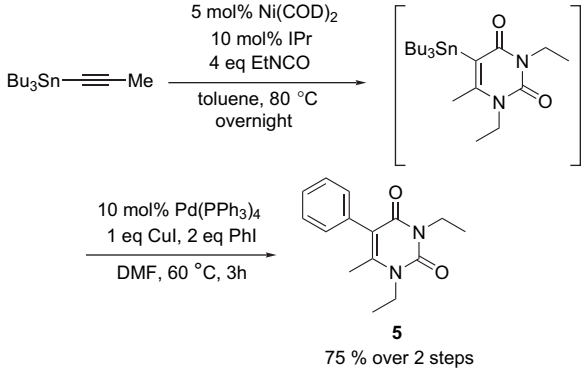
A variety of pyrimidine-diones were prepared via this procedure (Table 2). Pyrimidine-diones were obtained with aryl isocyanates although pyridone products were also observed in some cases (entries 2–4). Alkyl isocyanates were cleanly converted to the corresponding pyrimidine-dione (entries 5–7). Electron-withdrawing groups (such as $–CO_2Et$ and $–C_2H_3$) were also tolerated (entries 8, 9). Dialkyl-substituted acetylene such as 4,4-dimethyl-2-pentyne also worked well under the cyclization conditions to give the corresponding product in good yield (entry 10). Less sterically-encumbered alkynes such as 4-methyl-2-pentyne gave lower yields and selectivities (entry 11). A mixture of the pyrimidine-dione regioisomers and pyridone products were obtained (entry 11).

Tributyl(1-propynyl)tin cyclized to afford a pyrimidine-dione selectively (Scheme 2). Furthermore, exposure of the cycloaddition reaction mixture directly to standard Stille coupling conditions[8] resulted in the phenyl-substituted pyrimidine-dione **5** in 75% yield (Scheme 2). Thus, aryl pyrimidine-diones can be readily prepared through a two-step, one-pot reaction.

Table 2. Pyrimidine-diones prepared from Ni-catalyzed cycloaddition[a]

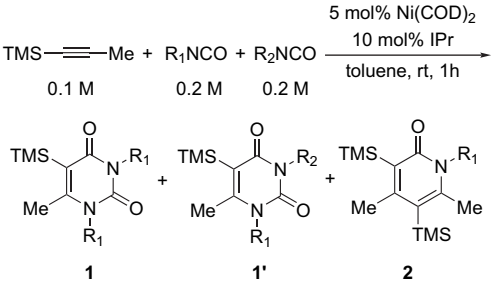
Entry	RNCO	Alkyne		Pyrimidine-dione **1** (% yield)[b]	Pyridone **2** (% yield)[b]
	R	R_1	R_2		
1	Ph	TMS	Me	**1d** (75)[c]	—
2	4-MeOPh	TMS	Me	**1e** (68)	**2e** (24)
3	3-MeOPh	TMS	Me	**1f** (49)	**2f** (24)
4	4-CF_3Ph	TMS	Me	**1g** (17)	**2g** (68)
5	Et	TMS	Me	**1h** (83)	—
6	Bn	TMS	Me	**1i** (72)[d]	—
7[e]	Cy	TMS	Me	**1j** (60)	—
8[f]	Cy	TMS	CO_2Et	**1k** (43)	—
9	Ph	TMS	C_2H_3	**1l** (38)[c]	**2l** (38)
10	Et	^{t}Bu	Me	**1m** (81)[d]	—
11	Ph	^{i}Pr	Me	**1n** (35)[g]	**2n** (18)

[a] Reaction conditions: 0.1 M diyne, 0.2 M isocyanate, 5 mol % $Ni(COD)_2$, 10 mol % IPr, toluene, rt.
[b] Isolated yields (average of two runs).
[c] Isocyanate (0.8 M) was used.
[d] Isocyanate (0.4 M) was used.
[e] Desilylated pyridone product was observed.
[f] Cyclotrimerized alkyne product (**3k**) was obtained in 45% yield.
[g] The other regioisomer (**1′n**) was also obtained in 14%.



Scheme 2. One-pot cycloaddition and Stille coupling.

Further insights into the mechanism of the cycloaddition were obtained through the competition reaction of 1-trimethylsilyl-1-propyne and two different isocyanates (Scheme 3). When 1-trimethylsilyl-1-propyne was exposed to equal concentrations of 4-CF_3PhNCO and 4-MeOPhNCO, a mixture of heterocyclic products was obtained (Table 3, entry 1). The product mixture included pyrimidine-dione **1g** (derived from the cycloaddition of only the electron-deficient isocyanate) as well as pyrimidine-dione **1′g** (derived from the cycloaddition of both isocyanates). Other pyrimidine-dione regioisomers were not observed. Similarly, when the same alkyne was subjected to equal mixtures of 4-MeOPhNCO and EtNCO, only two (out of the possible eight) pyrimidine-dione products were observed (entry 2). Only one pyridone was obtained in both competition reactions. Thus, the product distributions provide further evidence that hetero-oxidative coupling occurs (Scheme 1) and that nickelacycle **3** can react with either an alkyne or an isocyanate. The first step, oxidative coupling of the alkyne and an isocyanate, favors the more electron-deficient isocyanate (such as 4-CF_3PhNCO and 4-MeOPhNCO in entries 1 and 2, Table 3, respectively) and all observed heterocyclic products reflect this phenomenon. Nickelacycle **3** can insert either an alkyne or isocyanate to give pyridones or pyrimidine-diones, respectively.



Scheme 3. Cycloaddition with a mixture of isocyanates.

Table 3. Yields of pyrimidine-diones and pyridones

Entry	R_1	R_2	**1**	% Yield[a] **1′**	**2**
1	4-CF_3Ph	4-MeOPh	**1g** (11)	**1′g** (14)	**2g** (44)
2	4-MeOPh	Et	**1e** (28)	**1′e** (29)	**2e** (18)

[a] Isolated yields.

3. Conclusion

The combination of Ni and IPr catalyzes the cycloaddition of alkynes and isocyanates. When untethered alkynes that possess a large substituent are employed, coupling of two isocyanates and an alkyne affords pyrimidine-diones. Competition reactions suggest that initial hetero-oxidative coupling between an isocyanate and an alkyne occurs. Further application of this chemistry in the synthesis of other heterocycles is currently being investigated.

4. Experimental

4.1. General

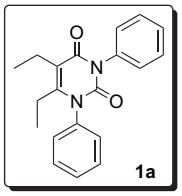
$Ni(COD)_2$ was purchased from Strem and used without further purification. 1,3-Bis(2,6-diisopropylphenyl)-imidazol-2-ylidene (IPr) was prepared according to literature procedure.[9] Phenyl isocyanate, ethyl isocyanate, benzyl isocyanate, 3-methoxyphenyl isocyanate, 4-methoxyphenyl isocyanate, α,α,α-trifluoro-*p*-tolyl isocyanate, cyclohexyl isocyanate, and butyl isocyanate were purchased from Aldrich, dried over phosphorous pentoxide, and degassed prior to use. 4-Methyl 2-pentyne (Aldrich), ethyl 3-(trimethylsilyl)propynoate (Aldrich), tributyl(1-propynyl)tin (Aldrich), and 4,4-dimethyl-2-pentyne (GFS) were purchased, dried over calcium hydride, and degassed prior to use. 1-Trimethylsilyl-pent-3-en-1-yne was prepared according to literature procedure.[10] ^1H and ^{13}C NMR spectra were recorded on a Varian VXL-300 spectrometer and a Varian VXR-500 spectrometer and referenced to residual protiated solvent (resonances downfield to the standard are reported as positive). All ^{13}C NMR spectra were proton decoupled. IR bands were measured as a thin film on a NaCl plate on a Bruker Tensor 27 FTIR spectrometer. The assignments of atom connectivity and spatial relationships are exclusively based on 2D NMR correlation (NOESY, $^1H/^{13}C$ HMBC, and $^1H/^{13}C$ HMQC) and 1D NOESY. Elemental analyses were performed at Midwest Microlab LLC., Indianapolis, IN.

4.2. General cycloaddition procedure of alkynes and isocyanates

A toluene solution of $Ni(COD)_2$ and IPr was prepared and allowed to equilibrate for at least 6 h.[4a] In a glove box, a solution of alkyne and isocyanate in toluene was added to an oven-dried vial equipped with a stir bar. To the stirring solution, a solution of $Ni(COD)_2$ and IPr was added and the reaction was stirred at room temperature for 1 h, unless otherwise stated. The mixture was then concentrated and purified by column chromatography with silica gel that was pre-treated with triethyl amine.

4.2.1. 5,6-Diethyl-1,3-diphenylpyrimidine-2,4(1*H*,3*H*)-dione (1a) and 3,4,5,6-tetraethyl-1-phenylpyridin-2(1*H*)-one (2a). The general procedure was used with 3-hexyne (28 mg, 0.34 mmol, 0.1 M), phenyl isocyanate (325 mg, 2.27 mmol, 0.8 M), $Ni(COD)_2$ (4.7 mg, 0.017 mmol, 5 mol %), IPr (13 mg, 0.034 mmol, 10 mol %), and 3.4 mL of toluene. The reaction mixture was purified first by column chromatography on silica gel (5:40:55 acetone/methylene chloride/hexane). Compound **1a** was further purified by column chromatography on silica gel (20% ethyl acetate/hexane then methylene chloride) to afford **1a** (33 mg, 30%) as a white solid. Compound **2a** was further purified by column chromatography on silica gel (10% acetone/methylene chloride) to afford **2a** (26 mg, 53%) as a white solid.[4c]

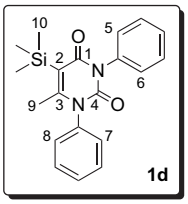
4.2.1.1. Analytical data for 1a.



^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.51–7.26 (m, 10H), 2.52 (q, 7.4 Hz, 2H), 2.37 (q, 7.4 Hz, 2H), 1.19 (t, 7.4 Hz, 3H), 1.03 (t, 7.4 Hz, 3H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$, ppm): δ 163.3, 152.5, 152.1, 137.5, 135.6, 129.7, 129.4, 129.3, 129.2, 128.6, 128.5, 113.6, 23.2, 19.9, 14.2, 13.3. IR ($CHCl_3$, cm^{-1}): 1707. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74, found: C, 74.88; H, 6.31; N, 8.69.

4.2.2. 6-Methyl-5-(trimethylsilyl)-1,3-diphenylpyrimidine-2,4(1*H*,3*H*)-dione (1d). The general procedure was used with 1-trimethylsilyl-1-propyne (35 mg, 0.31 mmol, 0.1 M), phenyl isocyanate (297 mg, 2.49 mmol, 0.8 M), $Ni(COD)_2$ (4.3 mg, 0.016 mmol, 5 mol %), IPr (12 mg, 0.032 mmol, 10 mol %), and 3.1 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (20% acetone/hexane then 10% ethyl acetate/hexane) to afford **1d** as a white solid (82 mg, 75%).

4.2.2.1. Analytical data for 1d.

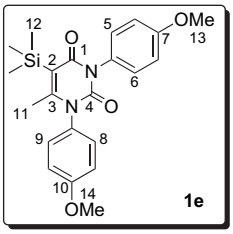


^1H NMR (300 MHz, CD_2Cl_2, ppm): δ 7.52–7.40 (m, 6H), 7.30–7.23 (m, 4H), 1.96 (s, 3H), 0.31 (s, 9H). ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm): δ 165.6, 157.3, 152.5, 138.5, 136.5, 130.2, 129.6, 129.5, 129.3, 129.1, 128.7, 108.4, 21.9, 1.9. HMBC cross-peaks: H9 and C2, C3; H10 and C2 and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for aromatic protons and H9. IR (CH_2Cl_2, cm^{-1}): 1710, 1652, 1581. Anal. Calcd for $C_{20}H_{22}N_2O_2Si$: C, 68.54; H, 6.33; N, 7.99, found: C, 68.49; H, 6.52; N, 7.87.

4.2.3. 1,3-Bis(4-methoxyphenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1e) and 1-(4-methoxyphenyl)-4,6-dimethyl-3,5-bis(trimethylsilyl)pyridin-2(1*H*)-one (2e). The general procedure was used with

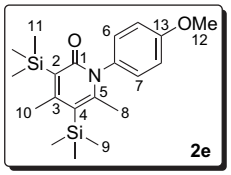
1-trimethylsilyl-1-propyne (35 mg, 0.31 mmol, 0.1 M), 4-methoxyphenyl isocyanate (93 mg, 0.62 mmol, 0.2 M), $Ni(COD)_2$ (4.3 mg, 0.016 mmol, 5 mol %), IPr (12 mg, 0.032 mmol, 10 mol %), and 3.1 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (10% ethyl acetate/hexane then 10% acetone/hexane) to afford **1e** (87 mg, 68%) and **2e** (14 mg, 24%) as white solids.

4.2.3.1. Analytical data for 1e.



^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.21–7.16 (m, 4H), 7.04–7.00 (m, 4H), 3.87 (s, 3H), 3.85 (s, 3H), 2.00 (s, 3H), 0.34 (s, 9H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$, ppm): δ 165.9, 160.4, 159.9, 157.8, 153.0, 131.1, 130.3, 130.0, 129.1, 115.3, 114.8, 108.2, 56.1, 56.0, 21.9, 1.9. HMBC cross-peaks: H11 and C2, C3; H12 and C2; H13 and C7; H14 and C10; and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for aromatic protons and H11. IR ($CHCl_3$, cm^{-1}): 1709, 1651. Anal. Calcd for $C_{22}H_{26}N_2O_4Si$: C, 64.36; H, 6.38; N, 6.82, found: C, 64.37; H, 6.41; N, 6.70.

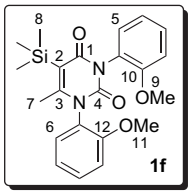
4.2.3.2. Analytical data for 2e.



^1H NMR (500 MHz, acetone, ppm): δ 7.08 (d, 8.8 Hz, 2H), 7.02 (d, 8.8 Hz, 2H), 3.86 (s, 3H), 2.40 (s, 3H), 2.06 (s, 3H), 0.38 (s, 9H), 0.28 (s, 9H). ^{13}C {^1H} NMR (125 MHz, acetone, ppm): δ 166.4, 162.8, 160.2, 153.2, 133.7, 130.4, 125.5, 115.4, 114.8, 55.9, 26.5, 24.1, 4.0, 2.3. HMBC cross-peaks: H8 and C4, C5; H9 and C4; H10 and C2, C3, C4; H11 and C2; H12 and C13; and other cross-peaks of aromatic protons and aromatic carbons. IR (CH_2Cl_2, cm^{-1}): 1629. HRMS (*m*/*z*): calcd for $C_{20}H_{31}NO_2Si$ (M^+) 373.1893, found 373.1880.

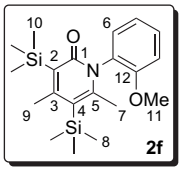
4.2.4. 1,3-Bis(3-methoxyphenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1f) and 1-(3-methoxyphenyl)-4,6-dimethyl-3,5-bis(trimethylsilyl)pyridin-2(1*H*)-one (2f). The general procedure was used with 1-trimethylsilyl-1-propyne (31 mg, 0.28 mmol, 0.1 M), 3-methoxyphenyl isocyanate (82 mg, 0.56 mmol, 0.2 M), $Ni(COD)_2$ (3.8 mg, 0.014 mmol, 5 mol %), IPr (11 mg, 0.028 mmol, 10 mol %), and 2.8 mL of toluene. The reaction mixture was purified first by column chromatography on silica gel (20% ethyl acetate/hexane). Compound **1f** was further purified by column chromatography on silica gel (methylene chloride) to afford **1f** as a white solid (56 mg, 49%). Compound **2f** was further purified by column chromatography on silica gel (1% acetone/methylene chloride) to afford **2f** as a white solid (12 mg, 24%).

4.2.4.1. Analytical data for 1f.



^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.42–7.33 (m, 2H), 7.01–6.81 (m, 6H), 3.83 (s, 3H), 3.80 (s, 3H), 2.05 (s, 3H), 0.36 (s, 9H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$, ppm): δ 165.2, 160.7, 160.4, 156.7, 152.0, 138.7, 136.4, 130.5, 130.0, 121.0, 120.7, 115.1, 114.7, 114.5, 114.1, 108.3, 55.6, 55.4, 21.4, 1.9. HMBC cross-peaks: H7 and C2, C3; H8 and C2; H9 and C10; H11 and C12; and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for aromatic protons and H7. IR ($CHCl_3$, cm^{-1}): 1710, 1651, 1603, 1582. Anal. Calcd for $C_{22}H_{26}N_2O_4Si$: C, 64.36; H, 6.38; N, 6.82, found: C, 64.20; H, 6.29; N, 6.68.

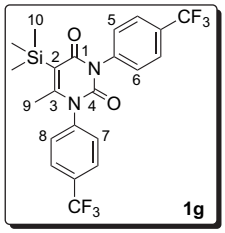
4.2.4.2. Analytical data for 2f.



^1H NMR (500 MHz, CD_2Cl_2, ppm): δ 7.44–7.41 (m, 1H); 7.00–6.98 (m, 1H), 6.76–6.69 (m, 2H), 3.85 (s, 3H), 2.41 (s, 3H), 2.07 (s, 3H), 0.41 (s, 9H), 0.33 (s, 9H). ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm): δ 166.1, 163.1, 161.2, 151.7, 141.9, 130.6, 125.7, 121.0, 115.2, 114.6, 114.2, 56.0, 26.7, 23.7, 4.0, 2.2. HMBC cross-peaks: H7 and C4, C5; H8 and C4; H9 and C2, C3, C4; H10 and C2; H11 and C12; and other cross-peaks of aromatic protons and aromatic carbons. IR (CH_2Cl_2, cm^{-1}): 1630, 1547. HRMS (*m*/*z*): calcd for $C_{20}H_{31}NO_2Si$ (M^+) 373.1893, found 373.1891.

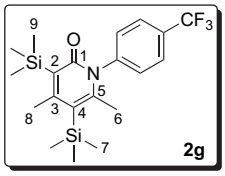
4.2.5. 1,3-Bis(4-(trifluoromethyl)phenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1g) and 1-(4-(trifluoromethyl)phenyl)-4,6-dimethyl-3,5-bis(trimethylsilyl)pyridin-2(1*H*)-one (2g). The general procedure was used with 1-trimethylsilyl-1-propyne (37 mg, 0.33 mmol, 0.1 M), α,α,α-trifluoro-*p*-tolyl isocyanate (123 mg, 0.66 mmol, 0.2 M), $Ni(COD)_2$ (4.5 mg, 0.016 mmol, 5 mol %), IPr (13 mg, 0.032 mmol, 10 mol %), and 3.3 mL of toluene. The reaction mixture was purified first by column chromatography on silica gel (5% ethyl acetate/hexane) to afford **2g** (46 mg, 68%) as a white solid. Compound **1g** was further purified by column chromatography on silica gel (10% acetone/hexane then 1:1 methylene chloride/hexane) to afford **1g** as a white solid (27 mg, 17%).

4.2.5.1. Analytical data for 1g.



^{1}H NMR (500 MHz, acetone, ppm): δ 7.91 (d, 8.3 Hz, 2H), 7.81 (d, 8.3 Hz, 2H), 7.75 (d, 8.3 Hz, 2H), 7.54 (d, 8.3 Hz, 2H), 2.08 (s, 3H), 0.33 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, acetone, ppm): δ 164.8, 156.9, 151.5, 142.0, 140.1, 130.61, (q, 32 Hz), 130.60, 130.2, 129.7 (q, 32 Hz), 126.8 (q, 3 Hz), 125.9 (q, 3 Hz), 124.5 (q, 271 Hz), 124.3 (q, 271 Hz), 107.5, 21.3, 1.21. HMBC cross-peaks: H9 and C2, C3; H10 and C2 and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for aromatic protons and H9. IR (CH_2Cl_2, cm^{-1}): 1712, 1657, 1586. HRMS (*m*/*z*): calcd for $C_{22}H_{20}N_2O_2SiF_6$ (M^+) 486.1198, found 486.1191.

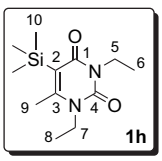
4.2.5.2. Analytical data for 2g.



^{1}H NMR (500 MHz, acetone, ppm): δ 7.87 (d, 8.3 Hz, 2H), 7.48 (d, 8.3 Hz, 2H), 2.43 (s, 3H), 2.08 (s, 3H), 0.40 (s, 9H), 0.29 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, acetone, ppm): δ 165.3, 162.8, 151.2, 144.3, 130.0–129.4 (m, 2C), 126.6 (m), 125.0, 124.5 (q, 271 Hz), 114.7, 25.9, 23.4, 3.2, 1.5. HMBC cross-peaks: H6 and C4, C5; H7 and C4; H8 and C2, C3; H9 and C2; and other cross-peaks of aromatic protons and aromatic carbons. IR (CH_2Cl_2, cm^{-1}): 1630, 1488. Anal. Calcd for $C_{20}H_{28}NOSi_2F_3$: C, 58.36; H, 6.86; N, 3.40, found: C, 58.74; H, 6.52; N, 3.51.

4.2.6. 1,3-Diethyl-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1h). The general procedure was used with 1-trimethylsilyl-1-propyne (51 mg, 0.45 mmol, 0.1 M), ethyl isocyanate (65 mg, 0.90 mmol, 0.2 M), Ni(COD)$_2$ (6.2 mg, 0.023 mmol, 5 mol %), IPr (17 mg, 0.046 mmol, 10 mol %), and 4.5 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (5% acetone/methylene chloride) to afford **1h** as a colorless oil (96 mg, 83%).

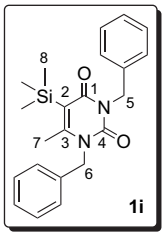
4.2.6.1. Analytical data for 1h.



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 3.94 (m, 4H), 2.31 (s, 3H), 1.27 (t, 7.0 Hz, 3H), 1.19 (t, 7.0 Hz, 3H), 0.30 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 165.0, 155.5, 151.9, 107.9, 40.4, 36.5, 19.5, 14.3, 13.0, 2.1. HMBC cross-peaks: H5 and C1, C4, C6; H6 and C5; H7 and C3, C4, C8; H8 and C7; H9 and C2, C3; H10 and C2. IR ($CHCl_3$, cm^{-1}): 1694, 1635, 1584. HRMS (*m*/*z*): calcd for $C_{12}H_{22}SiN_2O_2$ (M^+) 254.1451, found 254.1448.

4.2.7. 1,3-Dibenzyl-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1i). The general procedure was used with 1-trimethylsilyl-1-propyne (35 mg, 0.31 mmol, 0.1 M), benzyl isocyanate (166 mg, 1.24 mmol, 0.4 M), Ni(COD)$_2$ (8.6 mg, 0.032 mmol, 10 mol %), IPr (24 mg, 0.064 mmol, 20 mol %), and 3.1 mL of toluene. After stirring overnight at 80 °C, the reaction mixture was purified by column chromatography on silica gel (10% ethyl acetate/hexane) to afford **1i** as a white solid (85 mg, 72%).

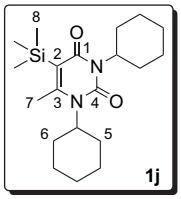
4.2.7.1. Analytical data for 1i.



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.51–7.15 (m, 10H), 5.19–5.18 (m, 4H), 2.25 (s, 3H), 0.33 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 165.0, 156.3, 153.0, 137.5, 136.7, 129.2, 129.1, 128.5, 127.8, 127.6, 126.3, 108.5, 48.4, 44.7, 20.0, 2.0. HMBC cross-peaks: H5 and C1, C4; H6 and C3, C4; H7 and C2, C3; H8 and C2 and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for H7 and H6 and aromatic protons. IR ($CHCl_3$, cm^{-1}): 1695, 1638, 1584. Anal. Calcd for $C_{22}H_{26}N_2O_2Si$: C, 69.80; H, 6.92; N, 7.40, found: C, 69.84; H, 6.91; N, 7.47.

4.2.8. 1,3-Dicyclohexyl-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1j). To a solution of Ni(COD)$_2$ (4.7 mg, 0.016 mmol, 5 mol %) and IPr (13 mg, 0.032 mmol, 10 mol %) in 1.4 mL of toluene was added dropwise a solution of 1-trimethylsilyl-1-propyne (38 mg, 0.34 mmol, 0.1 M), and cyclohexyl isocyanate (85 mg, 0.90 mmol, 0.2 M) in 2.0 mL of toluene. After stirring at room temperature for 1 h, the reaction mixture was purified by column chromatography on silica gel (2:3 methylene chloride/hexane) to afford **1j** as a white solid (74 mg, 60%). Some decomposition product of a pyridone product was also observed by ^{1}H NMR.

4.2.8.1. Analytical data for 1j.

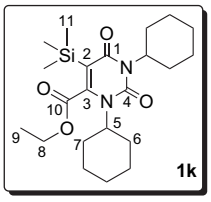


^{1}H NMR (500 MHz, CD_2Cl_2, ppm): δ 4.67–4.62 (m, 1H), 3.83 (m, 1H), 2.54–2.47 (m, 2H), 2.38–2.29 (m, 2H), 2.25 (s, 3H), 2.85–1.77 (m, 4H), 1.65–1.37 (m, 6H), 1.36–1.53 (m, 6H), 0.26 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, CD_2Cl_2,

ppm): δ 166.2, 156.4, 152.0, 108.4, 60.2, 29.8, 29.1, 27.1, 27.0, 26.1, 25.8, 20.9, 2.3. HMBC cross-peaks: H7 and C2, C3; H8 and C2, and other cross-peaks of cyclohexyl protons and cyclohexyl carbons. NOE was observed for cyclohexyl protons and H7. IR (CH_2Cl_2, cm^{-1}): 1697, 1637, 1582; Anal. Calcd for $C_{20}H_{34}N_2O_2Si$: C, 66.25; H, 9.45; N, 7.73, found: C, 66.36; H, 9.18; N, 7.60.

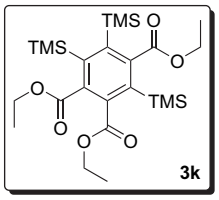
4.2.9. Triethyl 1,3-dicyclohexyl-1,2,3,6-tetrahydro-5-(trimethylsilyl)-2,6-dioxopyrimidine-4-carboxylate (1k) and triethyl 3,5,6-tris(trimethylsilyl)benzene-1,2,4-tricarboxylate (3k). The general procedure was used with ethyl 3-(trimethylsilyl)propynoate (46 mg, 0.27 mmol, 0.1 M), cyclohexyl isocyanate (68 mg, 0.54 mmol, 0.2 M), $Ni(COD)_2$ (3.7 mg, 0.013 mmol, 5 mol %), IPr (10 mg, 0.026 mmol, 10 mol %), and 2.7 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (5% ethyl acetate/hexane) to afford **1k** (49 mg, 43%) and **3k** as white solids (21 mg, 45%).

4.2.9.1. Analytical data for 1k.



^1H NMR (500 MHz, $CDCl_3$, ppm): δ 4.71–4.67 (m, 1H), 4.38–4.36 (m, 2H), 3.24–3.20 (m, 1H), 2.52–2.45 (m, 2H), 2.40–2.32 (m, 2H), 1.87–1.77 (m, 6H), 1.60–1.59 (m, 4H), 1.40–1.11 (m, 9H), 0.19 (s, 9H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$, ppm): δ 166.0, 163.5, 150.8, 150.3, 107.0, 64.5, 62.7, 54.3, 29.4, 28.7, 26.7, 26.5, 25.4, 25.1, 14.0, −0.3. HMBC cross-peaks: H5 and C3, C4, C6, C7; H8 and C9, C10; H9 and C8; H11 and C2; other cross-peaks of cyclohexyl protons and cyclohexyl carbons. IR ($CHCl_3$, cm^{-1}): 1742, 1704, 1647, 1590. Anal. Calcd for $C_{22}H_{36}N_2O_4Si$: C, 62.82; H, 8.63; N, 6.66, found: C, 62.99; H, 8.46; N, 6.68.

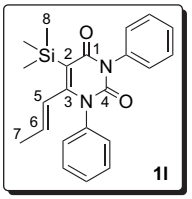
4.2.9.2. Analytical data for 3k.



^1H NMR (500 MHz, CD_2Cl_2, ppm): δ 4.33–4.21 (m, 6H), 1.39–1.29 (m, 9H), 0.36 (s, 9H), 0.33 (s, 9H), 0.26 (s, 9H). ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm): δ 170.7, 170.0, 153.5, 151.4, 147.7, 139.4, 139.2, 139.0, 62.3 (m, 3C), 14.3 (m, 3C), 4.4, 3.9, 1.8. IR (CH_2Cl_2, cm^{-1}): 1726. HRMS (*m*/*z*): calcd for $C_{24}H_{42}O_6Si_3$ (M^+) 510.2289, found 510.2291.

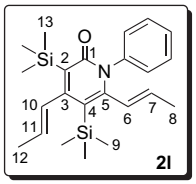
4.2.10. 5-(Trimethylsilyl)-1,3-diphenyl-6-((*Z*)-prop-1-enyl)pyrimidine-2,4(1*H*,3*H*)-dione (1l) and 3,5-bis(trimethylsilyl)-1-phenyl-4,6-di((*Z*)-prop-1-enyl)pyridin-2(1*H*)-one (2l). The general procedure was used with 1-trimethylsilyl-pent-3-en-1-yne (34 mg, 0.24 mmol, 0.1 M), phenyl isocyanate (234 mg, 1.96 mmol, 0.2 M), $Ni(COD)_2$ (3.4 mg, 0.012 mmol, 5 mol %), IPr (9 mg, 0.024 mmol, 10 mol %), and 2.4 mL of toluene. The reaction mixture was purified first by column chromatography on silica gel (methylene chloride) to afford **2l** (18 mg, 38%) as a white solid. **1l** was further purified by column chromatography on silica gel (5% ethyl acetate/hexane) to afford **1l** (35 mg, 38%) as a white solid.

4.2.10.1. Analytical data for 1l.



^1H NMR (500 MHz, CD_2Cl_2, ppm): δ 7.52–7.43 (m, 6H), 7.30–7.23 (m, 4H), 5.88–5.80 (m, 1H), 5.61 (dd, 1.5 and 15.7 Hz, 1H), 1.64 (dd, 1.5 and 7.0 Hz, 3H), 0.25 (s, 9H). ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm): δ 166.3, 158.1, 152.3, 138.4, 137.0, 136.5, 130.0, 129.8, 129.6, 129.3, 129.2, 128.8, 126.3, 108.8, 18.4, 2.1. HMBC cross-peaks: H5 and C2, C3, C6, C7; H6 and C3, C5, C7; H7 and C5, C6; H8 and C2; and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for aromatic protons and H5. IR (CH_2Cl_2, cm^{-1}): 1711, 1653, 1569. Anal. Calcd for $C_{22}H_{24}N_2O_2Si$: C, 70.18; H, 6.42; N, 7.44, found: C, 70.15; H, 6.51; N, 7.41.

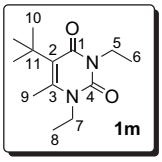
4.2.10.2. Analytical data for 2l.



^1H NMR (300 MHz, CD_2Cl_2, ppm): δ 7.47–7.34 (m, 3H), 7.09–7.06 (m, 2H), 6.59 (dq, 1.8 and 15.8 Hz, 1H), 5.77–5.55 (m, 3H), 1.84 (d, 6.6 Hz, 3H), 1.58 (d, 6.6 Hz, 3H), 0.22 (s, 9H), 0.15 (s, 9H). ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm): δ 165.8, 164.9, 154.8, 140.2, 135.7, 135.3, 130.7, 129.7, 129.5, 128.4, 125.8, 114.8, 18.5, 18.3, 4.3, 2.0. HMBC cross-peaks: H8 and C6, C7; H9 and C4; H10 and C2, C3, C4, C11, C12; H12 and C10, C11; H13 and C2; and other cross-peaks of olefinic/aromatic protons and olefinic/aromatic carbons. IR (CH_2Cl_2, cm^{-1}): 1632. Anal. Calcd for $C_{23}H_{33}NOSi_2$: C, 69.81; H, 8.41; N, 3.54, found: C, 69.41; H, 8.25; N, 3.36.

4.2.11. 5-Tert-butyl-1,3-diethyl-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (1m). The general procedure was used with 4,4-dimethyl-2-pentyne (34 mg, 0.35 mmol, 0.1 M), ethyl isocyanate (100 mg, 1.42 mmol, 0.4 M), $Ni(COD)_2$ (9.7 mg, 0.035 mmol, 10 mol %), IPr (27 mg, 0.070 mmol, 20 mol %), and 3.5 mL of toluene. After stirring at 80 °C overnight, the reaction mixture was purified by column chromatography on silica gel (20% ethyl acetate/hexane) to afford **1m** as a yellow solid (68 mg, 81%).

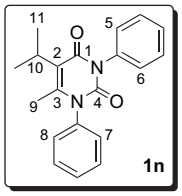
4.2.11.1. Analytical data for 1m.



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.01–3.92 (m, 4H), 2.39 (s, 3H), 1.44 (s, 9H), 1.28 (t, 7.0 Hz, 3H), 1.21 (t, 7.0 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 162.2, 151.1, 146.5, 120.2, 40.4, 36.9, 35.7, 32.0, 18.9, 14.5, 13.1. HMBC cross-peaks: H5 and C1, C4, C6; H6 and C5; H7 and C3, C4, C8; H8 and C7; H9 and C2, C3; H10 and C2, C11. IR ($CHCl_3$, cm^{-1}): 1693, 1644, 1587. Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.75, found: C, 65.69; H, 9.49; N, 11.64.

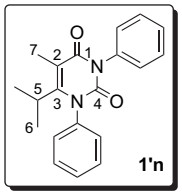
4.2.12. 5-Isopropyl-6-methyl-1,3-diphenylpyrimidine-2,4(1*H*,3*H*)-dione (1n), 6-isopropyl-5-methyl-1,3-diphenylpyrimidine-2,4(1*H*,3*H*)-dione (1′n), and 3,5-diisopropyl-4,6-dimethyl-1-phenylpyridin-2(1*H*)-one (2n). The general procedure was used with 4-methyl 2-pentyne (53 mg, 0.65 mmol, 0.1 M), phenyl isocyanate (154 mg, 1.30 mmol, 0.2 M), $Ni(COD)_2$ (8.9 mg, 0.032 mmol, 5 mol %), IPr (25 mg, 0.064 mmol, 10 mol %), and 6.5 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (15–25% ethyl acetate/hexane) to afford **1n** (72 mg, 35%) and **1′n** (29 mg, 14%) as white solids. A fraction was also determined to be the impure pyridone **2n** (16 mg, 18%).

4.2.12.1. Analytical data for dione 1n.



^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.50–7.26 (m, 10H), 3.08–3.05 (sept, 7.0 Hz, 1H), 1.96 (s, 3H), 1.35 (d, 7.0 Hz, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 162.3, 151.8, 146.9, 138.0, 135.5, 129.9, 129.3, 129.2, 129.0, 128.6, 128.5, 117.2, 28.5, 20.7, 18.1. HMBC cross-peaks: H9 and C2, C3; H10 and C1, C2, C3, C11; H11 and C10; and other cross-peaks of aromatic protons and aromatic carbons. IR ($CHCl_3$, cm^{-1}): 1708, 1656. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74, found: C, 75.0; H, 6.36; N, 8.73.

4.2.12.2. Analytical data for dione 1′n.



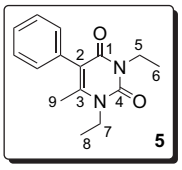
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.54–7.35 (m, 6H), 7.29–7.26 (m, 4H), 2.74 (sept, 7.1 Hz, 1H), 2.17 (s, 3H), 1.26 (d, 7.1 Hz, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 164.2, 155.7, 152.1, 138.3, 135.6, 130.0, 129.3, 129.2, 128.9, 128.6, 128.4, 108.2, 30.9, 19.7, 12.0. HMBC cross-peaks: H5 and C2, C3; H6 and C3, C5; H7 and C1, C2, C3; and other cross-peaks of aromatic protons and aromatic carbons. IR ($CHCl_3$, cm^{-1}): 1709, 1654. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74, found: C, 74.70; H, 6.46; N, 8.43.

4.2.12.3. Analytical data for 2n (impure). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.51–7.36 (3H); 7.18–7.14 (2H), 3.36–3.23 (m, 2H), 2.29 (s, 3H), 1.95 (s, 3H); 1.35–1.31 (m, 12H).

4.2.13. One-pot cycloaddition followed by Stille coupling: 1,3-diethyl-6-methyl-5-phenylpyrimidine-2,4(1*H*,3*H*)-dione. The general procedure for cycloaddition was used with tributyl(1-propynyl)tin (134 mg, 0.41 mmol, 0.1 M), ethyl isocyanate (116 mg, 1.64 mmol, 0.4 M), $Ni(COD)_2$ (5.6 mg, 0.020 mmol, 5 mol %), IPr (16 mg, 0.040 mmol, 10 mol %), and 4.1 mL of toluene. After stirring at 80 °C overnight, the solvent was removed.

In a glove box, to a Schlenk flask equipped with a stir bar, $Pd(PPh_3)_4$ (47 mg, 0.041 mmol, 10 mol %), phenyl iodide (166 mg, 0.082 mmol, 200 mol %), *N*,*N*-dimethyl formamide (4.1 mL), and copper iodide (78 mg, 0.41 mmol, 100 mol %) were successively added. After stirring for 1 min, the residue from the cycloaddition mixture was added. The flask was then taken out of the glove box and stirred under N_2 at 60 °C for 3 h. The reaction mixture was cooled down, diluted with Et_2O, and washed with water. The aqueous layer was further extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate/hexane then 3% methanol/methylene chloride) to afford **5** as a white solid (79 mg, 75%).

4.2.13.1. Analytical data for 5.

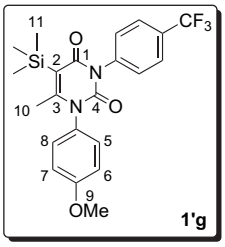


^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.42–7.33 (m, 3H), 7.22–7.20 (m, 2H), 4.08–3.99 (m, 4H), 2.17 (s, 3H), 1.35 (t, 7.1 Hz, 3H), 1.26 (t, 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 162.0, 151.4, 147.9, 134.5, 131.0, 128.5, 127.8, 114.6, 40.8, 37.0, 17.5, 14.3, 13.0. HMBC cross-peaks: H5 and C1, C4; H6 and C5; H7 and C3, C4, C8; H9 and C2, C3; and other cross-peaks of aromatic protons and aromatic carbons. IR ($CHCl_3$, cm^{-1}): 1696, 1644. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84, found: C, 69.44; H, 6.83; N, 10.76.

4.2.14. 3-(4-(Trifluoromethyl)phenyl)-1-(4-methoxyphenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1g), 1,3-bis(4-(trifluoromethyl)phenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1′g), and 1-(4-(trifluoromethyl)phenyl)-4,6-dimethyl-3,5-bis(trimethylsilyl)pyridin-2(1*H*)-one (2g). The general procedure was used with 1-trimethylsilyl-1-propyne (32 mg,

0.29 mmol, 0.1 M), α,α,α-trifluoro-*p*-tolyl isocyanate (107 mg, 0.58 mmol, 0.2 M), 4-methoxyphenyl isocyanate (85 mg, 0.58 mmol, 0.2 M), $Ni(COD)_2$ (3.9 mg, 0.014 mmol, 5 mol %), IPr (11 mg, 0.028 mmol, 10 mol %), and 2.9 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (4:6 hexane/methylene chloride then 10% ethyl acetate/hexane) to give **1g** (15 mg, 11%), **1′g** (18 mg, 14%), and **2g** (26 mg, 44%) as white solids.

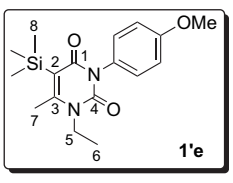
4.2.14.1. Analytical data for 1′g.



^1H NMR (500 MHz, acetone, ppm): δ 7.80 (d, 8.8 Hz, 2H), 7.52 (d, 8.8 Hz, 2H), 7.34 (d, 8.8 Hz, 2H), 7.05 (d, 8.8 Hz, 2H), 3.85 (s, 3H), 2.05 (s, 3H), 0.30 (s, 9H). ^{13}C {^1H} NMR (125 MHz, acetone, ppm): δ 164.9, 160.1, 158.4, 151.8, 140.4, 130.9, 130.2, 129.6 (q, 33 Hz), 125.9, 124.6 (q, 271 Hz), 114.7, 106.7, 55.2, 21.2, 1.2. HMBC cross-peaks: H5 and C2, C3; H6 and C2; and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for H5/H8 and H6, H7, H10; H6/H7 and H9. IR (CH_2Cl_2, cm^{-1}): 1710, 1654. HRMS (*m/z*): calcd for $C_{22}H_{23}N_2O_3SiF_3$ (M^+) 448.1430, found 448.1426.

4.2.15. 1,3-Bis(4-methoxyphenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1e), 1-(4-methoxyphenyl)-4,6-dimethyl-3,5-bis(trimethylsilyl)pyridin-2(1*H*)-one (2e), and 1-ethyl-3-(4-methoxyphenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1′e). The general procedure was used with 1-trimethylsilyl-1-propyne (33 mg, 0.29 mmol, 0.1 M), 4-methoxyphenyl isocyanate (88 mg, 0.58 mmol, 0.2 M), ethyl isocyanate (42 mg, 0.58 mmol, 0.2 M), $Ni(COD)_2$ (3.9 mg, 0.014 mmol, 5 mol %), IPr (11 mg, 0.028 mmol, 10 mol %), and 2.9 mL of toluene. The reaction mixture was purified by column chromatography on silica gel with 10–25% ethyl acetate/hexane to obtain **2e** (10 mg, 18%), then with 10% acetone/hexane to obtain **1′e** (28 mg, 29%), and then with 5% acetone/methylene chloride to obtain **1e** (34 mg, 28%).

4.2.15.1. Analytical data for 1′e.



^1H NMR (300 MHz, CD_2Cl_2, ppm): δ 7.09 (d, 9.0 Hz, 2H), 6.98 (d, 9.0 Hz, 2H), 3.97 (q, 7.1 Hz, 2H), 3.84 (s, 3H), 2.39 (s, 3H), 1.29 (t, 7.1 Hz, 3H), 0.30 (s, 9H). ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm): δ 165.6, 159.8, 157.1, 152.7, 130.0, 129.4, 114.8, 108.3, 56.0, 40.9, 20.1, 14.4, 2.1. HMBC cross-peaks: H5 and C3, C4, C6; H7 and C2, C3; H8 and C2. IR (CH_2Cl_2, cm^{-1}): 1700, 1642, 1580. Anal. Calcd for $C_{17}H_{24}N_2O_3Si$: C, 61.41; H, 7.28; N, 8.43, found: C, 61.46; H, 7.23; N, 8.34.

Acknowledgements

We gratefully acknowledge the University of Utah, Merck, NSF (Career Award), the Camille-Dreyfus Foundation, and the NIGMS for support of this research.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.03.119.

References and notes

1. For a review, see: (a) Varela, J. A.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787; (b) Louie, J. *Curr. Org. Chem.* **2005**, *9*, 605.
2. (a) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786; (b) Hong, P.; Yamazaki, H. *Tetrahedron Lett.* **1977**, 1333; (c) Naiman, A.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 708; (d) Vollhardt, K. P. C. *Angew. Chem.* **1984**, *96*, 525.
3. (a) Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001**, *3*, 2117; (b) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6189; (c) Varela, J. A.; Castedo, L.; Saa, C. *J. Org. Chem.* **2003**, *68*, 8595.
4. (a) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188; (b) Tekavec, T. N.; Arif, A. M.; Louie, J. *Tetrahedron* **2004**, *60*, 7431; (c) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438; (d) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030; (e) Duong, H. A.; Louie, J. *J. Organomet. Chem.* **2005**, *690*, 5098; (f) Tekavec, T. N.; Louie, J. *Org. Lett.* **2005**, *7*, 4037; (g) Hoberg, H.; Oster, B. W. *Synthesis* **1982**, 324.
5. Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1983**, *252*, 359.
6. IPr=1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene; SIPr=1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazolin-2-ylidene.
7. Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1982**, *234*, C37.
8. (a) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600; (b) Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993**, *58*, 408.
9. (a) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523; (b) Bohm, V. P. W.; Weskammp, T.; Gstottmayr, W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602.
10. Bialy, L.; Waldmann, H. *Chem.—Eur. J.* **2004**, *10*, 2759.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7560–7566
Tetrahedron

Alkyne hydrosilylation catalyzed by nickel complexes of *N*-heterocyclic carbenes

Mani Raj Chaulagain, Gireesh M. Mahandru and John Montgomery*

Department of Chemistry, University of Michigan, 930 N. University Ave. Ann Arbor, MI 48109-1055, USA

Received 7 December 2005; revised 1 March 2006; accepted 1 March 2006
Available online 19 June 2006

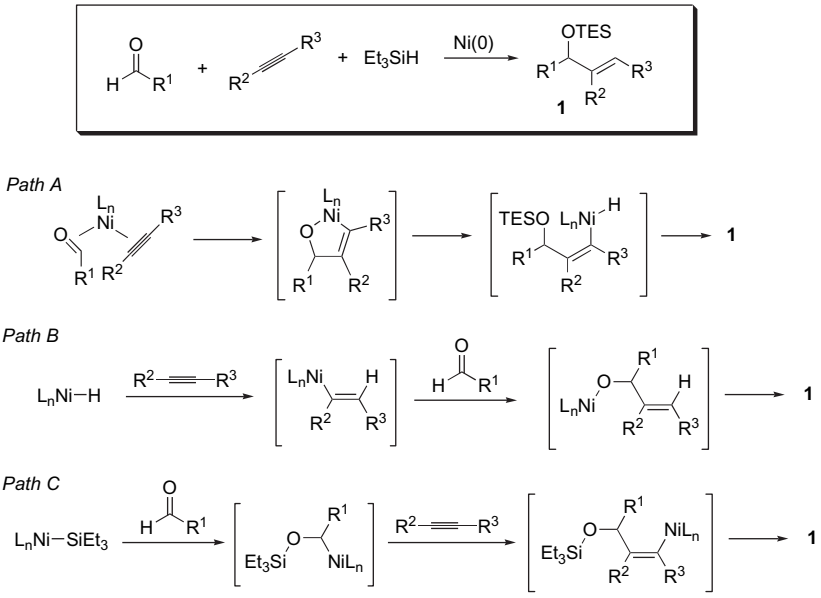
Dedicated to Professor Günther Wilke for his seminal contributions to the field of organonickel chemistry

Abstract—The addition of triethylsilane, triphenylsilane, and triethoxysilane to a variety of alkynes is catalyzed by complexes derived from $Ni(COD)_2$ and *N*-heterocyclic carbenes. A description of the reaction scope and potential mechanistic implications in nickel-catalyzed additions of aldehydes, alkynes, and silanes is provided.

1. Introduction

Vinyl silanes are useful building blocks for a variety of synthetic processes including electrophilic substitutions[1] and palladium-catalyzed cross-couplings.[2] While many methods for preparation of vinyl silanes exist, catalytic additions of silanes to alkynes are perhaps the most powerful.[3] In metal-catalyzed alkyne hydrosilylations, regioselectivity and stereoselectivity issues are both important to control. Regioselectivity is typically highly dependent upon structure of the catalyst, alkyne, and silane, and either cis- or trans-additions may be observed.

We have become interested in the nickel-catalyzed hydrosilylation of alkynes not only because of the synthetic interest in vinyl silanes, but also because we felt that understanding the addition chemistry of silanes and alkynes could potentially shed light on mechanistic issues in the three-component



Scheme 1.

* Corresponding author. Tel.: +1 734 764 4424; fax: +1 734 763 1106; e-mail: jmontg@umich.edu

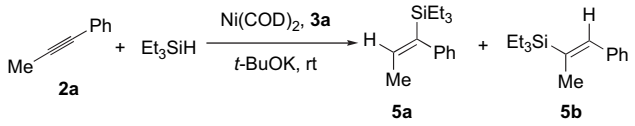
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.120

coupling of aldehydes, alkynes, and silanes to produce protected allylic alcohols **1** being developed in our laboratory.[4] Prior studies in our lab involving crossover experiments had demonstrated that the mechanism of aldehyde/alkyne/silane couplings catalyzed by nickel phosphine complexes proceeded by a different mechanism than the corresponding couplings involving nickel complexes of *N*-heterocyclic carbenes.[4c,5] The related system developed by Jamison involving triethylborane-mediated aldehyde/alkyne couplings poses similar questions, and evidence for a ligand-based mechanistic switch in alkene-directed couplings of 1,5-enynes was provided.[6] A multitude of mechanistic possibilities for these processes exist, including the formation of metallacycles from Ni(0), aldehydes, and alkynes (path A, Scheme 1), hydrometallation of alkynes followed by aldehyde insertion (path B), and silylmetallation of aldehydes followed by alkyne insertion (path C).[7] In path B, the trialkylsilyl may or may not be directly coordinated to nickel throughout the sequence shown. Similarly, in path C, a hydride may or may not be directly coordinated to nickel throughout the sequence shown. Variation in the active catalyst structure and oxidation state leads to several possibilities within each of these three pathways. Given these mechanistic complexities, we envisioned that understanding the reactivity patterns of simple alkyne hydrosilylations could be useful in further understanding the corresponding three-component couplings with aldehydes.

2. Results

The catalyst derived from $Ni(COD)_2$ and tributylphosphine is ineffective in promoting the hydrosilylation of either alkynes or aldehydes with triethylsilane under conditions that are effective in three-component couplings of alkynes, aldehydes, and triethylsilane.[8] This observation was an important feature that led us to propose the metallacycle-based mechanism in the first reports of the nickel-catalyzed reductive coupling of alkynes and aldehydes.[4a,e] The catalyst derived from $Ni(COD)_2$ and *N*-heterocyclic carbenes, however, are effective in alkyne hydrosilylations.[9] Direct treatment of 1-phenyl-1-propyne and triethylsilane in THF with the catalyst derived from $Ni(COD)_2$, *t*-butoxide, and imidazolium salt **3a** provided a 6:1 mixture of adducts derived from the 2:1 coupling of the alkyne and silane in 50% yield (Scheme 2).[10] The major isomer of the 2:1 coupling was determined to be structure **4**. In order to suppress incorporation of the second alkyne, the above experiment was repeated with syringe drive addition of the alkyne, and product **5**, derived from 1:1 coupling of the alkyne and silane, was obtained (Scheme 2). A brief study of solvent effects illustrated that toluene, ether, and *t*-butanol were also effective solvents although yields were highest in THF (Table 1). Only cis addition products were observed, and the regioisomer **5a** was the sole product except for one instance in which **5b** was observed in low yield.

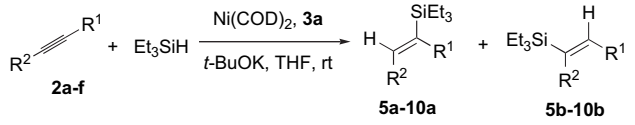
Table 1



Entry	Solvent	Combined yield (%)	**5a**:**5b** Ratio
1	THF	74	>95:5
2	Toluene	56	89:11
3	Ether	49	>95:5
4	*t*-BuOH	37	>95:5

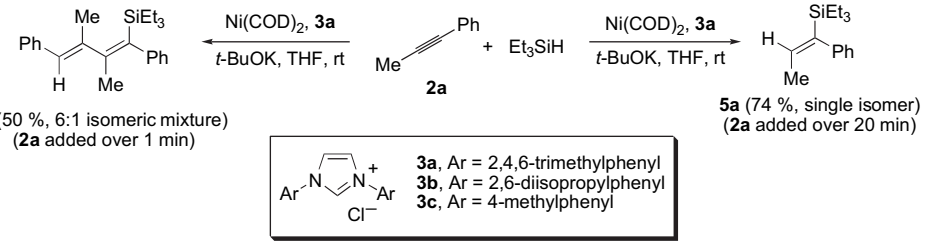
A short study of the range of alkynes tolerated was carried out (Table 2). Hydrosilylation of symmetrical internal alkynes **2b** and **2c** proceeded cleanly to afford products **6** and **7**, respectively, and unsymmetrical alkynes **2a** and **2d**–**2f** underwent efficient couplings with varying degrees of regioselection. As noted above, couplings of phenylpropyne **2a** were completely selective, whereas the regioselectivity with internal doubly aliphatic substituted alkynes **2d** and **2e** varied according to the steric difference in alkyne substituents. Interestingly, terminal alkyne **2f** was an effective participant, but with relatively poor regioselection. In all cases other than activated aromatic alkynes, the silicon unit was preferentially installed at the least hindered alkyne carbon.

Table 2



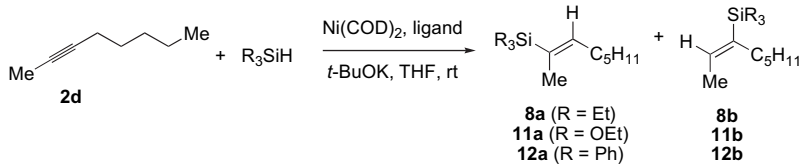
Alkyne	R^1	R^2	Product (% yield)	**a**:**b** Ratio
2a	Ph	Me	**5** (74)	>95:5
2b	*n*-Propyl	*n*-Propyl	**6** (87)	—
2c	Ph	Ph	**7** (92)	—
2d	Me	*n*-Pentyl	**8** (99)	75:25
2e	Me	*t*-Bu	**9** (74)	>95:5
2f	H	*n*-Hexyl	**10** (80)	67:33

Considering the poor regioselection with alkyne **2d**, we examined the impact of varying ligand and silane structures with this alkyne (Table 3). Whereas 3:1 selectivity was noted



Scheme 2.

Table 3



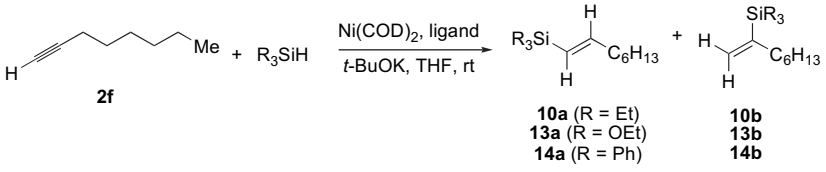
Entry	Ligand	R_3SiH	Product (% yield)	**a**:**b** Ratio
1	**3a**	Et_3SiH	**8** (99)	75:25
2	**3b**	Et_3SiH	**8** (99)	90:10
3	**3c**	Et_3SiH	**8** (75)	67:33
4	**3a**	$(EtO)_3SiH$	**11** (71)	60:40
5	**3a**	Ph_3SiH	**12** (53)	76:24

with **3a**, reactions with more hindered ligand derived from **3b** proceeded in near quantitative yield with very good regioselection (Table 3, entry 2). With smaller *p*-tolyl carbene derived from **3c**, regioselectivity worsened to 2:1 in diminishing yield (Table 3, entry 3). In varying the silane structure, we found with alkyne **2d** that the regioselectivity was only minimally impacted. Triethylsilane and triphenylsilane afforded nearly identical regioselectivities with the carbene derived from **3a**, whereas triethoxysilane participated with lower regioselectivity and yield (Table 3, entries 4–5). Thus, with internal alkynes possessing aliphatic substituents, ligand structure provides the best strategy for controlling regioselection.

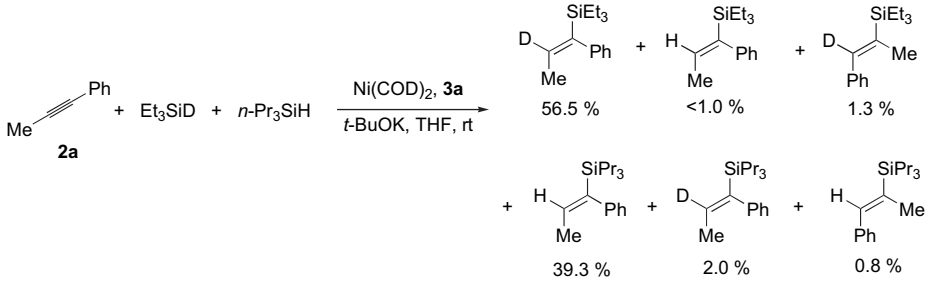
With terminal alkyne **2f**, however, silane structure displayed an enormous impact (Table 4). Whereas reactions with the ligand derived from **3a** afforded a 2:1 ratio of products **10a/10b** with triethylsilane, the corresponding reaction with triphenylsilane afforded the terminal silane **14a** with 7:1 regioselection. In contrast, the coupling of alkyne **2f**, triethoxysilane, and the ligand derived from **3a** favored the internal silane isomer **13b** in 3:1 regioselection. Coupling of **2f** and triphenylsilane with the ligand derived from **3b** afforded improved regioselectivity (relative to reactions with **3a**) in favor of **14a**, whereas the coupling of **2f** and triethoxysilane with the ligand derived from **3b** provided the reversed regioselectivity (relative to reactions with **3a**) in favor of **13a**. Surprisingly, the ligand from **3b** was not effective in couplings of **2f** and triethylsilane. Thus, variation of the silane structure provides a good handle for controlling regioselection in hydrosilylations of terminal alkynes, but the impact of ligand variation is highly substrate dependent.

Given the utility of a crossover study in illustrating the mechanistic differences between phosphine and *N*-heterocyclic catalyst systems in three-component alkyne, aldehyde, and silane additions,[4c] we examined the crossover reaction of 1-phenyl-1-propyne **2a** with 3.0 equiv each of Et_3SiD and Pr_3SiH in the presence of the catalyst derived from **3a** (Scheme 3). In this experiment, only a small amount

Table 4



Entry	Ligand	R_3SiH	Product (% yield)	**a**:**b** Ratio
1	**3a**	Et_3SiH	**10** (80)	67:33
2	**3a**	Ph_3SiH	**14** (76)	89:11
3	**3a**	$(EtO)_3SiH$	**13** (72)	25:75
4	**3b**	Ph_3SiH	**14** (63)	>95:5
5	**3b**	$(EtO)_3SiH$	**13** (70)	83:17

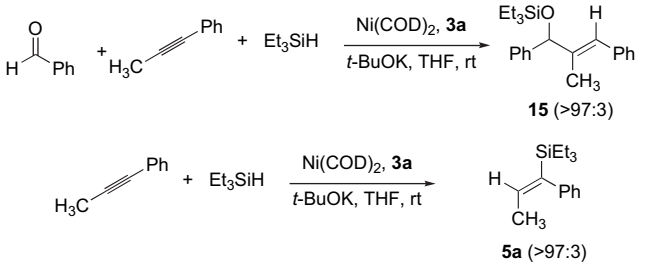


Scheme 3.

(<2%) of crossover products were observed, illustrating that the R_3Si and H units in the product are largely derived from a single molecule of trialkylsilane. Control experiments illustrated that Et_3SiD and Pr_3SiH underwent addition at similar rates.

3. Discussion

Several points from the above study are potentially relevant in analyzing the mechanism of three-component nickel-catalyzed couplings of aldehydes, alkynes, and silanes. In particular, the regioselection of phenylpropyne, benzaldehyde, and triethylsilane with Ni(0)/IMes ligand from **3a** is very clean for the production of isomer **15** (Scheme 4). In contrast, the identical reaction carried out in the absence of benzaldehyde cleanly affords compound **5a**. Notably, the position of introduction of the silane-derived hydrogen atom is reversed in these two reactions. This suggests that hydrometallation of the alkyne (path B, Scheme 1) is not a common first step in both reactions unless coordination of the aldehyde has a dramatic and an unexpected effect on the regioselection.



Scheme 4.

Additionally, since crossover was not observed to an appreciable extent in either the two component couplings of alkynes and silanes or the three-component couplings of alkynes, silanes, and aldehydes, then both reactions involve mechanisms in which the silicon and hydrogen atoms of the Si–H bond are simultaneously delivered to a metal complex.

4. Conclusions

In summary, an efficient method for the hydrosilylation of alkynes involving Ni(0) complexes of *N*-heterocyclic carbenes has been developed. The scope of both alkynes and silanes tolerated is broad, and regioselectivities often depend on the structure of the alkyne, silane, and *N*-heterocyclic carbene ligand. The impact of these variables on the regioselectivity in alkyne hydrosilylations was compared to the regioselectivity of three-component couplings of alkynes, aldehydes, and silanes, and the comparison suggests that alkyne hydrometallation is not a common first step in both groups of reactions.

5. Experimental

5.1. General

All reagents were used as received unless otherwise noted. All alkynes were freshly distilled prior to use. $Ni(COD)_2$, imidazolium salts, and potassium *tert*-butoxide were stored and weighed in an inert atmosphere glove box. All reactions were conducted in flame-dried glassware under argon or nitrogen.

5.2. General procedure for $Ni(COD)_2$/carbene catalyzed hydrosilylation of alkynes

$Ni(COD)_2$ (28 mg, 0.10 mmol), ligand (0.10 mmol), and potassium *tert*-butoxide (11 mg, 0.10 mmol) were weighed together in a 15-mL flask in a glove box. Solvent (8 mL) was added to the mixture under an inert atmosphere at rt. The solution was stirred for 10 min and silane (2.0 mmol) was added dropwise to the stirring mixture and allowed to stir for 10 min. Alkyne (1.00 mmol) was dissolved in 2 mL solvent under nitrogen and was added to the mixture over 20 min via syringe drive. Reactions were usually complete after the addition of alkyne was complete. Solvents were removed in vacuo and the crude product was purified by column chromatography (SiO_2, hexanes, unless otherwise noted) and the vinyl silanes were isolated as colorless oils unless otherwise noted.

5.2.1. ((1*Z*,3*E*)-2,3-Dimethyl-1,4-diphenylbuta-1,3-dienyl)triethylsilane (4). Following the general procedure (except that alkyne was added over 1 min), $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethylsilane (0.32 mL, 2.0 mmol), and 1-phenylpropyne (116 mg, 1.00 mmol) were employed to give 6:1 mixture of regioisomers of **4** (176 mg, 0.50 mmol, 50%), after column chromatography (SiO_2, hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.42 (m, 8H), 6.97–7.10 (m, 2H), 6.54 (q, J=1.2 Hz, 0.14H, minor regioisomer), 6.44 (m, 0.86H, major regioisomer), 2.06 (d, J=1.6 Hz, 2.59H, major regioisomer), 1.77 (d, J=1.2 Hz, 0.41H, minor regioisomer), 1.71 (s, 0.42H, minor regioisomer), 1.65 (s, 2.58H, major regioisomer), 0.99 (t, J=8.0 Hz, 1.26H, minor regioisomer), 0.89 (t, J=8.0 Hz, 7.74H, major regioisomer), 0.73 (q, J=8.0 Hz, 0.84H, minor regioisomer), 0.51 (q, J=8.0 Hz, 5.16H, major regioisomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 145.3, 142.2, 137.8, 136.2, 129.2, 129.0, 128.47, 128.9, 128.3, 128.2, 128.1, 127.9, 126.3, 126.0, 124.8, 21.0, 20.7, 18.1, 17.5, 7.9, 7.8, 4.6, 4.3; HRMS (EI) *m/z* calculated for $C_{24}H_{32}Si$ 348.2273, found 348.2267 (M^+).

Compound **4** was converted into the previously reported compound ((1*E*,3*E*)-2,3-dimethylbuta-1,3-diene-1,4-diyl)-dibenzene by stirring with $(n\text{-}Bu)_4NF$ for 24 h at rt. Spectroscopic data were identical to that previously reported.[11]

5.2.2. (*E*)-Triethyl(1-phenylprop-1-enyl)silane (5). Following the general procedure, $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethylsilane (0.32 mL, 2.0 mmol), and 1-phenyl-1-propyne (116 mg, 1.00 mmol) were employed to give (*E*)-triethyl(1-phenylprop-1-enyl)silane (171 mg, 0.74 mmol, 74%, single regioisomer), after column chromatography (SiO_2, hexanes) as a colorless oil. Spectroscopic data were identical to that previously reported.[12]

5.2.3. (*E*)-Triethyl(oct-4-en-4-yl)silane (6). Following the general procedure, $Ni(COD)_2$ (28 mg, 0.10 mmol),

imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethylsilane (0.32 mL, 2.0 mmol), and oct-4-yne (110 mg, 1.00 mmol) were employed to give (*E*)-triethyl(oct-4-en-4-yl)silane (197 mg, 0.87 mmol, 87%), after column chromatography (SiO_2, hexanes) as a colorless oil. Spectroscopic data were identical to that previously reported.[13]

5.2.4. (*E*)-(1,2-Diphenylvinyl)triethylsilane (7). Following the general procedure, $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethylsilane (0.32 mL, 2.0 mmol), and 1,2-diphenylethyne (178 mg, 1.00 mmol) were employed to give (*E*)-(1,2-diphenylvinyl)triethylsilane (269 mg, 0.92 mmol, 92%), after column chromatography (SiO_2, hexanes) as a colorless solid. Spectroscopic data were identical to that previously reported.[12]

5.2.5. (*E*)-Triethyl(oct-2-en-2-yl)silane (8a) and (*E*)-triethyl(oct-2-en-3-yl)silane (8b) with 3a. Following the general procedure, $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethylsilane (0.32 mL, 2.0 mmol), and oct-2-yne (110 mg, 1.00 mmol) were employed to give a mixture of (*E*)-triethyl(oct-2-en-2-yl)silane and (*E*)-triethyl(oct-2-en-3-yl)silane (225 mg, 0.99 mmol, 99%, 3:1 mixture of regioisomer), after column chromatography (SiO_2, hexanes) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (q, J=6.5 Hz, 0.25H, minor isomer), 5.71 (tq, J=6.5, 1.5 Hz, 0.75H, major regioisomer), 2.07–2.15 (m, 2H), 1.71 (d, J=6.5 Hz, 0.75H, minor regioisomer), 1.66 (m, 2.25H), 1.26–1.43 (m, 6H), 0.89–0.93 (m, 12H), 0.47–0.62 (m, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 141.4, 139.0, 135.5, 132.6, 32.5, 31.8, 29.8, 29.6, 29.2, 28.5, 22.8, 15.1, 14.3, 14.2, 7.6, 6.9, 6.6, 3.3, 2.8; IR (film, cm^{-1}) 2972, 2910, 2860, 1434, 1425, 1332, 1254, 1064, 965, 912, 697, 617; HRMS (EI) *m*/*z* calculated for $C_{14}H_{30}Si$ 226.2116, found 226.2113(M^+).

5.2.6. (*E*)-Triethyl(oct-2-en-2-yl)silane (8a) and (*E*)-triethyl(oct-2-en-3-yl)silane (8b) with 3b. Following the general procedure, $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3b** (43 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethylsilane (0.32 mL, 2.0 mmol), and oct-2-yne (110 mg, 1.00 mmol) were employed to give a mixture of (*E*)-triethyl(oct-2-en-2-yl)silane and (*E*)-triethyl(oct-2-en-3-yl)silane (225 mg, 0.99 mmol, 99%, 9:1 mixture of regioisomer), after column chromatography (SiO_2, hexanes) as a colorless oil.

5.2.7. (*E*)-(4,4-Dimethylpent-2-en-2-yl)triethyl silane (9a). Following the general procedure, $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethylsilane (0.32 mL, 2.0 mmol), and 4,4-dimethylpent-2-yne (96 mg, 1.00 mmol) were employed to give (*E*)-(4,4-dimethylpent-2-en-2-yl)-triethyl silane (157 mg, 0.74 mmol, 74%, single regioisomer), after column chromatography (SiO_2, hexanes) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.58 (q, J=1.6 Hz, 1H), 1.74 (d, J=1.6 Hz, 3H), 1.09 (s, 9H), 0.87 (t, J=8.0 Hz, 9H), 0.51 (q, J=8.0 Hz, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 150.1, 131.2, 34.4, 30.7, 15.7, 7.3, 2.5; IR (film, cm^{-1}) 2954, 2910, 2875, 1463, 1362, 1074, 1007, 729; HRMS (EI) *m*/*z* calculated for $C_{13}H_{28}Si$ 212.1954, found 212.1968(M^+).

5.2.8. (*E*)-Triethyl(oct-1-enyl)silane (10a) and triethyl-(oct-1-en-2-yl)silane (10b). Following the general procedure, $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethylsilane (0.32 mL, 2.0 mmol), and oct-1-yne (110 mg, 1.00 mmol) were employed to give a mixture of (*E*)-triethyl(oct-1-enyl)silane and triethyl(oct-1-en-2-yl)silane (181 mg, 0.80 mmol, 80%, 2:1 mixture of regioisomers), after column chromatography (SiO_2, hexanes) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 (dt, J=18.4, 6.4 Hz, 0.66H, major isomer), 5.58–5.61 (m, 0.34H, minor isomer), 5.50 (dt, J=18.4, 1.6 Hz, 0.66H, major isomer), 5.25 (dt, J=2.7, 0.8 Hz, 0.34H, minor isomer), 2.02–2.12 (m, 2H), 1.22–1.40 (m, 8H), 0.82–0.94 (m, 12H), 0.48–0.60 (m, 6H). Data for **10a** matches those previously reported.[14]

5.2.9. (*E*)-Triethoxy(oct-2-en-2-yl)silane (11a) and (*E*)-triethoxy(oct-2-en-3-yl)silane (11b). Following the general procedure, $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethoxysilane (0.37 mL, 2.0 mmol), and oct-1-yne (110 mg, 1.00 mmol) were employed to give a 1.5:1 mixture of (*E*)-triethoxy(oct-2-en-3-yl)silane and (*E*)-triethoxy(oct-2-en-2-yl)silane, after column chromatography (SiO_2, hexanes) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (qt, J=6.4, 0.8 Hz, 0.4H, minor regioisomer), 6.06 (tq, J=6.8, 1.6 Hz, 0.6H, major regioisomer), 3.72–3.80 (m, 6H), 2.03–2.11 (m, 2H), 1.63–1.67 (m, 3H), 1.22–1.38 (m, 6H), 1.13–2.0 (m, 9H), 0.81–0.86 (m, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 146.0, 139.6, 134.0, 126.9, 58.3, 58.2, 32.0, 31.5, 29.0, 28.6, 28.5, 28.2, 22.4, 18.1, 14.1, 14.0, 13.9; IR (film, cm^{-1}) 2973, 2927, 1620, 1442, 1389, 1167, 1104, 1081, 957, 779; HRMS (EI) *m*/*z* calculated for $C_{14}H_{30}O_3Si$ 274.1964, found 274.1759(M^+).

5.2.10. (*E*)-Oct-2-en-2-yltriphenylsilane (12a) and (*E*)-oct-2-en-3-yltriphenylsilane (12b). Following the general procedure (with the modification in silane stoichiometry), $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triphenylsilane (260 mg, 1.0 mmol in 2 mL THF), and oct-2-yne (110 mg, 1.00 mmol) were employed to give a 3.2:1 mixture of regioisomers (*E*)-oct-2-en-2-yltriphenylsilane and (*E*)-oct-2-en-3-yltriphenylsilane (196 mg, 0.53 mmol, 53%), after column chromatography (SiO_2, hexanes) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.58 (m, 6H), 7.32–7.42 (m, 9H), 6.05 (q, J=6.4 Hz, 0.24H, minor regioisomer), 5.94 (tq, J=6.8, 1.6 Hz, 0.76H, major regioisomer), 2.16–2.25 (m, 2H), 1.81–1.84 (m, 0.24H, minor regioisomer), 1.79 (d, J=6.4 Hz, 0.76H, major regioisomer), 1.24–1.42 (m, 4H), 1.05–1.11 (m, 2H), 0.88 (t, J=6.8 Hz, 2.27H, major regioisomer), 0.72 (t, J=6.8 Hz, 0.73H, minor regioisomer); ^{13}C (125 MHz, $CDCl_3$) δ 147.3, 141.0, 136.3, 136.2, 134.9, 134.5, 129.9, 129.5, 129.2, 127.7, 127.6, 32.0, 31.6, 29.9, 29.1, 28.8, 28.7, 22.5, 16.1, 14.8, 14.1, 13.9; IR (film, cm^{-1}) 3068, 2955, 2927, 2856, 1613, 1428, 1188, 1108, 741, 512; HRMS (EI) *m*/*z* calculated for $C_{26}H_{30}Si$ 370.2116, found 370.2120(M^+).

5.2.11. (*E*)-Triethoxy(oct-1-enyl)silane (13a) and triethoxy(oct-1-en-2-yl)silane (13b) with 3a. Following the general procedure, $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethoxysilane (0.37 mL, 2.0 mmol), and oct-1-yne (110 mg, 1.00 mmol) were employed to give a 3:1 mixture of regioisomers triethoxy(oct-1-en-2-yl)silane and (*E*)-triethoxy(oct-1-enyl)silane (196 mg, 0.72 mmol, 72%), after column chromatography (SiO_2, ethyl acetate/hexanes, 1:19) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (dt, J=18.8, 6.4 Hz, 0.25H, minor regioisomer), 5.65–5.68 (m, 0.75H, major regioisomer), 5.56–5.59 (m, 0.75H, major regioisomer), 5.36 (dt, J=18.8, 1.6 Hz, minor regioisomer), 3.77 (q, J=7.2 Hz, 6H), 2.06–2.12 (m, 2H), 1.32–1.44 (m, 2H), 1.21–1.27 (m, 6H), 1.18 (t, J=7.2 Hz, 9H), 0.80–0.86 (m, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 154.0, 143.7, 128.9, 118.6, 58.3, 36.5, 35.9, 31.7, 31.6, 29.0, 28.7, 28.6, 28.1, 22.6, 22.5, 18.2, 18.1, 14.0, 13.9; IR (film, cm^{-1}) 2925.8, 1389.5, 1074.7, 956.2, 734.4; HRMS (EI) *m*/*z* calculated for $C_{14}H_{30}O_3Si$ 274.1964, found 274.1963(M^+).

5.2.12. (*E*)-Triethoxy(oct-1-enyl)silane (13a) and triethoxy(oct-1-en-2-yl)silane (13b) with 3b. Following the general procedure, $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3b** (43 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triethoxysilane (0.37 mL, 2.0 mmol), and oct-1-yne (110 mg, 1.00 mmol) were employed to give a 1:5 mixture of regioisomers triethoxy(oct-1-en-2-yl)silane and (*E*)-triethoxy(oct-1-enyl)silane (192 mg, 0.70 mmol, 70%, single regioisomer), after column chromatography (SiO_2, ethyl acetate/hexanes, 1:19) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (dt, J=18.8, 6.4 Hz, 0.83H, major regioisomer), 5.64–5.67 (m, 0.17H, minor regioisomer), 5.55–5.58 (m, 0.17H, minor regioisomer), 5.35 (dt, J=18.8, 1.6 Hz, 0.83H, major regioisomer), 3.77 (m, 6H), 2.06–2.13 (m, 2H), 1.30–1.40 (m, 2H), 1.12–1.28 (m, 15H), 0.80–0.86 (m, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 154.0, 143.7, 118.6, 59.0, 58.3, 36.5, 31.7, 31.6, 28.7, 28.1, 22.6, 22.5, 18.2, 18.1, 14.0, 13.9; IR (film, cm^{-1}) 2925.8, 1389.5, 1074.7, 956.2, 734.4; HRMS (EI) *m*/*z* calculated for $C_{14}H_{30}O_3Si$ 274.1964, found 274.1963(M^+).

5.2.13. (*E*)-Oct-1-enyltriphenylsilane (14a) and oct-1-en-2-yltriphenylsilane (14b). Following the general procedure (with the modification in silane stoichiometry), $Ni(COD)_2$ (28 mg, 0.10 mmol), imidazolium salt, **3a** (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), triphenylsilane (260 mg, 1.0 mmol in 2 mL THF), and oct-1-yne (110 mg, 1.00 mmol) were employed to give a 8:1 mixture of regioisomers (*E*)-oct-1-enyltriphenylsilane and oct-1-en-2-yltriphenylsilane (280 mg, 0.74 mmol, 74%), after column chromatography (SiO_2, hexanes) as a colorless solid (mp 53–55 °C). ^1H NMR (400 MHz, C_6D_6) δ 7.58–7.66 (m, 6H), 7.10–7.14 (m, 9H), 6.25 (dt, J=18.4, 5.6 Hz, 0.89H, major isomer), 6.19 (d, J=18.8 Hz, 0.89H, major isomer), 5.93–5.96 (m, 0.11H, minor isomer), 5.64–5.66 (d, J=2.8 Hz, 0.11H, minor isomer), 2.26 (t, J=7.8 Hz, 0.22H, minor regioisomer), 2.00–2.08 (m, 1.78H, major regioisomer), 1.20–1.34 (m, 8H), 0.72–0.84 (m, 3H); ^{13}C (125 MHz, C_6D_6) δ 153.7, 136.3, 136.0, 135.1, 129.3, 127.8, 123.6, 36.9, 31.5, 28.8, 28.4, 22.5, 13.8; IR (film, cm^{-1}) 3068, 2926, 2855, 1615, 1465, 1428, 1187, 1110, 998, 784, 737; HRMS (EI) *m*/*z* calculated for $C_{26}H_{30}Si$ 370.2117, found 370.2103(M^+).

5.3. Crossover reaction

$Ni(COD)_2$ (3 mg, 0.01 mmol), ligand, **3a** (4 mg, 0.01 mmol), and *t*-BuOK (1 mg, 0.01 mmol) were weighed in glove box and 1.5 mL THF was added to the mixture under argon. The dark green solution obtained was stirred for 10 min at rt. Triethylsilane-*d* (48 μL, 0.30 mmol) and tripropylsilane (56 μL, 0.30 mmol) were added simultaneously and stirred for 10 more minutes. Alkyne (12 mg, 0.10 mmol) was dissolved in 0.5 mL THF under argon and was added to the reaction mixture over 20 min via syringe drive. The progress of the reaction was monitored in 10 and 20 min in GCMS.

5.3.1. Analysis of the crossover experiment. Pure samples of products derived from Et_3SiH (MW 232), Et_3SiD (MW 233), and Pr_3SiH (MW 274) were independently prepared and GCMS analysis was performed. Based on the similarity of the molecular ion regions of the Et_3SiH and Et_3SiD-derived product, the molecular ion region of the Pr_3SiD-derived product was assumed to appear as the molecular ion region of the Pr_3SiH-derived product, shifted by one mass unit. Relative peak heights in the molecular ion region of the spectra of each pure compound were normalized, with a value of 1 assigned to the base peak.

In the crude product of an experiment that employed 1 equiv each of Et_3SiD and Pr_3SiH, the ratio of Et_3Si products to Pr_3Si products was determined by GC. From the crude GCMS, the relative intensity of the 232 and 233 products were normalized, with the value of 1 assigned to the base peak. The ratio of the Et_3Si-(H) product to Et_3Si-(D) product was determined as follows:

$$\frac{\text{intensity of 232 peak in crossover experiment}}{\text{intensity of 233 peak in crossover experiment}} = \frac{[X]\times[\text{rel height of 232 peak in pure } Et_3Si\text{-(H) product}] + [Y]\times[\text{rel height of 232 peak in pure } Et_3Si\text{-(D) product}]}{[X]\times[\text{rel height of 233 peak in pure } Et_3Si\text{-(H) product}] + [Y]\times[\text{rel height of 233 peak in pure } Et_3Si\text{-(D) product}]}$$

$X = 1/100\times$relative % of Et_3Si-(H) product

$Y = 1/100\times$relative % of Et_3Si-(D) product $= 1-X$

In the above equation, after substitution of $[1-X]$ for $[Y]$, the experimental values were inserted and the equation was solved for $[X]$. The ratio of Pr_3Si-(H) product to the

Pr_3Si-(D) products was determined in a similar fashion. Merging the GC ratios of Et_3Si products to Pr_3Si products with the data calculated from the above equation, an overall ratio of the six products were obtained.

Acknowledgements

We thank the National Institutes of Health (GM57014) for support of this research. Beth Knapp-Reed and Kanicha Sa-ei are thanked for helpful discussions.

References and notes

1. (a) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57; (b) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.
2. (a) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845; (b) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.
3. For a comprehensive overview of hydrosilylations of alkynes, see: (a) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, *6*, 853; For representative additional recent methods, see: (b) Maifeld, S. V.; Tran, M. N.; Lee, D. *Tetrahedron Lett.* **2005**, *46*, 105; (c) Takahashi, T.; Bao, F.; Gao, G.; Ogasawara, M. *Org. Lett.* **2003**, *5*, 3479; (d) Kawanami, Y.; Sonoda, Y.; Mori, T.; Yamamoto, K. *Org. Lett.* **2002**, *4*, 2825.
4. (a) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098; (b) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950; (c) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698; (d) Knapp-Reed, B.; Mahandru, G. M.; Montgomery, J. *J. Am. Chem. Soc.* **2005**, *127*, 13156; (e) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065.
5. For other three-component couplings involving aldehydes, silanes, and nickel catalysts with *N*-heterocyclic carbene ligands, see: (a) Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510; (b) Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* **2004**, *6*, 1131; (c) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 7320; (d) Ng, S.-S.; Jamison, T. F. *Tetrahedron* **2005**, *61*, 11405.
6. Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342.
7. For a review, see: Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890.
8. For examples of nickel-catalyzed hydrosilylations that employ phosphine ligands under conditions different from those employed in our three-component couplings, see: (a) Lappert, M. F.; Nile, T. A.; Takahashi, S. *J. Organomet. Chem.* **1974**, *72*, 425; (b) Tillack, A.; Pulst, S.; Baumann, W.; Baudisch, H.; Kortus, K.; Rosenthal, U. *J. Organomet. Chem.* **1997**, *532*, 117.
9. For preparation and characterization of nickel complexes of *N*-heterocyclic carbenes, see: Arduengo, A. J.; Gamper, S. F.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1994**, *116*, 4391.
10. (a) For examples of 2:1 couplings of alkynes and silanes, see: Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539 and references therein; (b) For related nickel-catalyzed silaborative dimerization of alkynes, see: Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **1998**, *17*, 5233; (c) For palladium-catalyzed 2:1 couplings of alkynes and silanes, see: Kawanami, Y.; Yamamoto, K. *Synlett* **1995**, 1232.
11. Yang, L.; Liu, R. S. H.; Wendt, N. L.; Liu, J. *J. Am. Chem. Soc.* **2005**, *127*, 9378.
12. Chauhan, M.; Hauck, B. J.; Keller, L. P.; Boudjouk, P. *J. Organomet. Chem.* **2002**, *645*, 1.
13. Cornish, A. J.; Lappert, M. F. *J. Organomet. Chem.* **1984**, *271*, 153.
14. Takeuchi, R.; Nitta, S.; Watanabe, D. *J. Org. Chem.* **1995**, *60*, 3045.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 7567–7576

Arylcyanation of alkynes catalyzed by nickel

Yoshiaki Nakao,* Shinichi Oda, Akira Yada and Tamejiro Hiyama*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan

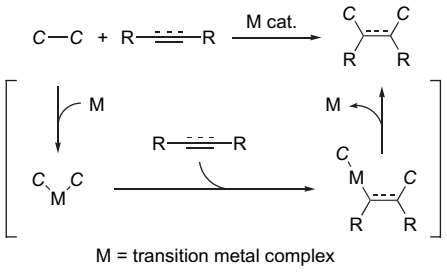
Received 19 November 2005; revised 28 February 2006; accepted 28 February 2006
Available online 21 June 2006

Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry

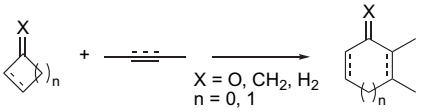
Abstract—A nickel catalyst prepared from $Ni(cod)_2$ and PMe_3 is found to effect arylcyanation reaction of alkynes, namely, cleavage of a C–CN bond of an aryl cyanide followed by addition of each fragment across an alkyne. A wide range of functional groups in aryl cyanides tolerated the catalysis, giving variously functionalized β-arylalkenenitriles stereoselectively.

1. Introduction

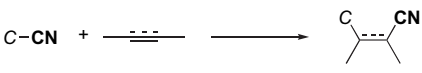
Transition metal-catalyzed cleavage of C–C single bonds followed by addition of the resulting two fragments across unsaturated bonds allows simultaneous formation of two C–C bonds without forming by-products and thus should be of great synthetic potential (Scheme 1). The catalysis may be initiated by oxidative addition of a C–C bond followed by insertion of an unsaturated bond into the resulting C–M bond and reductive elimination to complete the catalytic cycle. However, the initiation is not necessarily feasible due to a directionally and sterically constrained C–C σ-bond having a high bond dissociation energy (~85 kcal/mol).[1] Accordingly, successful catalytic processes reported so far have been limited to those involving activation of strained C–C bonds in such small rings as methylenecyclopropanes,[2] cyclopropenones,[3] cyclobutanes,[4] cyclobutenones,[5] and cyclobutanones (Eq. 1).[6] On the other hand, C–CN bonds that are very common and ubiquitous in many organic molecules have also been found cleavable upon treatment with certain transition metal complexes, in spite of its higher bond dissociation energies (>100 kcal/mol), owing presumably to cyano groups that have affinity to metals and electron-withdrawing nature.[7,8] Indeed, nitriles coordinate to transition metals either in an η^1-fashion or η^2-fashion (Scheme 2).[9] In particular, η^2-coordination is known to further trigger the activation of a C–CN bond via oxidative addition (path A) or via formation of silylisonitrile complexes when a Lewis acidic silyl ligand is located on a metal (path B). A few seminal reports of catalytic reactions utilizing these elemental reactions are available.[10] We envisioned that the oxidative addition of C–CN bonds (path A in Scheme 2) would constitute an initiation step of the catalysis shown in Scheme 1 to achieve addition reaction of nitriles across unsaturated bonds (Eq. 2). Although an addition reaction of benzoyl cyanide across arylacetylenes was recorded some years ago, the suggested mechanism involves acylation of terminal alkynes followed by hydrocyanation of the resulting alkynyl ketones and isomerization, making the reaction scope extensively limited.[11] Very recently, cyanoformate esters are found to add across norbornene and norbornadiene.[12] Herein, we report details of the addition reaction of aryl cyanides across alkynes to give various β-aryl-substituted alkenenitriles.[13]



Scheme 1. Metal-catalyzed cleavage of C–C σ-bonds followed by insertion of unsaturated bonds.



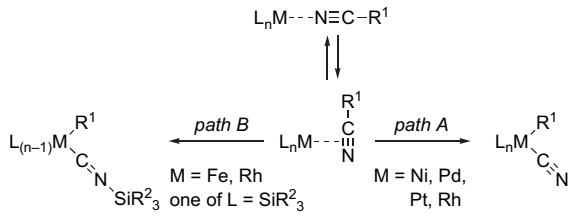
(1)



(2)

Keywords: Nickel; C–C bond activation; Nitrile; Alkyne.
* Corresponding authors. Tel.: +81 75 383 2443; fax: +81 75 383 2445 (Y.N.); tel.: +81 75 383 2446; fax: +81 75 383 2445 (T.H.); e-mail addresses: nakao@npc05.kuic.kyoto-u.ac.jp; thiyama@npc05.kuic.kyoto-u.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.086

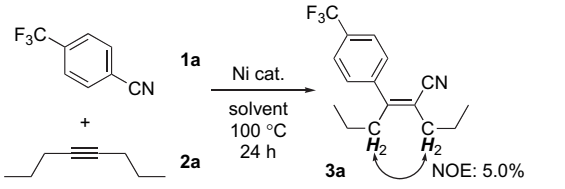


Scheme 2. Activation of C–CN bonds by transition metal complexes.

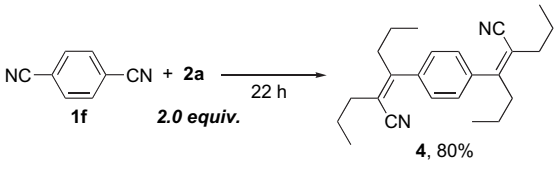
2. Results and discussion

To bring our working hypothesis to reality, we first screened catalysts and solvents effective for an equimolar reaction of 4-(trifluoromethyl)benzonitrile (**1a**) with 4-octyne (**2a**) (Eq. 3 and Table 1). Of the catalysts examined, we found that a combination of $Ni(cod)_2$ with PMe_3 (2.0 equiv to Ni) was the optimum to give expected (*Z*)-3-[4-(trifluoromethyl)phenyl]-2-propyl-2-hexenenitrile (**3a**) in 80% yield after 24 h at 100 °C (entry 1). Stereochemistry of **3a** was determined unambiguously by NOE experiments of ^1H NMR. A similar but more practically useful catalyst was prepared in situ by the reduction of air-stable and commercially available $(Me_3P)_2NiCl_2$[14] with DIBAL-H (2.0 equiv to Ni) and shown to be equally effective (entry 2). Although conversion was high, yield of the desired product was lower with PMe_2Ph or $PMePh_2$ (entries 3 and 4). Other trialkylphosphines such as $P(n\text{-}Bu)_3$, PCy_3, and $P(t\text{-}Bu)_3$ (entries 6–8) as well as PPh_3 (entry 5) gave inferior results.[15] Bidentate ligands, $Me_2P(CH_2)_2PMe_2$, and 2,2′-bipyridyl, and polar solvents like 1,4-dioxane and DMF were less effective (9–12). Other metal complexes such as $Cp(\eta^3\text{-allyl})Pd$, $Pt(cod)_2$, $[RhCl(cod)]_2$, and $[IrCl(cod)]_2$ along with PMe_3 completely retarded the catalysis.

We examined the scope of aryl cyanides under the optimized conditions (Table 2). Benzonitriles having an electron-withdrawing substituent at the *para*-position reacted in good to excellent yields. A wide variety of functional groups including fluoro, keto, ester, and formyl[16] were tolerated to give the corresponding arylcyanation products (entries 1–4). In particular, 1,4-dicyanobenzene (**1f**) reacted at one of the C–CN bonds exclusively with an equimolar amount of 4-octyne (**2a**) (entry 5), whereas double arylcyanation product **4** was obtained with two molar equivalents of **2a** (Eq. 4). The reaction rate and yield were reduced with an electron-neutral or -donating substituent at the *para*-position (entries 6–9). A boryl group that is convertible to various organic groups by the Suzuki–Miyaura coupling survived the present conditions (entry 10). *Meta*- and *ortho*-substituents do not affect the reaction (entries 11–16). Heteroaryl cyanides were also examined as substrates (entries 17–22). Use of PMe_2Ph as a ligand instead of PMe_3 gave superior results with 2-cyanofuran and 2-cyanothiophene (entries 17 and 18); the reaction of 2-cyanothiophene took 90 h for completion, and the yield was modest presumably due to the presence of a sulfur atom. *N*-Boc-3-cyanoindole gave the corresponding 3-functionalized indole albeit in a modest yield (entry 19). Whereas 4- or 3-cyanopyridine participated in the reaction successfully (entries 20 and 21), the addition of 2-cyanopyridine was sluggish and gave an *E*-isomer as a minor product (entry 22). The isomer would be derived from the initially formed *Z*-adduct as the ratio varied depending on the reaction period (*Z*:*E*=78:22 at 22 h). Although the course of the isomerization is yet to be clarified, chelation-assisted formation of a nickelacycle such as **5** or, alternatively, conjugate addition of a nucleophile like PMe_2Ph to the *Z*-isomer might be operative to induce the partial isomerization to the *E*-isomer, which would be thermodynamically more favorable (Scheme 3).



(3)



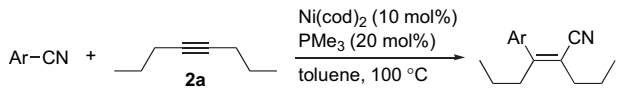
(4)

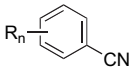
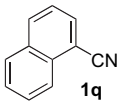
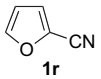
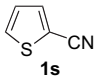
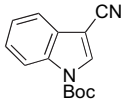
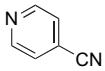
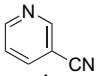
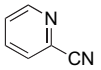
Table 1. Nickel-catalyzed arylcyanation of 4-octyne using 4-(trifluoromethyl)benzonitrile[a]

Entry	Nickel complex	Ligand	Solvent	Conv. of **1a** (%)[b]	Yield of **3a** (%)[b]
1	$Ni(cod)_2$	PMe_3	Toluene	91	84 (80)[c]
2[d]	$(Me_3P)_2NiCl_2$	—	Toluene	93	80
3	$Ni(cod)_2$	PMe_2Ph	Toluene	94	76
4	$Ni(cod)_2$	$PMePh_2$	Toluene	87	44
5	$Ni(cod)_2$	PPh_3	Toluene	54	31
6	$Ni(cod)_2$	$P(n\text{-}Bu)_3$	Toluene	50	30
7	$Ni(cod)_2$	PCy_3	Toluene	69	35
8	$Ni(cod)_2$	$P(t\text{-}Bu)_3$	Toluene	39	13
9	$Ni(cod)_2$	$Me_2P(CH_2)_2PMe_2$	Toluene	24	<5
10	$Ni(cod)_2$	2,2-Bipyridyl	Toluene	14	<5
11	$Ni(cod)_2$	PMe_3	1,4-Dioxane	75	60
12	$Ni(cod)_2$	PMe_3	DMF	58	47

[a] Reactions were carried out using **1a** (171 mg, 1.0 mmol), 4-octyne (110 mg, 1.0 mmol), $Ni(cod)_2$ (28 mg, 0.10 mmol), and a ligand (0.20 mmol) in a solvent (2.5 mL) at 100 °C for 24 h.
[b] Estimated by ^{19}F NMR using 4-F_3C-C_6H_4-I as an internal standard.
[c] Isolated yield.
[d] A catalyst was prepared from $(Me_3P)_2NiCl_2$ (28 mg, 0.10 mmol) and DIBAL-H (1.5 M solution in toluene, 0.20 mmol).

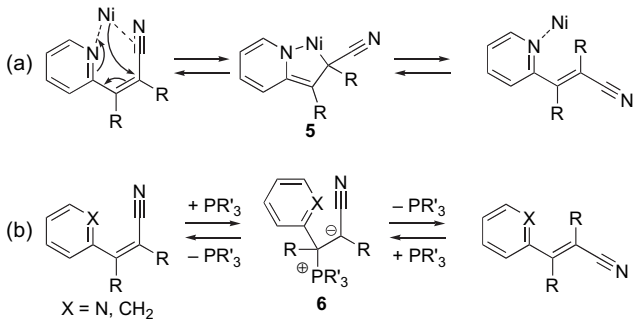
Table 2. Nickel-catalyzed arylcyanation of 4-octyne[a]



Entry	Ar–CN		Time (h)	Yield (%)[b]
1		R= 4-F (**1b**)	30	81 (**3b**)
2		4-C(O)Me (**1c**)	30	73 (**3c**)
3		4-CO_2Me (**1d**)	24	96 (**3d**)
4		4-CHO (**1e**)	25	67 (**3e**)
5		4-CN (**1f**)	19	67 (**3f**)
6		4-Ph (**1g**)	45	78 (**3g**)
7		H (**1h**)	45	64 (**3h**)
8		4-Me (**1i**)	40	70 (**3i**)
9		4-MeO (**1j**)	111	54 (**3j**)
10		4-B(pin) (**1k**)	30	61 (**3k**)
11		3-MeO (**1l**)	38	70 (**3l**)
12		3,5-$(MeO)_2$ (**1m**)	92	76 (**3m**)
13		3,4,5-$(MeO)_3$ (**1n**)	47	67 (**3n**)
14		2-CF_3 (**1o**)	159	76 (**3o**)
15		5-F-2-Me (**1p**)	26	62 (**3p**)
16	 **1q**		48	61 (**3q**)
17[c]	 **1r**		46	75 (**3r**)
18[c]	 **1s**		90	44 (**3s**)
19	 **1t**		45	40 (**3t**)
20	 **1u**		24	85 (**3u**)
21	 **1v**		15	86 (**3v**)
22[c]	 **1w**		44	36 (**3w**)[d]

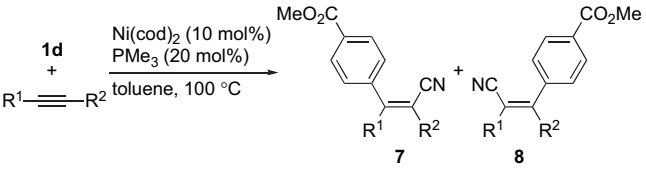
[a] Reactions were carried out using an aryl cyanide (1.0 mmol), 4-octyne (110 mg, 1.0 mmol), $Ni(cod)_2$ (28 mg, 0.10 mmol), and PMe_3 (15.2 mg, 0.20 mmol) in toluene (2.5 mL) at 100 °C for 24 h.
[b] Isolated yield based on an aryl cyanide.
[c] PMe_2Ph (0.20 mmol) was used as a ligand.
[d] *Z*:*E*=68:32.

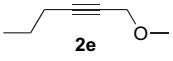
We next examined the scope of alkynes (Table 3). The reaction of methyl 4-cyanobenzoate with 2-butyne (**2b**) proceeded similarly to give the corresponding adduct **7b** in 70% yield (entry 1); an unsymmetrical alkyne, 4-methyl-2-pentyne (**2c**), gave a mixture of regioisomers **7c** and **8c** (entry 2), whereas 4,4-dimethyl-2-pentyne (**2d**) gave **7d** as the sole product (entry 3). The regio- and stereochemistry of **7d** was unambiguously confirmed by X-ray crystallographic analysis (Fig. 1).[17] Thus, an isomer having a cyano group at the carbon bearing a larger substituent was



Scheme 3. Plausible mechanism of *E*–*Z* isomerization of arylcyanation products.

Table 3. Nickel-catalyzed arylcyanation of alkynes using methyl 4-cyanobenzoate (**1d**)[a]



Entry	R^1—≡—R^2	Time (h)	Yield (%)[b]	**7**:**8**[c]
1	Me—≡—Me **2b**	20	70 (**7b**)	—
2	Me—≡—*i*-Pr **2c**	26	84 (**7c**, **8c**)	62:38
3	Me—≡—*t*-Bu **2d**	86	59 (**7d**)	>99:1
4	 **2e**	67	59 (**7e**, **8e**)	37:63
5	Me—≡—$SiMe_3$ **2f**	49	82 (**7f**, **8f**)	85[d]:15

[a] Reactions were carried out using methyl 4-cyanobenzoate (**1d**, 161 mg, 1.0 mmol), an alkyne (1.0 mmol), $Ni(cod)_2$ (28 mg, 0.10 mmol), and PMe_3 (15.2 mg, 0.20 mmol) in toluene (2.5 mL) at 100 °C.
[b] Isolated yield.
[c] Determined by GC.
[d] *Z*:*E*=59:41.

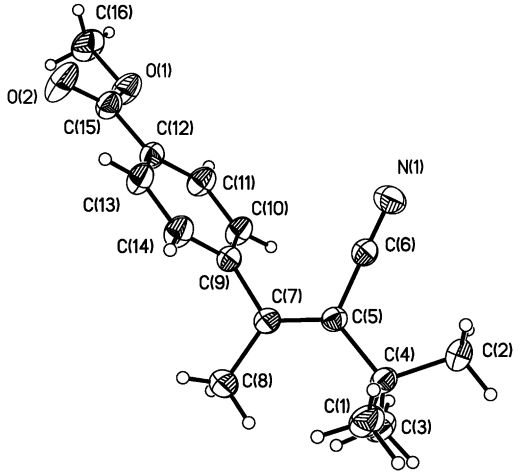
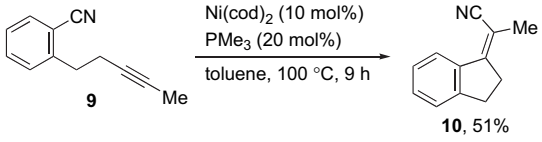


Figure 1. ORTEP drawing for **7d**.

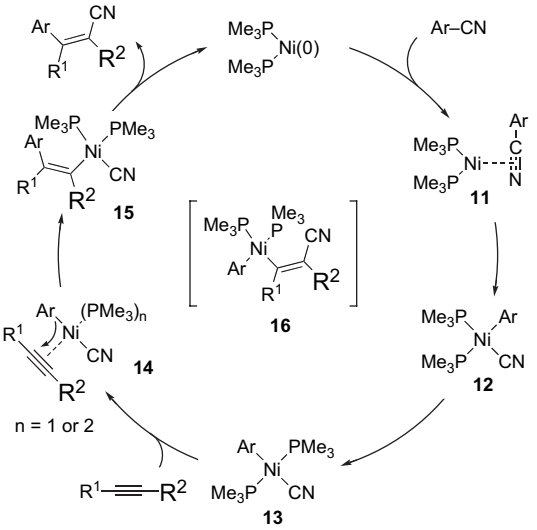
exclusively formed. A 37:63 mixture of two regioisomers, **7e** and **8e**, was obtained with 2-hexynyl methyl ether (**2e**), suggesting that an oxygen atom has no significant influence on the regiochemistry (entry 4). Trimethyl(1-propynyl)silane (**2f**) also participated in the reaction with the same regiochemistry but gave a mixture of stereoisomers of **7f**. Predominant formation of *cis*-adduct (*E*)-**7f** at the beginning of the reaction (*Z*:*E*=15:85 at 1 h) may suggest that an isomerization process is operative that was observed with 2-cyanopyridine (vide supra). Particularly, the silyl group of **7f** can stabilize an anion generated at its β-position in an intermediate like **6** (Scheme 3) during the possible phosphine-mediated isomerization process. Terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reaction due presumably to rapid oligomerization and/or trimerization of alkynes.

Intramolecular arylcyanation was next examined with **9**, which was prepared from *o*-tolunitrile (Eq. 5).[18] As expected, cyclization in a 5-*exo*-*dig* fashion took place to give **10** in 51% yield, whose structure was determined by X-ray crystallographic analysis (Fig. 2).[17]



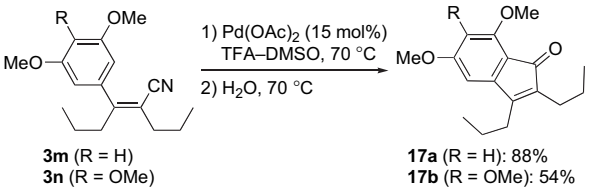
(5)

A plausible mechanism of the arylcyanation is provided in Scheme 4. The catalysis would be initiated by the oxidative addition of a C–CN bond of an aryl cyanide to nickel(0) to give *trans*-nickel(II) complex **13** via π-coordinating intermediate **11** and *cis*-oxidative adduct **12**.[7j] The nickel center of **13** would be coordinated by an alkyne substrate in the direction avoiding the steric repulsion between bulkier R^2 and aryl groups on the nickel to give four- or five-coordinated nickel(II) intermediate **14**. The aryl group would then migrate to the less hindered alkyne-carbon to give alkenylnickel **15** (arylnickelation), which reductively eliminates an arylcyanation product and regenerates the nickel(0). Although insertion of an alkyne into the Ni–CN bond (cyanonickelation) forming **16** cannot be ruled out, this cyanonickelation pathway has no precedents compared to the arylnickelation pathway, which frequently constitutes an elemental step of nickel catalysis.[19]



Scheme 4. Plausible mechanism of the arylcyanation of alkynes.

Arylcyanation products readily undergo intramolecular cyclization reaction to give 2-indenones by utilizing Larock's protocol (Eq. 6).[20] It is worth noting that metal-catalyzed C–C and C–H functionalization processes are demonstrated sequentially to synthesize substituted 2-indenones in a highly atom-economical manner.[21]



(6)

In conclusion, we have demonstrated that a simple catalyst derived from $Ni(cod)_2$ and PMe_3 accomplishes the arylcyanation reaction of alkynes for the first time. The reaction provides us with a ready access to various β-arylalkenenitriles having a diverse range of functional groups, which would be difficult to prepare otherwise. The arylcyanation products are shown to be versatile precursors for functionalized 2-indenones, and would also have broad synthetic applications to functional molecules by virtue of the rich chemistry of a cyano group. The chemistry shown herein is considered to open a door to a new class of transformations of organonitriles to make C–C bonds with perfect atom economy, which are currently under investigation.

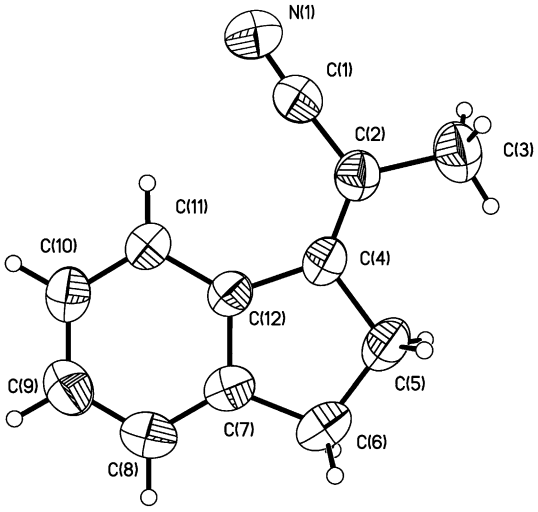


Figure 2. ORTEP drawing for **10**.

3. Experimental

3.1. General

All manipulations of oxygen- and moisture-sensitive materials were conducted with a standard Schlenk technique under an argon atmosphere or in a dry box under a nitrogen

atmosphere. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} (0.25 mm) plates. Visualization was accomplished with UV light (254 nm) and/or an aqueous alkaline $KMnO_4$ solution followed by heating. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian UNITY-INOVA 500 (^{1}H NMR, 500 MHz; ^{13}C NMR, 126 MHz) spectrometer, Varian Mercury 400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 101 MHz), JEOL EX-270 (^{13}C, 67.8 MHz), or Varian Mercury 200 (^{1}H, 200 MHz; ^{19}F, 188 MHz; ^{13}C, 50.3 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, sext=sextet, m=multiplet, br=broad), coupling constants (hertz), and integration. GC analysis was performed on a Shimadzu GC 14B equipped with an OV-1701 column (25 m×0.25 mm, pressure = 570 kPa, detector = FID, 290 °C) with helium gas as carrier. Preparative recycling gel permeation chromatography (GPC) and preparative recycling silica gel chromatography were performed with a JAI LC-908 chromatograph equipped with JAIGEL-1H and -2H (chloroform as an eluent) and JAIGEL-SIL or Nacalai tesque 5SL-II (hexane–ethyl acetate as an eluent). High-resolution mass spectra were obtained with a JEOL JMS-700 (EI) or JEOL JMS-HX110A (FAB+) spectrometer. Unless otherwise noted, reagents were commercially available and were used without purification. Solvents were distilled from a suitable drying reagent as follows: sodium/benzophenone ketyl for toluene and 1,4-dioxane; calcium hydride for DMF. Anhydrous DMSO was purchased from Aldrich and used without further purification. 2-Hexynyl methyl ether was prepared by the reported procedure[22] using methyl propargyl ether and 1-iodopropane.

3.2. Arylcyanation of alkynes: a general procedure

A solution of $Ni(cod)_2$ (28 mg, 0.10 mmol) and PMe_3 (15.2 mg, 0.20 mmol) in toluene (2.5 mL) was added to a nitrile (1.0 mmol). To this was added an alkyne (1.0 mmol), and the resulting mixture was stirred at 100 °C. The mixture was filtered through a silica gel pad, and the solvent was concentrated in vacuo. The residue was purified by flash chromatography on silica gel. Unreacted nitrile and/or regioisomer(s) were further separated by preparative GPC and/or recycling silica gel chromatography.

3.2.1. (*Z*)-3-[4-(Trifluoromethyl)phenyl]-2-propyl-2-hexenenitrile (3a). A colorless oil, R_f 0.12 (hexane–ethyl acetate = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, J=8.1, 0.7 Hz, 2H), 7.42 (dd, J=8.1, 0.7 Hz, 2H), 2.52 (t, J=7.8 Hz, 2H), 2.38 (t, J=7.8 Hz, 2H), 1.69 (tq, J=7.8, 7.6 Hz, 2H), 1.31 (tq, J=7.8, 7.6 Hz, 2H), 1.03 (t, J=7.6 Hz, 3H), 0.88 (t, J=7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 143.7, 130.5 (q, J=32.6 Hz), 128.2, 125.5 (q, J=3.8 Hz), 123.9 (q, J=272.1 Hz), 119.0, 113.1, 35.5, 32.4, 21.7, 20.9, 13.7, 13.5; IR (neat): 2964, 2934, 2874, 2212, 1614, 1464, 1435, 1406, 1381, 1325, 1167, 1128, 1069, 1018, 847 cm^{-1}; Anal. Calcd for $C_{16}H_{18}F_3N$: C, 68.31; H, 6.45. Found: C, 68.57; H, 6.52.

3.2.2. (*Z*)-3-(4-Fluorophenyl)-2-propyl-2-hexenenitrile (3b). A colorless oil, R_f 0.43 (hexane–ethyl acetate = 10:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.24 (m, 2H), 7.14–7.02 (m, 2H), 2.48 (t, J=7.6 Hz, 2H), 2.35 (t, J=7.6 Hz, 2H), 1.67 (tq, J=7.6, 7.3 Hz, 2H), 1.29 (tq, J=7.6, 7.3 Hz, 2H), 1.02 (t, J=7.3 Hz, 3H), 0.87 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 162.5 (d, J=246.6 Hz), 157.5, 135.9 (d, J=3.3 Hz), 129.5 (d, J=8.9 Hz), 119.3, 115.4 (d, J=22.3 Hz), 112.1, 35.7, 32.5, 21.8, 21.1, 13.8, 13.6; IR (neat): 2964, 2934, 2874, 2210, 1603, 1508, 1464, 1232, 1159, 1094, 840 cm^{-1}; Anal. Calcd for $C_{15}H_{18}FN$: C, 77.89; H, 7.84. Found: C, 77.95; H, 7.84.

3.2.3. (*Z*)-3-(4-Acetylphenyl)-2-propyl-2-hexenenitrile (3c). A colorless oil, R_f 0.51 (hexane–ethyl acetate = 2:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, J=8.6 Hz, 2H), 7.41 (d, J=8.6 Hz, 2H), 2.62 (s, 3H), 2.54 (t, J=7.6 Hz, 2H), 2.39 (t, J=7.6 Hz, 2H), 1.69 (tq, J=7.6, 7.3 Hz, 2H), 1.31 (tq, J=7.6, 7.3 Hz, 2H), 1.03 (t, J=7.3 Hz, 3H), 0.86 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 197.1, 157.5, 144.7, 136.8, 128.4, 128.0, 119.0, 112.7, 35.5, 32.5, 26.7, 21.8, 21.1, 13.9, 13.6; IR (neat): 2963, 2934, 2874, 2210, 1684, 1605, 1558, 1456, 1402, 1360, 1265, 959, 845 cm^{-1}; Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29. Found: C, 80.23; H, 8.35.

3.2.4. (*Z*)-3-[4-(Methoxycarbonyl)phenyl]-2-propyl-2-hexenenitrile (3d). A colorless oil, R_f 0.62 (hexane–ethyl acetate = 2:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06 (d, J=8.4 Hz, 2H), 7.37 (d, J=8.4 Hz, 2H), 3.92 (s, 3H), 2.52 (t, J=7.6 Hz, 2H), 2.37 (t, J=7.5 Hz, 2H), 1.68 (tq, J=7.5, 7.3 Hz, 2H), 1.30 (tq, J=7.6, 7.3 Hz, 2H), 1.02 (t, J=7.3 Hz, 3H), 0.87 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.4, 157.5, 144.6, 130.1, 129.7, 127.8, 119.0, 112.7, 52.2, 35.6, 32.5, 21.8, 21.1, 13.9, 13.6; IR (neat): 2963, 2934, 2874, 2210, 1726, 1607, 1435, 1404, 1279, 1180, 1115, 1020, 966, 862, 770, 712 cm^{-1}; Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80. Found: C, 75.22; H, 7.88.

3.2.5. (*Z*)-3-(4-Formylphenyl)-2-propyl-2-hexenenitrile (3e). A colorless oil, R_f 0.18 (hexane–ethyl acetate = 9:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.92 (d, J=8.1 Hz, 2H), 7.47 (d, J=8.1 Hz, 2H), 2.54 (t, J=7.7 Hz, 2H), 2.39 (t, J=7.7 Hz, 2H), 1.69 (tq, J=7.7, 7.3 Hz, 2H), 1.31 (tq, J=7.7, 7.3 Hz, 2H), 1.03 (t, J=7.3 Hz, 3H), 0.89 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 191.5, 157.3, 146.2, 136.1, 129.8, 128.5, 118.9, 113.0, 35.4, 32.3, 21.6, 20.9, 13.7, 13.4; IR (neat): 2964, 2934, 2874, 2212, 1705, 1605, 1464, 1385, 1306, 1209, 1171, 1103, 914, 841, 735 cm^{-1}; Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.63; H, 8.05.

3.2.6. (*Z*)-3-(4-Cyanophenyl)-2-propyl-2-hexenenitrile (3f). A colorless oil, R_f 0.15 (hexane–ethyl acetate = 10:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69 (d, J=8.2 Hz, 2H), 7.41 (d, J=8.2 Hz, 2H), 2.51 (t, J=7.7 Hz, 2H), 2.37 (t, J=7.6 Hz, 2H), 1.67 (tq, J=7.6, 7.4 Hz, 2H), 1.29 (tq, J=7.7, 7.4 Hz, 2H), 1.02 (t, J=7.4 Hz, 3H), 0.88 (t, J=7.4 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 156.5, 144.6, 132.2, 128.5, 118.6, 118.3, 113.5, 112.3, 35.4, 32.4, 21.7, 21.0, 13.8, 13.6; IR (neat): 2963, 2934, 2874, 2230, 2212, 1605, 1502, 1464, 1381, 1273, 1103, 1020, 847, 789, 741,

557 cm^{-1}; Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61. Found: C, 80.76; H, 7.64.

3.2.7. (*Z*)-3-(*p*-Biphenyl)-2-propyl-2-hexenenitrile (3g). A colorless oil, R_f 0.22 (hexane–ethyl acetate = 20:1). ^1H NMR (200 MHz, $CDCl_3$) δ 7.68–7.58 (m, 5H), 7.52–7.32 (m, 4H), 2.56 (t, J=7.6 Hz, 2H), 2.40 (t, J=7.6 Hz, 2H), 1.71 (tq, J=7.6, 7.5 Hz, 2H), 1.37 (tq, J=7.6, 7.4 Hz, 2H), 1.05 (t, J=7.5 Hz, 3H), 0.91 (t, J=7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 141.4, 140.4, 138.9, 128.8, 128.2, 127.5, 127.08, 127.07, 119.7, 111.6, 35.6, 32.5, 21.8, 21.1, 13.8, 13.5; IR (neat): 3030, 2963, 2932, 2872, 2210, 1609, 1580, 1487, 1464, 1431, 1402, 1381, 1105, 1078, 1007, 843, 766, 739, 696 cm^{-1}; Anal. Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01. Found: C, 87.32; H, 8.01.

3.2.8. (*Z*)-3-Phenyl-2-propyl-2-hexenenitrile (3h). A colorless oil, R_f 0.43 (hexane–ethyl acetate = 10:1). ^1H NMR (200 MHz, $CDCl_3$) δ 7.45–7.26 (m, 5H), 2.51 (t, J= 7.6 Hz, 2H), 2.36 (t, J=7.6 Hz, 2H), 1.64 (tq, J=7.6, 7.3 Hz, 2H), 1.32 (tq, J=7.6, 7.3 Hz, 2H), 1.02 (t, J=7.3 Hz, 3H), 0.88 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 158.6, 140.0, 128.4, 128.3, 127.6, 119.5, 111.6, 35.8, 32.5, 21.8, 21.1, 13.9, 13.6; IR (neat): 2963, 2932, 2872, 2210, 1443, 758, 700 cm^{-1}; Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98. Found: C, 84.32; H, 8.98.

3.2.9. (*Z*)-3-(4-Methylphenyl)-2-propyl-2-hexenenitrile (3i). A colorless oil, R_f 0.18 (hexane–ethyl acetate = 20:1). ^1H NMR (200 MHz, $CDCl_3$) δ 7.20 (s, 4H), 2.50 (t, J=7.6 Hz, 2H), 2.37 (s, 3H), 2.35 (t, J=7.6 Hz, 2H), 1.67 (tq, J=7.6, 7.4 Hz, 2H), 1.31 (tq, J=7.6, 7.4 Hz, 2H), 1.02 (t, J=7.4 Hz, 3H), 0.87 (t, J=7.4 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 158.6, 138.3, 137.0, 129.0, 127.5, 119.7, 111.1, 35.7, 32.5, 21.8, 21.3, 21.2, 13.9, 13.6; IR (neat): 2963, 2932, 2872, 2208, 1508, 1456, 822, 548 cm^{-1}; Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31. Found: C, 84.59; H, 9.27.

3.2.10. (*Z*)-3-(4-Methoxyphenyl)-2-propyl-2-hexenenitrile (3j). A colorless oil, R_f 0.20 (hexane–ethyl acetate = 10:1). ^1H NMR (200 MHz, $CDCl_3$) δ 7.27 (d, J=9.0 Hz, 2H), 6.91 (d, J=9.0 Hz, 2H), 3.82 (s, 3H), 2.49 (t, J=7.3 Hz, 2H), 2.34 (t, J=7.3 Hz, 2H), 1.66 (qt, J=7.4, 7.3 Hz, 2H), 1.31 (qt, J=7.4, 7.3 Hz, 2H), 1.01 (t, J= 7.4 Hz, 3H), 0.87 (t, J=7.4 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 159.6, 158.2, 132.2, 129.0, 120.0, 113.7, 110.8, 55.2, 35.6, 32.6, 21.9, 21.3, 13.9, 13.6; IR (neat): 2961, 2932, 2872, 2873, 2208, 1697, 1607, 1574, 1510, 1462, 1439, 1379, 1288, 1250, 1178, 1119, 1103, 1034, 835, 787, 727, 696, 544 cm^{-1}; Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70. Found: C, 79.13; H, 8.94.

3.2.11. (*Z*)-3-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propyl-2-hexenenitrile (3k). A colorless solid (mp 101.7–102.7 °C), R_f 0.44 (hexane–ethyl acetate = 5:1). ^1H NMR (200 MHz, $CDCl_3$) δ 7.83 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 2.51 (t, J=7.9 Hz, 2H), 2.36 (t, J=7.9 Hz, 2H), 1.67 (tq, J=7.9, 7.3 Hz, 2H), 1.34 (tq, J=7.9, 7.3 Hz, 2H), 1.29 (s, 12H), 1.02 (t, J= 7.3 Hz, 3H), 0.86 (t, J=7.3 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 158.7, 142.9, 134.8, 127.0, 119.4, 111.8, 83.8, 35.5, 32.4, 24.8, 21.7, 21.0, 13.8, 13.5; IR (KBr): 2964, 2934, 2874, 2208, 1609, 1506, 1456, 1398, 1362, 1325, 1271, 1144, 1088, 1020, 962, 858, 658 cm^{-1}; Anal. Calcd for $C_{21}H_{30}BNO_2$: C, 74.34; H, 8.91. Found: C, 74.07; H, 8.83.

3.2.12. (*Z*)-3-(3-Methoxyphenyl)-2-propyl-2-hexenenitrile (3l). A colorless oil, R_f 0.30 (hexane–ethyl acetate = 10:1). ^1H NMR (200 MHz, $CDCl_3$) δ 7.31 (d, J= 8.4 Hz, 1H), 6.93–6.80 (m, 3H), 3.81 (s, 3H), 2.49 (t, J=7.6 Hz, 2H), 2.35 (t, J=7.6 Hz, 2H), 1.67 (qt, J=7.6, 7.5 Hz, 2H), 1.32 (qt, J=7.6, 7.4 Hz, 2H), 1.01 (t, J= 7.5 Hz, 3H), 0.87 (t, J=7.4 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 159.2, 158.3, 141.3, 129.3, 120.0, 119.3, 113.7, 113.4, 111.5, 55.2, 35.7, 32.5, 21.8, 21.1, 13.9, 13.5; IR (neat): 2963, 2934, 2872, 2208, 1578, 1487, 1464, 1429, 1317, 1286, 1246, 1217, 1163, 1045, 874, 781, 705 cm^{-1}; Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70. Found: C, 79.11; H, 8.70.

3.2.13. (*Z*)-3-(3,5-Dimethoxyphenyl)-2-propyl-2-hexenenitrile (3m). A colorless oil, R_f 0.15 (hexane–ethyl acetate = 10:1). ^1H NMR (200 MHz, $CDCl_3$) δ 6.43 (s, 3H), 3.80 (s, 6H), 2.45 (t, J=7.6 Hz, 2H), 2.34 (t, J=7.6 Hz, 2H), 1.66 (qt, J=7.6, 7.3 Hz, 2H), 1.33 (qt, J=7.6, 7.3 Hz, 2H), 1.01 (t, J=7.3 Hz, 3H), 0.88 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 160.4, 158.4, 141.9, 119.3, 111.5, 105.9, 100.2, 55.4, 35.7, 32.5, 21.8, 21.1, 13.9, 13.6; IR (neat): 2963, 2934, 2872, 2839, 2208, 1591, 1456, 1421, 1350, 1265, 1205, 1155, 1063, 927, 847 cm^{-1}; Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.99; H, 8.82.

3.2.14. (*Z*)-3-(3,4,5-Trimethoxyphenyl)-2-propyl-2-hexenenitrile (3n). A colorless oil, R_f 0.23 (hexane–ethyl acetate = 5:1). ^1H NMR (200 MHz, $CDCl_3$) δ 6.50 (s, 2H), 3.84 (s, 9H), 2.46 (t, J=7.6 Hz, 2H), 2.32 (t, J=7.6 Hz, 2H), 1.65 (tq, J=7.6, 7.3 Hz, 2H), 1.32 (tq, J=7.6, 7.3 Hz, 2H), 1.00 (t, J=7.3 Hz, 3H), 0.87 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 158.3, 152.8, 138.1, 135.2, 119.4, 111.2, 105.1, 60.8, 56.2, 35.6, 32.6, 21.8, 21.2, 13.9, 13.6; IR (neat): 2936, 2872, 2839, 2251, 2206, 1582, 1504, 1454, 1433, 1410, 1381, 1348, 1269, 1238, 1184, 1128, 1009, 957, 914, 883, 843, 733, 648, 532 cm^{-1}; Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31. Found: C, 71.07; H, 8.04.

3.2.15. (*Z*)-3-[2-(Trifluoromethyl)phenyl]-2-propyl-2-hexenenitrile (3o). A colorless oil, R_f 0.20 (hexane–ethyl acetate = 10:1). ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, J=7.4 Hz, 1H), 7.62–7.43 (m, 2H), 7.17 (d, J=6.8 Hz, 1H), 2.74–2.56 (m, 1H), 2.52–2.16 (m, 3H), 1.68 (tq, J=7.6, 7.2 Hz, 2H), 1.51–1.16 (m, 2H), 1.03 (t, J=7.2 Hz, 3H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 156.3, 138.8, 131.7, 130.0, 128.3, 127.4 (q, J=31.3 Hz), 126.8 (q, J=5.2 Hz), 123.9 (q, J=272.2 Hz), 118.2, 114.8 (q, J=2.2 Hz), 36.0 (q, J=2.2 Hz), 31.8, 21.5, 20.9, 14.2, 13.5; IR (neat): 2966, 2936, 2876, 2216, 1603, 1576, 1448, 1381, 1315, 1263, 1171, 1126, 1065, 1034, 770, 650 cm^{-1}; Anal. Calcd for $C_{16}H_{18}F_3N$: C, 68.31; H, 6.45. Found: C, 68.51; H, 6.37.

3.2.16. (*Z*)-3-(5-Fluoro-2-methylphenyl)-2-propyl-2-hexenenitrile (3p). A colorless oil, R_f 0.27 (hexane–ethyl

acetate = 20:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18 (dd, J=8.4, 5.8 Hz, 1H), 6.92 (ddd, J=8.7, 8.4, 2.7 Hz, 1H), 6.75 (dd, J=8.7, 2.7 Hz, 1H), 2.58–2.26 (m, 4H), 2.22 (s, 3H), 1.69 (tq, J=7.4, 7.3 Hz, 2H), 1.52–1.22 (m, 2H), 1.03 (t, J=7.3 Hz, 3H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 160.5 (d, J=244.4 Hz), 157.3, 141.3 (d, J=7.8 Hz), 131.8 (d, J=7.8 Hz), 130.2 (d, J=3.3 Hz), 118.4, 114.8 (d, J=21.2 Hz), 114.6 (d, J=22.3 Hz), 113.7, 35.8, 31.7, 21.7, 20.7, 18.6, 14.2, 13.5; IR (neat): 2964, 2934, 2874, 2212, 1609, 1585, 1493, 1464, 1470, 1381, 1263, 1238, 1211, 1161, 870, 814, 754 cm^{-1}; Anal. Calcd for $C_{16}H_{20}FN$: C, 78.33; H, 8.22. Found: C, 78.19; H, 8.28.

3.2.17. (*Z*)-3-(1-Naphthyl)-2-propyl-2-hexenenitrile (3q). A colorless oil, R_f 0.23 (hexane–ethyl acetate = 20:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.92–7.81 (m, 2H), 7.73–7.63 (m, 1H), 7.56–7.42 (m, 3H), 7.24 (s, 1H), 2.78–2.36 (m, 4H), 1.76 (tq, J=7.4, 7.3 Hz, 2H), 1.48–1.22 (m, 2H), 1.09 (t, J=7.3 Hz, 3H), 0.88 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 157.9, 137.9, 133.6, 130.3, 128.6, 126.3, 125.9, 125.7, 125.1, 124.5, 118.7, 114.5, 36.5, 32.0, 21.9, 21.4, 14.1, 13.7; IR (neat): 2963, 2932, 2872, 2212, 1506, 1456, 804, 779 cm^{-1}; Anal. Calcd for $C_{19}H_{21}N$: C, 86.65; H, 8.04. Found: C, 86.88; H, 8.12.

3.2.18. (*Z*)-3-(2-Furyl)-2-propyl-2-hexenenitrile (3r). A colorless oil, R_f 0.30 (hexane–ethyl acetate = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J=1.8 Hz, 1H), 7.00 (d, J=3.7 Hz, 1H), 6.45 (dd J=3.7, 1.8 Hz, 1H), 2.51 (t, J=8.0 Hz, 2H), 2.33 (t, J=7.6 Hz, 2H), 1.47 (tq, J=7.6, 7.5 Hz, 2H), 1.47 (sext, J=7.6 Hz, 2H), 0.98 (t, J=7.5 Hz, 3H), 0.95 (t, J=7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5, 144.4, 142.9, 120.2, 112.0, 111.7, 105.9, 32.7, 31.8, 22.5, 21.7, 14.0, 13.5; IR (neat): 2964, 2934, 2874, 2205, 1599, 1464, 1381, 1157, 1086, 1026, 934, 903, 887, 818, 745 cm^{-1}; Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 77.00; H, 8.43.

3.2.19. (*Z*)-3-(2-Thienyl)-2-propyl-2-hexenenitrile (3s). A colorless oil, R_f 0.38 (hexane–ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J=3.7, 1.1 Hz, 1H), 7.38 (dd, J=5.1, 1.1 Hz, 1H), 7.06 (dd, J=5.1, 3.7 Hz, 1H), 2.53 (t, J=7.8 Hz, 2H), 2.36 (t, J=7.8 Hz, 2H), 1.68 (tq, J=7.8, 7.3 Hz, 2H), 1.46 (tq, J=7.8, 7.3 Hz, 2H), 1.01 (t, J=7.3 Hz, 3H), 0.94 (t, J=7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 141.5, 128.2, 127.4, 126.9, 120.1, 109.5, 36.6, 33.1, 22.0, 21.7, 13.9, 13.6; IR (neat): 2963, 2932, 2872, 2205, 1589, 1462, 1425, 1379, 1232, 1111, 1088, 853, 837, 706 cm^{-1}; Anal. Calcd for $C_{13}H_{17}NS$: C, 71.18; H, 7.81. Found: C, 71.45; H, 7.89.

3.2.20. (*Z*)-3-(*N*-*tert*-Butoxycarbonyl-3-indolyl)-2-propyl-2-hexenenitrile (3t). A colorless oil, R_f 0.27 (hexane–ethyl acetate=10:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.17 (br d, J=8.1 Hz, 1H), 7.64 (s, 1H), 7.50–7.22 (m, 3H), 2.58 (t, J=7.6 Hz, 2H), 2.43 (t, J=7.6 Hz, 2H), 1.73 (tq, J=7.6, 7.3 Hz, 2H), 1.69 (s, 9H), 1.38 (tq, J=7.6, 7.3 Hz, 2H), 1.06 (t, J=7.3 Hz, 3H), 0.89 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 150.6, 149.3, 135.1, 128.6, 124.6, 124.4, 122.7, 120.1, 119.7, 119.3, 115.4, 113.3, 84.2, 35.5, 32.4, 28.2, 21.9, 21.5, 14.0, 13.7; IR (neat): 2963, 2934, 2872, 2210, 1738, 1607, 1556, 1454, 1373, 1310, 1286, 1250, 1155, 1111, 1082, 1055, 1020, 854, 837, 748 cm^{-1}; Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01. Found: C, 75.21; H, 7.91.

3.2.21. (*Z*)-3-(4-Pyridyl)-2-propyl-2-hexenenitrile (3u). A colorless oil, R_f 0.16 (hexane–ethyl acetate = 2:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.64 (br d, J=3.7 Hz, 2H), 7.20 (br d, J=5.7 Hz, 2H), 2.49 (t, J=7.7 Hz, 2H), 2.36 (t, J=7.6 Hz, 2H), 1.66 (tq, J=7.6, 7.3 Hz, 2H), 1.29 (tq, J=7.7, 7.3 Hz, 2H), 1.00 (t, J=7.3 Hz, 3H), 0.87 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 155.6, 149.9, 147.7, 122.4, 118.4, 113.4, 35.1, 32.4, 21.7, 21.0, 13.8, 13.5; IR (neat): 2963, 2934, 2874, 2212, 1593, 1543, 1456, 1410, 991, 831 cm^{-1}; Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47. Found: C, 78.44; H, 8.56.

3.2.22. (*Z*)-3-(3-Pyridyl)-2-propyl-2-hexenenitrile (3v). A colorless oil, R_f 0.16 (hexane–ethyl acetate = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60–8.54 (br m, 2H), 7.65–7.63 (m, 1H), 7.35–7.28 (m, 1H), 2.50 (t, J=7.7 Hz, 2H), 2.36 (t, J=7.7 Hz, 2H), 1.64 (tq, J=7.7, 7.4 Hz, 2H), 1.29 (tq, J=7.7, 7.4 Hz, 2H), 1.00 (t, J=7.4 Hz, 3H), 0.87 (t, J=7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 149.6, 148.3, 135.8, 135.4, 123.2, 118.8, 113.7, 35.4, 32.3, 21.6, 20.8, 13.7, 13.4; IR (neat): 3030, 2963, 2934, 2874, 2210, 1614, 1585, 1566, 1464, 1410, 1381, 1340, 1196, 1105, 1024, 816, 785, 741, 718, 625 cm^{-1}; Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47. Found: C, 78.36; H, 8.42.

3.2.23. (*Z*)-3-(2-Pyridyl)-2-propyl-2-hexenenitrile [(*Z*)-3w]. A colorless oil, R_f 0.40 (hexane–ethyl acetate = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66–8.64 (m, 1H), 7.73 (td, J=7.7, 1.8 Hz, 1H), 7.50 (dt, J=7.7, 1.1 Hz, 1H), 7.27 (ddd, J=7.7, 4.8, 1.1 Hz, 1H), 2.69 (t, J=7.8 Hz, 2H), 2.40 (t, J=7.8 Hz, 2H), 1.69 (tq, J=7.8, 7.3 Hz, 2H), 1.31 (tq, J=7.8, 7.3 Hz, 2H), 1.02 (t, J=7.3 Hz, 3H), 0.88 (t, J=7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 157.4, 149.4, 136.5, 123.8, 123.3, 119.2, 113.0, 34.0, 32.7, 21.6, 21.2, 13.9, 13.6; IR (neat): 2963, 2932, 2874, 2210, 1585, 1566, 1464, 1431, 1381, 1151, 1111, 1090, 991, 800, 772, 748 cm^{-1}; Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47. Found [as a mixture with (*E*)-**3w**]: C, 78.42; H, 8.37.

3.2.24. (*E*)-3-(2-Pyridyl)-2-propyl-2-hexenenitrile [(*E*)-3w]. A colorless oil, R_f 0.40 (hexane–ethyl acetate = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (br d, J=4.0 Hz, 1H), 7.72 (td, J=7.7, 1.8 Hz, 1H), 7.25 (td, J=7.7, 1.0 Hz, 1H), 7.14 (d, 7.7 Hz, 1H), 2.82 (t, J=7.6 Hz, 2H), 2.11 (t, J=7.6 Hz, 2H), 1.59 (tq, J=7.6, 7.3 Hz, 2H), 1.35 (tq, J=7.6, 7.3 Hz, 2H), 0.92 (t, J=7.3 Hz, 3H), 0.84 (t, J=7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9, 156.7, 149.8, 136.2, 123.3, 122.8, 118.7, 113.6, 39.0, 32.5, 21.6, 21.1, 13.6, 13.4; IR (neat): 2963, 2932, 2874, 2210, 1583, 1566, 1464, 1429, 1379, 1242, 1047, 991, 750 cm^{-1}.

3.2.25. 3,3′-(*p*-Phenylene)bis[(*Z*)-2-propyl-2-hexenenitrile] (4). A colorless oil, R_f 0.25 (hexane–ethyl acetate = 10:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (s, 4H), 2.52 (t, J=7.6 Hz, 4H), 2.37 (t, J=7.6 Hz, 4H), 1.68 (tq, J=7.6, 7.3 Hz, 4H), 1.33 (tq, J=7.6, 7.3 Hz, 4H), 1.02 (t, J=7.3 Hz, 6H), 0.88 (t, J=7.3 Hz, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 158.0, 140.2, 127.8, 119.4, 111.8, 35.5, 32.5, 21.7, 21.1, 13.8, 13.4; IR (neat): 3017, 2932, 2872, 2208, 1611, 1506, 1464, 1433, 1402, 1379, 1217,

1101, 847, 756, 667 cm^{-1}; Anal. Calcd for $C_{24}H_{32}N_2$: C, 82.71; H, 9.25. Found: C, 82.61; H, 9.20.

3.2.26. (*Z*)-3-[4-(Methoxycarbonyl)phenyl]-2-methyl-2-butenenitrile (7b). A colorless solid (mp 91.8–92.4 °C), R_f 0.31 (hexane–ethyl acetate = 5:1). ^1H NMR (200 MHz, $CDCl_3$) δ 8.05 (d, J=8.2 Hz, 2H), 7.43 (d, J=8.2 Hz, 2H), 3.91 (s, 3H), 2.17 (d, J=1.1 Hz, 3H), 2.07 (d, J=0.9 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.3, 153.0, 145.2, 130.1, 129.7, 127.3, 119.7, 106.5, 52.2, 20.5, 17.7; IR (KBr): 3003, 2955, 2208, 1724, 1609, 1429, 1308, 1294, 1279, 1194, 1117, 860, 773, 708 cm^{-1}; Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.49; H, 6.18.

3.2.27. (*Z*)-3-[4-(Methoxycarbonyl)phenyl]-2-isopropyl-2-butenenitrile (7c). A colorless oil, R_f 0.45 (hexane–ethyl acetate = 5:1). ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J=8.7 Hz, 2H), 7.41 (d, J=8.7 Hz, 2H), 3.92 (s, 3H), 2.97–2.89 (m, 1H), 2.20 (s, 3H), 1.22 (d, J=6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 150.9, 145.8, 130.1, 129.7, 127.5, 119.5, 117.3, 52.2, 29.1, 21.1, 20.2; IR (neat): 2970, 2934, 2874, 2212, 1724, 1609, 1464, 1435, 1404, 1387, 1367, 1312, 1285, 1182, 1113, 1078, 1047, 1018, 1007, 964, 860, 833, 773, 710 cm^{-1}; Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04. Found (as a mixture with **8c**): C, 74.28; H, 7.12.

3.2.28. (*Z*)-3-[4-(Methoxycarbonyl)phenyl]-2,4-dimethyl-2-pentenenitrile (8c). A colorless oil, ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (br d, J=8.2 Hz, 2H), 7.19 (d, J=8.2 Hz, 2H), 3.91 (s, 3H), 3.13–3.05 (m, 1H), 2.06 (s, 3H), 0.98 (d, J=7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 163.3, 142.7, 129.8, 129.5, 127.5, 119.3, 106.9, 52.1, 30.5, 20.4, 15.9.

3.2.29. (*Z*)-3-[4-(Methoxycarbonyl)phenyl]-2-*tert*-butyl-2-butenenitrile (7d). A colorless solid (mp 127.5–128.3 °C), R_f 0.64 (hexane–ethyl acetate = 2:1). ^1H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, J=8.7 Hz, 2H), 7.32 (d, J=8.7 Hz, 2H), 3.88 (s, 3H), 2.27 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.2, 154.2, 148.0, 129.6, 127.1, 122.0, 118.3, 52.0, 34.1, 30.4, 22.7; IR (KBr): 2974, 2955, 2206, 1717, 1601, 1431, 1400, 1373, 1306, 1277, 1242, 1209, 1192, 1177, 1111, 1031, 1016, 961, 856, 827, 772, 708 cm^{-1}; Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.67; H, 7.57.

3.2.30. (*E*)-3-[4-(Methoxycarbonyl)phenyl]-2-methoxymethyl-2-hexenenitrile (7e). A colorless oil, R_f 0.14 (hexane–ethyl acetate=5:1). ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J=8.5 Hz, 2H), 7.40 (d, J=8.5 Hz, 2H), 4.20 (s, 2H), 3.92 (s, 3H), 3.45 (s, 3H), 2.59 (t, J=7.7 Hz, 2H), 1.31 (tq, J=7.7, 7.4 Hz, 2H), 0.87 (t, J=7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 162.1, 143.6, 130.6, 129.8, 127.6, 118.3, 110.0, 68.8, 58.5, 52.2, 35.7, 21.1, 13.7; IR (neat): 2963, 2934, 2874, 2826, 2214, 1724, 1607, 1437, 1404, 1379, 1279, 1190, 1105, 1018, 959, 916, 862, 770, 714 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{19}NO_3$: M^+, 273.1365. Found: *m*/*z* 273.1352.

3.2.31. (*E*)-3-[4-(Methoxycarbonyl)phenyl]-4-methoxy-2-propyl-2-butenenitrile (8e). A colorless oil, R_f 0.14 (hexane–ethyl acetate = 5:1). ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J=8.7 Hz, 2H), 7.47 (d, J=8.7 Hz, 2H), 4.30 (s, 2H), 3.92 (s, 3H), 3.30 (s, 3H), 2.44 (t, J=7.6 Hz, 2H), 1.70 (tq, J=7.6, 7.3 Hz, 2H), 1.02 (t, J=7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 152.2, 142.9, 130.4, 129.7, 128.0, 118.4, 116.6, 70.7, 58.7, 52.2, 32.6, 21.7, 13.4; IR (neat): 2961, 2932, 2874, 2822, 2214, 1724, 1609, 1566, 1435, 1406, 1379, 1281, 1190, 1113, 1018, 962, 914, 862, 775, 729, 710 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{20}NO_3$: $[M+H]^+$, 274.1443. Found: *m*/*z* 274.1447.

3.2.32. (*E*)-3-[4-(Methoxycarbonyl)phenyl]-2-trimethylsilyl-2-butenenitrile [(*E*)-7f]. A colorless solid (mp 101.8–102.5 °C), R_f 0.14 (hexane–ethyl acetate = 10:1). ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J=8.5 Hz, 2H), 7.45 (d, J=8.5 Hz, 2H), 3.91 (s, 3H), 2.31 (s, 3H), 0.38 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 166.2, 146.5, 130.3, 129.7, 126.7, 119.8, 112.0, 52.2, 24.4, −0.3; IR (KBr): 3009, 2953, 2903, 2197, 1720, 1611, 1583, 1492, 1400, 1371, 1310, 1277, 1254, 1188, 1177, 1115, 1016, 956, 853, 773, 762, 706, 660 cm^{-1}; Anal. Calcd for $C_{15}H_{19}NO_2Si$: C, 65.90; H, 7.00. Found: C, 66.06; H, 7.07.

3.2.33. (*Z*)-3-[4-(Methoxycarbonyl)phenyl]-2-trimethylsilyl-2-butenenitrile [(*Z*)-7f]. A colorless solid (mp 69.4–70.1 °C), R_f 0.20 (hexane–ethyl acetate = 10:1). ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J=8.6 Hz, 2H), 7.52 (d, J=8.6 Hz, 2H), 3.94 (s, 3H), 2.48 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 166.2, 146.4, 130.3, 129.6, 126.8, 119.6, 113.4, 52.3, 28.1, −0.3; IR (KBr): 3015, 2961, 2901, 2197, 1715, 1611, 1576, 1562, 1435, 1402, 1371, 1279, 1248, 1182, 1119, 1103, 1018, 984, 966, 847, 777, 760, 710, 635 cm^{-1}; Anal. Calcd for $C_{15}H_{19}NO_2Si$: C, 65.90; H, 7.00. Found: C, 66.06; H, 7.09.

3.2.34. (*E*)-3-[4-(Methoxycarbonyl)phenyl]-3-trimethylsilyl-2-methylpropenenitrile (8f). A colorless solid (mp 137.5–137.9 °C), R_f 0.20 (hexane–ethyl acetate = 10:1). ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J=8.5 Hz, 2H), 7.05 (d, J=8.5 Hz, 2H), 3.91 (s, 3H), 2.19 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 162.5, 147.6, 129.9, 128.9, 126.5, 119.8, 118.2, 52.1, 20.4, −0.5; IR (KBr): 2955, 2214, 1722, 1607, 1435, 1404, 1308, 1273, 1254, 1194, 1175, 1113, 1101, 1018, 914, 841, 822, 760, 710, 691 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{19}NO_2Si$: M^+, 273.1185. Found: *m*/*z* 273.1180.

3.3. Arylcyanation of 4-octyne with 1a using a catalyst prepared from $(Me_3P)_2NiCl_2$ and DIBAL-H

To a solution of $(Me_3P)_2NiCl_2$ (28 mg, 0.10 mmol) in toluene (2.4 mL) was added a 1.5 M solution of DIBAL-H in toluene (0.13 mL, 0.20 mmol) at 0 °C. After a few minutes, **1a** (171 mg, 1.0 mmol) and 4-octyne (110 mg, 1.0 mmol) were added at rt, and the resulting mixture was stirred at 100 °C for 24 h. The mixture was analyzed by ^{19}F NMR using 4-(trifluoromethyl)iodobenzene as an internal standard to estimate the yield of **3a** (80%).

3.4. Intramolecular arylcyanation

A solution of $Ni(cod)_2$ (28 mg, 0.10 mmol) and PMe_3 (15.2 mg, 0.20 mmol) in toluene (2.5 mL) was added to **9**

(167 mg, 1.0 mmol), and the resulting mixture was stirred at 100 °C for 9 h. The mixture was filtered through a silica gel pad and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give (*Z*)-2-indene-1-ylidenepropionitrile (**10**) (86 mg, 51%) as a colorless solid (mp 116.9–117.3 °C), R_f 0.28 (hexane–ethyl acetate = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, J=7.5 Hz, 1H), 7.30–7.20 (m, 3H), 2.97 (t, J=6.0 Hz, 2H), 2.79–2.73 (m, 2H), 2.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 149.3, 137.6, 130.4, 127.0, 125.4, 124.1, 120.4, 95.4, 31.1, 29.3, 18.5; IR (KBr): 2920, 2197, 1622, 1464, 1447, 1261, 1159, 762 cm^{-1}; HRMS (EI) Calcd for $C_{12}H_{11}N$: M^+, 169.0891. Found: *m/z* 169.0898.

3.5. Palladium-catalyzed intramolecular cyclization of 3m[20]

A solution of **3m** (27 mg, 0.10 mmol) and $Pd(OAc)_2$ (3.4 mg, 15 μmol) in trifluoroacetic acid (0.1 mL) and DMSO (2.5 mL) was stirred at 70 °C for 4 h before addition of H_2O (15 mL). Stirring was continued at the same temperature for 24 h, and then the mixture was extracted with Et_2O for three times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give 5,7-dimethoxy-2,3-dipropyl-1-indenone (**17a**, 24 mg, 88%) as a yellow solid (mp 78.4–78.9 °C), R_f 0.25 (hexane–ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J=1.7 Hz, 1H), 6.14 (d, J=1.7 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 2.44 (t, J=7.5 Hz, 2H), 2.20 (t, J=7.5 Hz, 2H), 1.60 (sext, J=7.5 Hz, 2H), 1.48 (sext, J=7.5 Hz, 2H), 1.00 (t, J=7.5 Hz, 3H), 0.91 (t, J=7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.2, 166.6, 157.7, 153.1, 150.2, 136.7, 108.9, 102.2, 95.5, 55.8, 55.7, 27.9, 24.9, 22.5, 21.9, 14.3, 14.1; IR (KBr): 2959, 1693, 1605, 1466, 1379, 1204, 1157 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_3$: M^+, 274.1569. Found: *m/z* 274.1579.

3.6. Palladium-catalyzed intramolecular cyclization of 3n[20]

A solution of **3n** (30 mg, 0.10 mmol) and $Pd(OAc)_2$ (3.4 mg, 15 μmol) in trifluoroacetic acid (0.1 mL) and DMSO (2.5 mL) was stirred at 70 °C for 20 h before addition of H_2O (15 mL). Stirring was continued at the same temperature for 2 h, and then the mixture was extracted with Et_2O for three times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel followed by preparative recycling silica gel chromatography to give 5,6,7-trimethoxy-2,3-dipropyl-1-indenone (**17b**, 16 mg, 54%) as a yellow oil, R_f 0.28 (hexane–ethyl acetate = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (s, 1H), 4.10 (s, 3H), 3.92 (s, 3H), 3.80 (s, 3H), 2.45 (t, J=7.5 Hz, 2H), 2.19 (t, J=7.5 Hz, 2H), 1.62 (sext, J=7.5 Hz, 2H), 1.47 (sext, J=7.5 Hz, 2H), 1.03 (t, J=7.5 Hz, 3H), 0.93 (t, J=7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.3, 157.4, 154.1, 152.2, 143.7, 141.1, 135.7, 113.4, 100.9, 62.4, 61.5, 56.7, 28.0, 25.4, 22.8, 22.1, 14.6, 14.4; IR (neat): 2961, 1697, 1597, 1470, 1404, 1369, 1244, 1132 cm^{-1}; Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.90; H, 7.86.

Acknowledgements

The authors are grateful to Professor Koichiro Oshima for generous use of 500 MHz NMR and to Professor Masaki Shimizu for X-ray crystallographic analysis. This work has been supported financially by Grant-in-Aids for Creative Scientific Research, No. 16GS0209 and COE Research on 'Elements Science' and on 'United Approach to New Material Science' from MEXT. Y.N. also acknowledges the NIPPON SHOKUBAI Award in Synthetic Organic Chemistry, Japan and Mitsubishi Chemical Corporation Fund.

References and notes

1. Murakami, M.; Ito, Y. *Top. Organomet. Chem.* **1999**, *3*, 97–129.
2. (a) Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780–5781; (b) Saito, S.; Masuda, M.; Komagawa, S. *J. Am. Chem. Soc.* **2004**, *126*, 10540–10541.
3. (a) Baba, A.; Ohshiro, Y.; Agawa, T. *J. Organomet. Chem.* **1976**, *110*, 121–127; (b) Kondo, T.; Kaneko, Y.; Taguchi, Y.; Nakamura, A.; Okada, T.; Shiotsuki, M.; Ura, Y.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **2002**, *124*, 6824–6825.
4. Noyori, R.; Suzuki, T.; Takaya, H. *J. Am. Chem. Soc.* **1971**, *93*, 5896–5897.
5. (a) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771–2772; (b) Kondo, T.; Taguchi, Y.; Kaneko, Y.; Niimi, M.; Mitsudo, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5369–5372.
6. (a) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976–13977; (b) Matsuda, T.; Fujimoto, A.; Ishibashi, M.; Murakami, M. *Chem. Lett.* **2004**, 876–877; (c) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932–6933.
7. (a) Burmeister, J. L.; Edwards, L. M. *J. Chem. Soc. A* **1971**, 1663–1666; (b) Gerlach, D. H.; Kane, A. R.; Parshall, G. W.; Jesson, J. P.; Muetterties, E. L. *J. Am. Chem. Soc.* **1971**, *93*, 3543–3544; (c) Parshall, G. W. *J. Am. Chem. Soc.* **1974**, *96*, 2360–2366; (d) Clarke, D. A.; Hunt, M. M.; Kemmitt, D. W. *J. Organomet. Chem.* **1979**, *175*, 303–313; (e) Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1981**, *208*, 103–113; (f) Favero, G.; Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1983**, *241*, 251–257; (g) Bianchini, C.; Masi, D.; Meli, A.; Sabat, M. *Organometallics* **1986**, *5*, 1670–1675; (h) Abla, M.; Yamamoto, T. *J. Organomet. Chem.* **1997**, *532*, 267–270; (i) Churchill, D.; Shin, J. H.; Hascall, T.; Hahn, J. M.; Bridgewater, B. M.; Parkin, G. *Organometallics* **1999**, *18*, 2403–2406; (j) García, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 9547–9555; (k) Liu, Q.-X.; Xu, F.-B.; Li, Q.-S.; Song, H.-B.; Zhang, Z.-Z. *Organometallics* **2004**, *23*, 610–614; (l) Brunkan, N. M.; Brestensky, D. M.; Jones, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 3627–3641; (m) García, J. J.; Arévalo, A.; Brunkan, N. M.; Jones, W. D. *Organometallics* **2004**, *23*, 3997–4002.
8. (a) Taw, F. L.; White, P. S.; Bergman, R. G.; Brookhart, M. *J. Am. Chem. Soc.* **2002**, *124*, 4192–4193; (b) Taw, F. L.; Mueller, A. H.; Bergman, R. G.; Brookhart, M. *J. Am. Chem. Soc.* **2003**, *125*, 9808–9813; (c) Nakazawa, H.; Kawasaki, T.; Miyoshi, K.; Suresh, C. H.; Koga, N. *Organometallics* **2004**, *23*, 117–126.
9. Storhoff, B. N.; Lewis, H. C., Jr. *Coord. Chem. Rev.* **1977**, *23*, 1–29.
10. Catalytic reactions via path A, see (a) Blum, J.; Oppenheimer, E.; Bergmann, E. D. *J. Am. Chem. Soc.* **1967**, *89*, 2338–2341;

(b) Murahashi, S.; Naota, T.; Nakajima, N. *J. Org. Chem.* **1986**, *51*, 898–901; (c) Miller, J. A. *Tetrahedron Lett.* **2001**, *42*, 6991–6993; (d) Miller, J. A.; Dankwardt, J. W. *Tetrahedron Lett.* **2003**, *44*, 1907–1910; (e) Miller, J. A.; Dankwardt, J. W.; Penney, J. M. *Synthesis* **2003**, 1643–1648; (f) Penney, J. M.; Miller, J. A. *Tetrahedron Lett.* **2004**, *45*, 4989–4992; (g) Chaumonnot, A.; Lamy, F.; Sabo-Etienne, S.; Donnadieu, B.; Chaudret, B.; Barthelat, J.-C.; Galland, J.-C. *Organometallics* **2004**, *23*, 3363–3365; (h) van der Vlugt, J. I.; Hewat, A. C.; Neto, S.; Sablong, R.; Mills, A. M.; Lutz, M.; Spek, A. L.; Müeller, C.; Vogt, D. *Adv. Synth. Catal.* **2004**, *346*, 993–1003; (i) Wilting, J.; Müller, C.; Hewat, A. C.; Ellis, D. D.; Tooke, D. M.; Spek, A. L.; Vogt, D. *Organometallics* **2005**, *24*, 13–15; Catalytic reactions via path B, see: (j) Nakazawa, H.; Kamata, K.; Itazaki, M. *Chem. Commun.* **2005**, 4004–4006.

11. (a) Nozaki, K.; Sato, N.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 2679–2681; (b) Nozaki, K.; Sato, N.; Takaya, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1629–1637.
12. Nishihara, Y.; Inoue, Y.; Itazaki, M.; Takagi, K. *Org. Lett.* **2005**, *7*, 2639–2641.
13. Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904–13905.
14. Available from Aldrich, catalog number: 567 671.
15. Use of highly electron-donating *N*-heterocyclic carbene ligands has been reported to induce the cycloaddition reactions of alkynes and nitriles to form pyridines, see: McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030–5031.
16. Formyl C–H bonds have been reported to add across alkynes in the presence of a Ni/P(n-Bu)$_3$ catalyst, see: Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554–2558.
17. Crystallographic data (excluding structure factors) for the structures of **7d** and **10** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 289 422 and CCDC 289 421. 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).
18. Kobayashi, K.; Ueda, T.; Takada, K.; Tanaka, H.; Kitamura, T.; Morikawa, O.; Konishi, H. *J. Org. Chem.* **1997**, *62*, 664–668.
19. For examples, see: (a) Stüdemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299–1316; (b) Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* **2001**, 2688–2689.
20. Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302–2303.
21. For recent examples of transition metal-catalyzed indenone synthesis, see: (a) Larock, R. C.; Doty, M. J. *J. Org. Chem.* **1993**, *58*, 4579–4583; (b) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1996**, *61*, 6941–6946; (c) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276–9287; (d) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339–3341.
22. Buck, M.; Chong, J. M. *Tetrahedron Lett.* **2001**, *42*, 5825–5827.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 7577–7582

Snapshots of the oxidative-addition process of silanes to nickel(0)

Vlad M. Iluc and Gregory L. Hillhouse*

Searle Chemistry Laboratory, Department of Chemistry, The University of Chicago, Chicago, IL 60637, USA

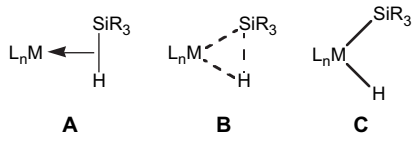
Received 3 February 2006; revised 13 March 2006; accepted 13 March 2006
Available online 21 June 2006

Dedicated to Professor Günther Wilke who has nurtured the field of organonickel chemistry from its infancy to its present state of maturity and importance

Abstract—Addition of hydridosilanes, Ar_2SiHX, to the labile Ni(0) benzene complex $[(dtbpe)Ni]_2(C_6H_6)$ (**1**; dtbpe=1,2-bis(di-*tert*-butylphosphino)ethane) gives mononuclear Ni(II) hydride silyl complexes of the formulation $(dtbpe)Ni(\mu\text{-}H)SiAr_2X$ (**2**, X=H, Ar=Mes; **3**, X=H, Ar=Ph; **4**, X=Me, Ar=Ph; **5**, X=Cl, Ar=Ph). Although the crystal structures of two representatives of the series indicate square-planar coordination around nickel, in solution structures having apparent C_{2v} symmetry are observed. We propose that this behavior is due to a fluxional process that involves η^2-SiH intermediates. Other data are also consistent with the facile reductive elimination of the silane to regenerate nickel(0) products. Oxidation of **2** and **3** with triphenylcarbenium tetrakis(pentafluorophenyl)borate results in silane elimination and formation of $[(dtbpe)Ni(\eta^3\text{-}C_6H_5CPh_2)^+][B(C_6F_5)_4^-]$ (**6**), the structure of which shows the CPh_3^- ligand bound to a Ni(II) center through a phenyl ring in an η^3-allylic fashion.

1. Introduction

Due to interest in silicon-containing materials, the chemistry of metal silyl–silylene complexes has received increased attention in recent years. Silyl complexes show distinct differences when compared to corresponding alkyl complexes, an important one being the facility of addition of Si–H bonds compared to the more problematical addition of C–H bonds to transition metal fragments.[1] Unlike C–H activation processes, which although known, are difficult, the oxidative addition of silanes is one of the main methods of preparing silyl complexes. The nature of the metal–SiH interaction has been intensively studied, but there is a structural continuum between the limiting extremes of η^2-SiH bonding (**A**) and complete oxidative addition (**C**); computational methods are also ambiguous (Scheme 1).[1a,c]



Scheme 1.

Due to the reactivity of most $[M](SiR_3)(H)$ species, there are very few instances where the primary product of Si–H oxidative addition has been isolated, that being even more true for the transition metals of the nickel triad. Moreover, complexes containing agostic or nonclassical Si–H interactions are relatively rare for the late-transition metals and few examples are known for mononuclear compounds.[2] Thus, insight into this process could be obtained from the isolation and characterization of complexes proposed to be intermediates in metal-hydrosilylation reactions. Our work with low valent nickel complexes supported by a bulky diphosphine ligand has provided us with the appropriate framework to study the direct interaction of a secondary silane and a Ni(0) species. The Ni(dtbpe) fragment (dtbpe= 1,2-bis(di-*tert*-butylphosphino)ethane) has been shown to be effective in supporting unusual low valent metal functionalities such as nitrene, phosphinidene, and carbene,[3] and we were intrigued by the possibility of accessing silylene analogues ($(dtbpe)Ni{=}SiR_2$) by double Si–H activation of hydridosilanes in processes similar to those reported by Tilley and co-workers in Pt, Ir, and W systems.[4] Herein, we present our findings on the interactions of $HSiXR_2$ (X=H, CH_3, Cl; R=phenyl, 2,4,6-trimethylphenyl) with the labile Ni(0) complex $[(dtbpe)Ni]_2(C_6H_6)$ (**1**)[5] and the characterization of nickel silyl hydride reaction products.

2. Experimental

2.1. General considerations

Unless otherwise stated, all manipulations were performed under an inert atmosphere using an MBraun Lab Master dry box, under a purified nitrogen atmosphere; *n*-pentane

* Corresponding author. Tel.: +1 773 702 7057; fax: +1 773 702 0805; e-mail: g-hillhouse@uchicago.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.055

was dried via passage through activated alumina and Q-5 columns and then stored over 4 Å molecular sieves. [(dtbpe)Ni]$_2$(C_6H_6) (**1**) and dimesitylsilane were synthesized according to the literature;[5,6] [Ph_3C^+][$B(C_6F_5)_4^-$] by adaptation of a published procedure.[7] All other chemicals were used as received. Infrared data (Nujol mulls on CaF_2 plates) were measured with a Nicolet 670-FTIR instrument. ^{1}H, ^{13}C, ^{31}P, and ^{29}Si NMR spectra were recorded on Bruker 500 and 400 MHz NMR spectrometers. ^{1}H and ^{13}C NMR are reported with reference to solvent resonances (for residual C_6D_5H, δ_H=7.16 and δ_C=128.0 in C_6D_6; for residual C_4HD_7O, δ_H=3.58 and δ_C=67.8; for residual $CHDCl_2$, δ_H=5.32 and δ_C=53.8 in CD_2Cl_2). ^{31}P NMR spectra are reported with respect to external 85% H_3PO_4 (0 ppm). ^{29}Si NMR spectra are reported with respect to external neat TMS (0 ppm). X-ray diffraction data were collected on a Siemens Platform goniometer with a Charged Coupled Device (CCD) detector. Structures were solved by direct methods using the SHELXTL (version 5.1) program library (G. Sheldrick, Bruker Analytical X-ray Systems, Madison, WI).

2.1.1. Synthesis and characterization of (dtbpe)Ni(μ-H)-SiH(Mes)$_2$ (2). To a suspension of **1** (100 mg, 0.12 mmol) in 5 mL of *n*-pentane was added a cold solution of dimesitylsilane (64.43 mg, 0.24 mmol) in 2 mL of *n*-pentane. After stirring the mixture for 1 h at room temperature, precipitation was induced by cooling the solution overnight at −35 °C. The solids were separated by filtration, washed with cold *n*-pentane, and dried under vacuum to yield yellow crystalline **2** (100 mg, 0.15 mmol, 65%). ^{1}H NMR (298 K, 400.13 MHz, THF-d_8): δ 6.62 (s, 4H, $C_6H_2(CH_3)_3$), 2.40 (s, 12H, *o*-$C_6H_2(CH_3)_3$), 2.14 (s, 6H, *p*-$C_6H_2(CH_3)_3$), 1.88 (d, 4H, J_{HP}=8.6 Hz, CH_2), 1.21 (d, 36H, J_{HP}=12.0 Hz, $C(CH_3)_3$), −0.17 (t, 2H, J_{HP}=30.3 Hz, SiH_2). ^{13}C{^{1}H} NMR (298 K, 100.62 MHz, THF-d_8): δ 144.25 (s, Ar), 141.53 (s, Ar), 135.77 (s, Ar), 128.71 (s, Ar), 35.47 (t, J_{CP}=6.9 Hz, $C(CH_3)_3$), 31.15 (s, $C(CH_3)_3$), 25.56 (s, *o*-$C_6H_2(CH_3)_3$), 23.89 (t, J_{CP}=15.6 Hz, CH_2), 21.23 (s, *p*-$C_6H_2(CH_3)_3$). ^{31}P{^{1}H} NMR (298 K, 202.45 MHz, THF-d_8): δ 90.55 (s, J_{PSi}=53.1 Hz). ^{29}Si{^{1}H} NMR (298 K, 79.51 MHz, THF-d_8): δ 53.36 (t, J_{SiP}=53.5 Hz). IR (Nujol, CaF_2): 3041 (w), 1990 (s), 1861 (m) cm^{-1}.

2.1.2. Single-crystal X-ray structure of 2. Crystal data for **2**·1/2(C_5H_{12}): $C_{38.5}H_{64}NiP_2Si$, M=675.64, triclinic, $P\bar{1}$, a=11.283(3), b=12.291(4), c=15.994(5) Å, α=85.697(6)°, β=81.859(6)°, γ=64.003(5)°, Z=2, t=100 K, μ(Mo Kα)=0.627 mm^{-1}. A yellow prism of **2** (0.16×0.1×0.06 mm) grown from *n*-pentane at −35 °C was mounted in inert oil and transferred to the 100 K gas stream of the diffractometer. Of 9040 total reflections ($1.29°<\theta<23.33°$), 5671 were independent and 4218 (R_{int}=4.71%) were observed with $I>2\sigma(I)$. The structure was solved using direct methods and refined by full-matrix least squares on F^2. All nonhydrogen atoms were refined anisotropically. H1 and H2 were located in the electron density map; all other hydrogen atoms were fit to idealized positions and refined isotropically. The solvation molecule of *n*-pentane is in the inversion center and is disordered over two positions. $R(F)$=5.26% and $R(wF)$=12.33%. CCDC reference no. 610081.

2.1.3. Synthesis and characterization of (dtbpe)Ni(μ-H)-SiH(C_6H_5)$_2$ (3). Complex **3** was synthesized following the protocol used for **2** except that diphenylsilane was employed. In this case, the product precipitates at room temperature and it was separated as bright yellow crystalline powder by filtration followed by washing with *n*-pentane and drying under vacuum to give pure **3** (121.28 mg, 0.22 mmol, 90%). ^{1}H NMR (298 K, 400.13 MHz, C_6D_6): δ 8.26 (d, 4H, J_{HH}=7.1 Hz, Ar), 7.33 (t, 4H, J_{HH}=7.5 Hz, Ar), 7.19 (t, 2H, J_{HH}=7.3 Hz, Ar), 1.32 (d, 4H, J_{HP}=9.4 Hz, CH_2), 1.09 (d, 36H, J_{HP}=12.0 Hz, $C(CH_3)_3$), 0.20 (t, br, 2H, J_{HP}=2.0 Hz, $SiH_2(C_6H_5)_2$). ^{13}C{^{1}H} NMR (298 K, 100.62 MHz, C_6D_6): δ 146.68 (s, Ar), 136.49 (s, Ar), 127.60 (s, Ar), 127.43 (s, Ar), 35.14 (t, J_{CP}=7.3 Hz, $C(CH_3)_3$), 30.56 (s, $C(CH_3)_3$), 23.69 (t, J_{CP}=16.2 Hz, CH_2). ^{31}P{^{1}H} NMR (298 K, 202.45 MHz, C_6D_6): δ 92.19 (s, J_{PSi}=51.6 Hz). ^{29}Si{^{1}H} NMR (298 K, 79.51 MHz, C_6D_6): δ 54.00 (t, J_{SiP}=51.6 Hz). IR (Nujol, CaF_2): 3058 (w), 3038 (w), 1993 (s), 1855 (m), 1179 (m) cm^{-1}.

2.1.4. Synthesis and characterization of (dtbpe)Ni(μ-H)-Si(CH_3)(C_6H_5)$_2$ (4). Complex **4** was synthesized following the protocol used for **2** except that diphenylmethylsilane was employed, yielding orange crystalline **4** (96.68 mg, 0.17 mmol, 70%). ^{1}H NMR (298 K, 500.13 MHz, THF-d_8): δ 7.52 (m, 4H, C_6H_5), 7.15–6.95 (m, 6H, C_6H_5), 1.83 (d, 4H, J_{HP}=8.8 Hz, CH_2), 1.19 (d, 36H, J_{HP}=12.0 Hz, $C(CH)_3$), 0.71 (s, 3H, $SiCH_3$), −6.49 (t, 1H, br, NiH). ^{13}C{^{1}H} NMR (298 K, 100.62 MHz, THF-d_8): δ 150.27 (s, C_6H_5), 135.99 (s, C_6H_5), 126.97 (s, C_6H_5), 126.03 (s, C_6H_5), 35.29 (t, J_{CP}=7.3 Hz, $C(CH_3)_3$), 30.96 (s, $C(CH_3)_3$), 24.41 (t, J_{CP}=16.9 Hz, CH_2), ^{31}P{^{1}H} NMR (298 K, 202.45 MHz, THF-d_8): δ 93.16 (s, br). ^{29}Si{^{1}H} NMR (298 K, 79.51 MHz, THF-d_8): δ 59.22 (t, J_{SiP}=51.2 Hz). IR (Nujol, CaF_2): 1845 (m), 1425 (s), 1181 (m) cm^{-1}.

2.1.5. Synthesis and characterization of (dtbpe)Ni(μ-H)-SiCl(C_6H_5)$_2$ (5). To a suspension of **1** (100 mg, 0.12 mmol) in 5 mL of *n*-pentane was added a 2 mL *n*-pentane solution of diphenylchlorosilane (55 mg, 0.25 mmol). The reaction mixture was stirred for 1 h at room temperature. The bright yellow precipitate was filtered and washed with 2 mL of *n*-pentane and vacuum dried to yield pure **5** (120 mg, 0.20 mmol, 84%). For **5**: ^{1}H NMR (298 K, 400.13 MHz, C_6D_6): δ 8.26 (dd, 4H, J_{HH}=8.0 Hz, J_{HH}=1.3 Hz, Ar), 7.31 (td, 4H, J_{HH}=7.7 Hz, J_{HH}=1.3 Hz, Ar), 7.18 (tt, 2H, J_{HH}=5.6 Hz, J_{HH}=1.3 Hz, Ar), 1.32 (d, 4H, J_{HP}=9.6 Hz, CH_2), 1.10 (d, 36H, J_{HP}=9.6 Hz, $C(CH_3)_3$), −8.29 (t, 1H, J_{HP}=29.8 Hz, J_{HSi}=5.0 Hz, $SiH(C_6H_5)_2$); (200 K, 500.13 MHz, C_7D_8): δ 1.20 (d, 18H, J_{HP}=11.0 Hz, $C(CH_3)_3$), 0.95 (d, 18H, J_{HP}=10.5 Hz, $C(CH_3)_3$), −8.19 (dd, 1H, J_{HP}=20.0 Hz, J_{HP}=90.0 Hz, $SiH(C_6H_5)_2$). ^{13}C{^{1}H} NMR (298 K, 100.62 MHz, C_6D_6): δ 147.98 (s, Ar), 135.53 (s, Ar), 129.06 (s, Ar), 127.44 (s, Ar), 34.82 (t, J_{CP}=7.4 Hz, $C(CH_3)_3$), 30.54 (s, $C(CH_3)_3$), 23.70 (s, br, CH_2). ^{31}P{^{1}H} NMR (298 K, 202.45 MHz, C_6D_6): δ 92.65 (s, J_{PSi}=77 Hz). ^{29}Si{^{1}H} NMR (298 K, 79.51 MHz, C_6D_6): δ 24.00 (t, J_{SiP}=77.6 Hz). IR (Nujol, CaF_2): 1883 (w), 1425 (w) cm^{-1}.

2.1.6. Single-crystal X-ray structure of 5. Crystal data for **5**: $C_{30}H_{51}ClNiP_2Si$, M=595.90, triclinic, $P\bar{1}$, a=9.8023(13), b=10.5891(13), c=16.608(2) Å, α=90.328(3)°, β=92.863(3)°, γ=113.578(2)°, Z=2, t=100 K, μ(Mo Kα)=0.856 mm^{-1}. A yellow block of **5** (0.1×0.08×0.08 mm)

grown from *n*-pentane at −35 °C was mounted in inert oil and transferred to the 100 K gas stream of the diffractometer. Of 9984 total reflections ($1.23°<\theta<28.27°$), 7059 were independent and 4893 (R_{int}=5.17%) were observed with $I>2\sigma(I)$. The structure was solved using direct methods and refined by full-matrix least squares on F^2. All nonhydrogen atoms were refined anisotropically. The hydride hydrogen atom was located in the electron density map, all other hydrogen atoms were fit to idealized positions and refined isotropically. $R(F)$=9.86% and $R(wF)$=14.64%. CCDC reference no. 610082.

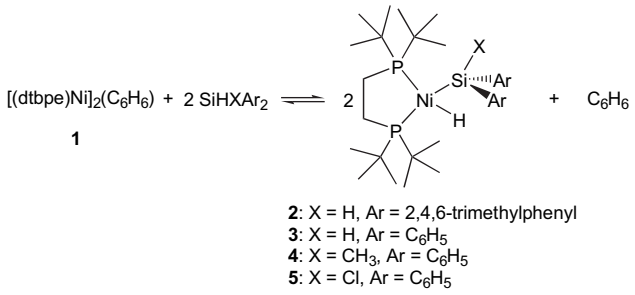
2.1.7. Synthesis of $[Ph_3C^+][B(C_6F_5)_4^-]$. This compound was synthesized adapting a published procedure for triphenylcarbenium tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate by using $Na^+[B(C_6F_5)_4^-]$ instead of sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.[7]

2.1.8. Synthesis and characterization of $[(dtbpe)Ni(\eta^3\text{-}C_6H_5CPh_2)^+][B(C_6F_5)_4^-]$ (6). *Method A*: To a cold solution of **2** (64.56 mg, 0.1 mmol, in 5 mL diethyl ether at −35 °C), a 5 mL solution of $[Ph_3C^+][B(C_6F_5)_4^-]$ (92.24 mg, 0.1 mmol) at −35 °C was added dropwise. The mixture was allowed to warm to room temperature and stir for another 30 min. After removal of solvent under vacuum, the solids were triturated with *n*-pentane (3×5 mL). The ^{1}H NMR of this fraction shows recovered silane in 95%. The yellow crude solid was recrystallized from a 1:1 diethyl ether–*n*-pentane mixture affording (**6**) in 80% isolated yield (103.96 mg, 0.08 mmol). Complex **3** reacts with $[Ph_3C^+][B(C_6F_5)_4^-]$ in an analogous fashion to give **6** in 80% isolated yield. *Method B*: To a cold solution of **1** (41.62 mg, 0.05 mmol, in 5 mL diethyl ether at −35 °C), a 5 mL solution of $[Ph_3C^+][B(C_6F_5)_4^-]$ (92.24 mg, 0.1 mmol) at −35 °C was added dropwise. The mixture was allowed to warm to room temperature and stir for another 30 min. After removal of solvent under vacuum, the solids were triturated with *n*-pentane (3×5 mL). The yellow crude solid was recrystallized from a 1:1 diethyl ether–*n*-pentane mixture affording **6** in 90% isolated yield (116.95 mg, 0.09 mmol). For **6**: ^{1}H NMR (298 K, 400.13 MHz, CD_2Cl_2): δ 7.39 (t, 2H, J_{HH}=7.0 Hz, Ph), 7.23–7.33 (m, 8H, Ph), 6.89 (dd, 2H, J_{HH}=8.8 Hz, J_{HH}=2.5 Hz, Ph), 6.23 (t, 1H, J_{HH}=5.1 Hz, Ph), 5.93 (t, 2H, J_{HH}=6.9 Hz, Ph), 1.87 (sextet, 2H, J=8.1 Hz, CH_2), 1.71 (sextet, 2H, J=8.0 Hz, CH_2), 1.90 (d, 18H, J_{HP}=13.1 Hz, $C(CH_3)_3$), 1.15 (d, 18H, J_{HP}=13.2 Hz, $C(CH_3)_3$). ^{13}C{^{1}H} NMR (298 K, 100.62 MHz, CD_2Cl_2): δ 148.45 (d, J_{HF}=241.5 Hz, C_6F_5), 142.81 (s, CPh_3), 138.56 (d, J_{HF}=247.8 Hz, C_6F_5), 167.65 (d, J_{HF}=244.8 Hz, C_6F_5), 136.55 (s, C_6F_5), 129.60 (s, Ph), 128.92 (s, Ph), 128.31 (s, Ph), 112.75 (s, Ph), 107.59 (d, J_{CP}=9.0 Hz, Ph), 71.35 (d, J_{CP}=9.2 Hz, Ph), 37.57 (d, J_{CP}=14.5 Hz, $C(CH_3)_3$), 36.07 (d, J_{CP}=13.6 Hz, $C(CH_3)_3$), 30.28 (d, J_{CP}=13.4 Hz, $C(CH_3)_3$), 22.96 (m, CH_2). ^{31}P{^{1}H} NMR (298 K, 202.45 MHz, CD_2Cl_2): δ 89.17 (d, J_{PP}=12.1 Hz), 86.12 (d, J_{PP}=12.2 Hz).

2.1.9. Single-crystal X-ray structure of 6. Crystal data for **6**: $C_{69}H_{67}BF_{24}NiP_2$, M=1483.69, triclinic, $P\bar{1}$, a=13.579(3), b=15.064(4), c=17.160(4) Å, α=97.363(5)°, β=104.497(5)°, γ=96.744(5)°, Z=2, t=100 K, μ(Mo Kα)=0.449 mm^{-1}. A yellow block of **5** (0.04×0.04×0.08 mm) grown from 1:1 diethyl ether–*n*-pentane at −35 °C was mounted in inert oil and transferred to the 100 K gas stream of the diffractometer. Of 15,032 total reflections ($1.24°<\theta<23.34°$), 9516 were independent and 7362 (R_{int}=7.69%) were observed with $I>2\sigma(I)$. The structure was solved using direct methods and refined by full-matrix least squares on F^2. All nonhydrogen atoms were refined anisotropically, hydrogen atoms were fit to idealized positions and refined isotropically. $R(F)$=4.91% and $R(wF)$=12.16%. CCDC reference no. 610083.

3. Results and discussion

Reaction of pentane solutions of $[(dtbpe)Ni]_2(C_6H_6)$ (**1**) with dimesitylsilane (Mes_2SiH_2) at room temperature affords (dtbpe)Ni(μ-H)SiH$(Mes)_2$ (**2**) in 65% isolated yield (Scheme 2). The solid-state structure of **2** was determined by X-ray crystallography and a perspective view of the complex is shown in Figure 1. The structure of **2** shows a square-planar nickel coordinated to the chelating dtbpe ligand, silicon, and hydrogen. The relative position of the hydride and the silyl fragments is consistent with arrested oxidative addition of the silane, i.e., a structure intermediate between **B** and **C** in Scheme 1. As expected, the Si–H(2) bond involving the bridging hydrogen at 1.92(4) Å is much longer than the terminal Si–H(1) bond distance of 1.42(4) Å. The Ni–Si bond length (2.245(2) Å) is in the range of known Ni–Si single bonds.[8]



Scheme 2.

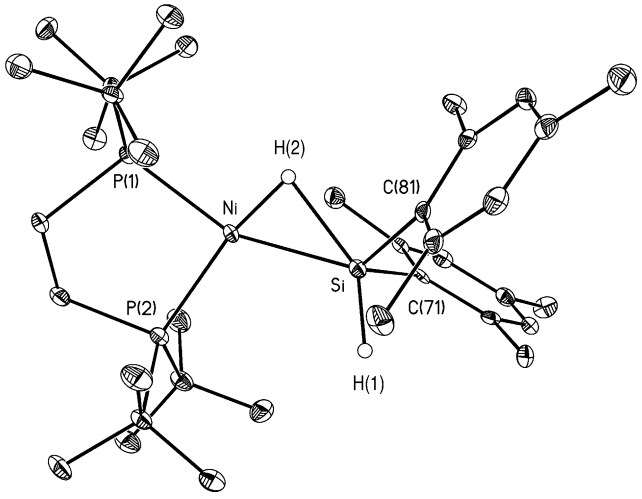


Figure 1. ORTEP view of complex **2** (35% probability thermal ellipsoids, H atoms except those attached to Si and Ni omitted for clarity). Selected bond distances (Å) and angles (°): Ni–P1=2.184(2), Ni–P2=2.195(2), Ni–Si=2.245(2), Ni–H(2)=1.41(4), Si–H(1)=1.42(4), Si–H(2)=1.92(4), Si–C(71)=1.936(4), Si–C(81)=1.918(4) Å; P(1)–Ni–P(2)=93.09(5), P(1)–Ni–H(2)=97(2), P(2)–Ni–Si=111.06(5), Si–Ni–H(2)=58(2), C(71)–Si–C(81)=106.3(2), C(71)–Si–Ni=116.42(15), C(81)–Si–Ni=119.63(13)°.

Because of unusual solution behavior of **2** (vide infra), we prepared several analogues of **2** using the same synthetic protocol. Thus, diphenylsilane, diphenylmethylsilane, and chlorodiphenylsilane react with **1** to yield (dtbpe)Ni(μ-H)-$SiH(C_6H_5)_2$ (**3**), (dtbpe)Ni(μ-H)$Si(CH_3)(C_6H_5)_2$ (**4**), and (dtbpe)Ni(μ-H)$SiCl(C_6H_5)_2$ (**5**), respectively (Scheme 2).

The solid-state structure of **5** was determined by X-ray crystallography and a perspective view of the complex is shown in Figure 2. Like that of **2**, the structure of **5** shows a square-planar nickel coordinated to the chelating dtbpe ligand, silicon, and hydrogen. Key metrical parameters in the nickel coordination sphere of **5**, Si–H=1.90(5) Å and Ni–Si= 2.222(2) Å, are essentially the same as those found in **2**. IR spectra confirm the crystal data, and a typical strong Si–H stretching vibration at ~2000 cm^{-1} is observed in **2** and **3** but is absent in **4** and **5.**

Solution NMR data for **2** indicate interesting dynamic, fluxional behavior. ^1H and ^{31}P measurements taken in benzene-d_6 show **2** to be in equilibrium with free Mes_2SiH_2 (^1H δ 5.29, SiH_2) and **1**-d_6, with **2** predominating at lower temperatures. NMR spectra of **2** in THF-d_8 show the presence of a C_{2v} symmetrical environment. Four equivalent *tert*-butyl groups are observed at δ 1.21 for the phosphine ligand and two equivalent protons at δ −0.17 for the coordinated silane in the ^1H NMR spectrum, and a singlet resonance is seen at δ 90.55 (with ^{29}Si satellites) in the ^{31}P spectrum. The observation of J_{PH}~30 Hz (SiH_2) in the ^1H spectrum and J_{SiP}~53 Hz in the ^{29}Si and ^{31}P spectra indicate that Mes_2SiH_2 is not undergoing dissociation from the nickel center on the NMR timescale in tetrahydrofuran solution, unlike in benzene. In the case of compound **2**, we were not able to freeze out (by NMR) a static solution structure on cooling. Consistent with these observations, spectra of (dtbpe)Ni(SiHD$(Mes)_2$ (**2**-d_1), prepared from **1** and Mes_2-SiHD, show the same chemical shift for the Si–H proton in the ^1H NMR spectrum as for the Si–D deuteron in the ^2H NMR spectrum indicating that these two are exchanging on the NMR timescale.

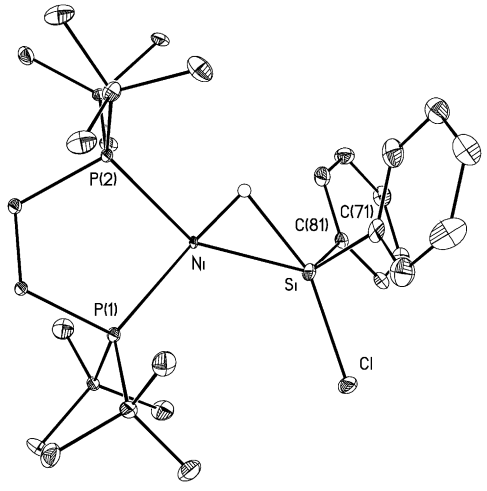
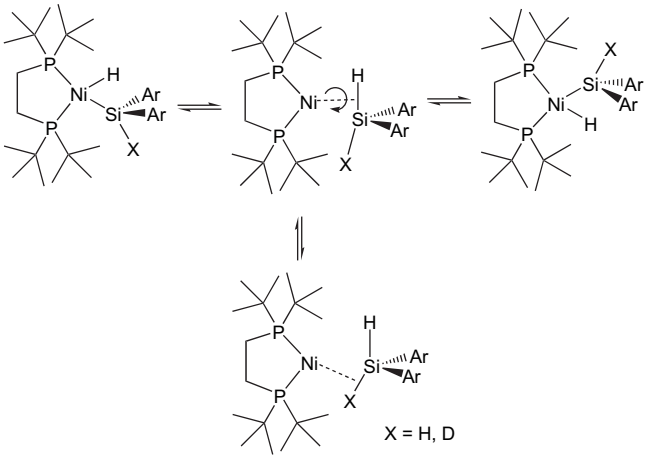


Figure 2. ORTEP view of the structure of complex **5** (35% probability thermal ellipsoids, H atoms except those attached to Si and Ni omitted for clarity). Selected bond distances (Å) and angles (°): Ni–P1=2.186(2), Ni–P2=2.189(2), Ni–Si=2.222(2), Ni–H=1.32(5), Si–H=1.90(5), Si–Cl=2.166(2), Si–C(71)=1.928(7), Si–C(81)=1.906(7) Å; P(1)–Ni–P(2)=95.51(6), P(2)–Ni–H=91(2), P(1)–Ni–Si=117.77(7), Si–Ni–H= 59(2), C(71)–Si–C(81)=108.2(3), C(71)–Si–Ni=106.5(2), C(81)–Si–Ni= 117.9(2), Cl–Si–Ni=122.22(9)°.

Similar solution fluxionality was observed for **3** and **4**, giving apparent C_{2v} symmetrical structures in solution. Interestingly, in contrast to **2**, complexes **3**, **4**, and **5** in benzene solution appear not to be in equilibrium with the free silane and **1**-d_6, perhaps a consequence of the smaller size of their aryl substituents compared with the two bulky mesityl silyl substituents in **2**. Moreover, in the case of compound **5**, this fluxional process is sufficiently slow at 200 K in the ^1H NMR spectrum (toluene-d_8) that the asymmetric solution structure consistent with the solid-state structure could be observed. The upfield triplet (δ −8.29, J_{PH}=30 Hz) for the hydride ligand observed at room temperature resolves on cooling (200 K) into the expected doublet-of-doublets (δ −8.19, J_{PH}=20 Hz, J_{PH}=90 Hz) due to coupling with the two inequivalent (*cis* and *trans*) ^{31}P nuclei. The *tert*-butyl resonances behave in a similar manner, splitting into two doublets at 200 K corresponding to pairwise inequivalent *tert*-butyls in the static structure. Chen et al. have reported similar fluxionality in $(Et_2PCH_2CH_2PEt_2)$Ni{[2-(SiH_3)-$C_6H_4]_2SiH_2$} in which the hydride ligand resonances partially resolve at 193 K.[9]

These data are consistent with dynamic processes illustrated in Scheme 3. The key feature is reversible oxidative addition via a Ni(0)-η^2 silane intermediate. Rapid rotation about the Ni–(H–Si) bond followed by oxidative addition allows equilibration of the two sides of phosphine ligand. When a secondary silane is employed, a second process that interchanges the two hydrogen positions is also occurring. This is reflected in the ^1H chemical shifts of the unique proton(s). In **4** and **5** in which there is no second (exchangeable) hydrogen, the resonances occur in the normal upfield hydride region (δ −6.5 and −8.3, respectively), whereas in **2** and **3** the exchanging protons resonate at δ~0, and average of the upfield hydride resonance and the downfield resonance for a typical Si–H moiety (δ~5).

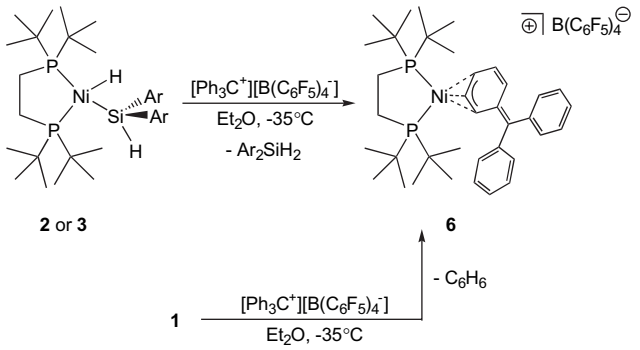


Scheme 3.

We have surveyed the reactions of complexes **2**–**5** with alkenes and alkynes in anticipation that they might participate in hydrosilylation of the unsaturated carbyl substrates, but the reactions invariably led to elimination of the original

silane. For example, **3** reacts with ethylene to give Ph_2SiH_2 and (dtbpe)Ni(C_2H_4),[10] and with alkynes to give the corresponding (dtbpe)Ni(C_2R_2) adducts.[11]

Given the stability of cationic Ni(II) alkyls in this system, like [(dtbpe)Ni(CH_2CMe_3)$^+$],[12] we attempted to prepare silyl analogues [(dtbpe)Ni($SiAr_2X$)$^+$] by hydride abstraction from **2** and **3**. Silane elimination also confounded our efforts here. Reaction of **2** or **3** with triphenylcarbenium tetrakis-(pentafluorophenyl)borate in diethyl ether results in silane elimination and formation of the unusual 'triphenylmethyl' complex [(dtbpe)Ni(η^3-$C_6H_5CPh_2$)$^+$][$B(C_6F_5)_4^-$] (**6**) in high yield (Scheme 4; Fig. 3). Complex **6** was characterized by NMR (^{1}H, ^{13}C, ^{31}P) spectroscopy and by single-crystal X-ray diffraction. Instead of hydride abstraction by trityl, elimination of Mes_2SiH_2 or Ph_2SiH_2 occurs to give a Ni(0) intermediate that undergoes two-electron oxidation by trityl with coordination of the resulting 'Ph_3C^-' fragment. Analysis of the organic fraction of the reaction mixture showed only Mes_2SiH_2 or Ph_2SiH_2. Consistent with this scenario is the observation that **6** alternatively can be prepared by the reaction of [CPh_3^+][$B(C_6F_5)_4^-$] with the benzene complex **1**.



Scheme 4.

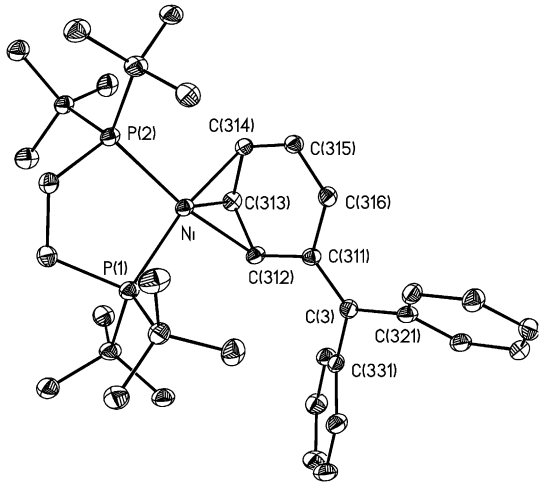


Figure 3. ORTEP view of the complex cation of **6** (35% probability thermal ellipsoids, H atoms and the counter anion omitted for clarity). Selected bond distances (Å) and angles (°): Ni–P(1)=2.2374(11), Ni–P(2)=2.224(1), Ni–C(312)=2.192(3), Ni–C(313)=1.991(3), Ni–C(314)=2.095(3), C(311)–C(312)=1.457(5), C(312)–C(313)=1.401(5), C(313)–C(314)=1.401(5), C(314)–C(315)=1.434(5), C(315)–C(316)=1.351(5), C(316)–C(311)=1.451(5), C(311)–C(3)=1.375(5), C(321)–C(3)=1.483(5), C(331)–C(3)=1.492(5) Å; P(1)–Ni–P(2)=92.03(4), C(311)–C(3)–C(321)=123.5(3), C(321)–C(3)–C(331)=114.7(3), C(331)–C(3)–C(311)=121.7(3)°.

The solid-state structure of **6** is an interesting one (Fig. 3). The CPh_3^- ligand is coordinated to nickel in an η^3-allylic fashion through adjacent *ortho*, *meta*, and *para* carbons of one of its phenyl rings, resulting in alternating C–C bond lengths in the coordinated phenyl group indicative of disruption of its 6-π aromaticity. The C(311)–C(312), C(311)–C(316), and C(314)–C(315) bond distances (1.457(5), 1.451(5), 1.434(5) Å) are in the range for C–C single bonds (~1.48 Å),[13] the C(315)–C(316) and C(311)–C(3) bond distances (1.351(5), 1.375(5) Å) are near the expected value for C=C double bonds (~1.33 Å),[13] and the bonds between the three carbon atoms bound to nickel, C(312), C(313), and C(314), exhibit intermediate bond distances (both 1.401(5) Å) as expected for a delocalized allylic fragment. The three phenyl groups of the Ph_3C^- ligand are arranged in a propeller fashion, and its central carbon (C(3)) is planar. The Ni–C bond distances range from 2.192(3) to 1.991(3) Å.

It is noteworthy that several late-transition metal complexes of Ph_3C^- have been reported, with various structures,[14] including [Pd(CPh_3)(μ-Cl)]$_2$ and Pd(acac)(CPh_3), which has an η^3-benzylic coordination mode (i.e., through the central carbon and the *ipso* and *ortho* carbons of one of the Ph rings).[14c] Structures of uncomplexed Ph_3C^- as encrypted alkali metal salts have also been reported.[15] The preference of trityl to coordinate to the Ni center in **6** through one of the phenyl rings in an allylic fashion (instead through central carbon in η^1- or η^3-modes) is probably a consequence of steric crowding engendered by the bulky dtbpe ligand.

4. Conclusions

In conclusion, the Ni complexes obtained by the reaction of **1** with several hydridosilanes allow insight into intermediate stages of the Si–H oxidative-addition reaction to a Ni(0) center. Of note is the highly fluxional nature of the η^2-SiH–Ni linkage. Reactivity studies on these compounds showed the silane addition to nickel is reversible and that the silicon-containing ligand is quite labile.

5. Crystallographic data

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 610081 for compound **2**, CCDC no. 610082 for compound **5**, and CCDC no. 610083 for compound **6**.

Acknowledgements

We are grateful to the National Science Foundation for financial support of this research through Grant CHE-0244239 to G.L.H.

References and notes

1. (a) Corey, Y. J.; Braddock-Wilking, J. *Chem. Rev.* **1999**, *99*, 175; (b) Crabtree, R. H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 789; (c) Schneider, J. J. *Angew. Chem., Int. Ed.* **1996**, *35*, 1068.

2. (a) Gehrhus, B.; Hitchcock, P. B.; Lappert, M. F.; Maciejewski, H. *Organometallics* **1998**, *17*, 5599; (b) Shimada, S.; Tanaka, M.; Shiro, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 1856; (c) Shimada, S.; Tanaka, M.; Honda, K. *J. Am. Chem. Soc.* **1995**, *117*, 8289.
3. (a) Mindiola, D. J.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2001**, *123*, 4623; (b) Melenkivitz, R.; Mindiola, D. J.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 3846; (c) Mindiola, D. J.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 9976.
4. (a) Peters, J. C.; Feldman, J. D.; Tilley, T. D. *J. Am. Chem. Soc.* **1999**, *121*, 9871; (b) Mitchell, G. P.; Tilley, T. D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2524; (c) Mork, B. V.; Tilley, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 9702.
5. Bach, I.; Pörschke, K.-R.; Goddard, R.; Kopiske, C.; Krüger, C.; Rufinska, A.; Seevogel, K. *Organometallics* **1996**, *15*, 4959.
6. Sadow, A. D.; Tilley, T. D. *J. Am. Chem. Soc.* **2002**, *124*, 6814.
7. Bahr, S. R.; Boudjouk, P. *J. Org. Chem.* **1992**, *57*, 5545.
8. (a) Shimada, S.; Rao, M. L. N.; Tanaka, M. *Organometallics* **1999**, *18*, 292; (b) Avent, A. G.; Gehrhus, B.; Hitchcock, P. B.; Lappert, M. F.; Maciejewski, H. *J. Organomet. Chem.* **2003**, *686*, 321; (c) Shimada, S.; Rao, M. L. N.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 213; (d) Bierchenk, T. R.; Guerra, M. A.; Juhlke, T. J.; Larson, S. B.; Lagow, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 4855; (e) Nlate, S.; Herdtweck, E.; Fischer, R. A. *Angew. Chem., Int. Ed.* **1996**, *35*, 1861; (f) Maciejewski, H.; Marciniec, B.; Kownacki, I. *J. Organomet. Chem.* **2000**, *597*, 175.
9. Chen, W.; Shimada, S.; Tanaka, M.; Kobayashi, Y.; Saigo, K. *J. Am. Chem. Soc.* **2004**, *126*, 8072.
10. Conroy-Lewis, F. M.; Mole, L.; Redhouse, A. D.; Litster, S. A.; Spencer, J. L. *J. Chem. Soc., Chem. Commun.* **1991**, 1601.
11. Waterman, R.; Hillhouse, G. L. *Organometallics* **2003**, *22*, 5182.
12. Kitiachvili, K. D.; Mindiola, D. J.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2004**, *126*, 10554.
13. Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960.
14. (a) Sonoda, A.; Mann, B. E.; Maitlis, P. M. *J. Chem. Soc., Chem. Commun.* **1975**, *4*, 108; (b) Mann, B. E.; Keasey, A.; Sonoda, A.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1979**, *2*, 338; (c) Sonoda, A.; Bailey, P. M.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1979**, *2*, 346; (d) Reid, S. J.; Baird, M. C. *Organometallics* **1997**, *16*, 2481; (e) Wilke, G.; Schott, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 583.
15. (a) Olmstead, M. M.; Power, P. P. *J. Am. Chem. Soc.* **1985**, *107*, 2174; (b) Hoffmann, D.; Bauer, W.; von Ragué Schleyer, P.; Pieper, U.; Stalke, D. *Organometallics* **1993**, *12*, 1193.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 7583–7588

Reaction of (η^2-arylaldehyde)nickel(0) complexes with Me_3SiX (X=OTf, Cl). Application to catalytic reductive homocoupling reaction of arylaldehyde

Sensuke Ogoshi,* Hirohumi Kamada and Hideo Kurosawa

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

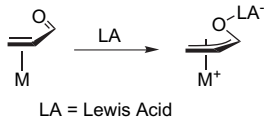
Received 21 November 2005; revised 6 March 2006; accepted 6 March 2006
Available online 19 June 2006

Dedicated to Professor Günther Wilke for his great contribution to the field of organonickel chemistry

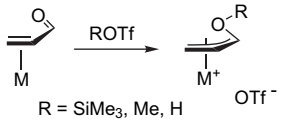
Abstract—Arylaldehydes can coordinate to nickel(0) in η^2-fashion to give η^2-arylaldehydenickel complexes, which react with Me_3SiOTf or Me_3SiCl to give η^1:η^1-siloxybenzylnickel or η^3-siloxybenzyl complex. In the presence of PCy_3 or CO, η^1:η^1-siloxybenzylnickel complex underwent homocoupling reaction to give a pinacol type product. In the presence of zinc dust, the reductive homocoupling reaction of arylaldehyde proceeded catalytically to form pinacol derivatives in 70–99% yield. On the other hand, η^3-siloxybenzylnickel complex regenerated benzaldehyde and Me_3SiOTf under a carbon monoxide pressure.

1. Introduction

The transformation of carbonyl compounds by transition metal catalysts is one of the very efficient methods to introduce oxygen into an organic molecule. However, only scattered studies on the reaction of carbonyl compounds coordinated to late transition metals have been reported. So far, we have reported the reaction of α,β-unsaturated carbonyl compounds coordinated to palladium or platinum in η^2-fashion with Lewis acids or electrophiles to give the corresponding η^3-allyl complexes having oxygen containing substituent at the allyl terminal carbon (Schemes 1 and 2).[1] As the hapticity of the enone coordination changes from η^2 to η^3, the carbonyl carbon–metal covalent bond is formed by the electron donation from palladium or platinum to carbonyl carbon, which is confirmed by the theoretical study.[1a] These results suggest that larger electron donating ability of the metal center is favorable for the formation of a covalent bond between a carbonyl carbon and a transition metal center. We thought η^2-coordination of carbonyl group to an electron rich transition metal center is one of the ideal situations for the formation of carbon–metal covalent bond by the addition of electrophiles. Although the coordination of aldehydes or ketones in η^2-mode is very rare for the late transition metals, several η^2-aldehyde and η^2-ketone complexes of nickel have been reported.[2,3] Moreover, recently, we reported the reaction of η^2-aldehyde complexes with Me_3SiOTf to give η^1:η^1-siloxymethylnickel complexes.[4] However, the reactivity and its application to catalytic reactions have not been studied yet. Here, we report the synthesis and reactivity of both η^3-siloxyarylmethylnickel and η^1:η^1-siloxybenzylnickel complexes generated by the reaction of η^2-aldehyde complex of nickel(0) with Me_3SiOTf or Me_3SiCl. The carbon–carbon bond formation by the homocoupling reactions of these complexes and its application to a catalytic reaction in the presence of zinc dust are also reported.



Scheme 1.



Scheme 2.

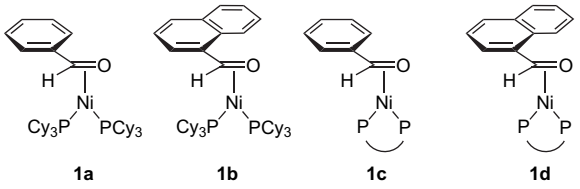
2. Results and discussion

η^2-Arylaldehydenickel complexes (**1a**–**1d**) were prepared conveniently in quantitative yield by the reaction of the corresponding arylaldehyde with $Ni(cod)_2$ and PCy_3 or DPPF

* Corresponding author. E-mail: ogoshi@chem.eng.osaka-u.ac.jp

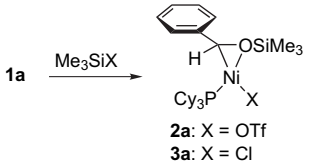
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.124

(Scheme 3). The X-ray structure analysis on **1a** reported by Walther showed η^2-coordination of benzaldehyde.[2] The formyl hydrogen and carbon in arylaldehyde coordinated to nickel are found far upfield in ^{1}H and ^{13}C NMR spectra compared to those of free arylaldehyde; ArC*H*O in **1a**–**1d** is at ca. δ 6.0–6.7 (δ 9.6–10.0 for free) and Ar*C*HO is at ca. δ 80–90 (δ 180–190 for free), which are consistent with the η^2-coordination of an arylaldehyde to a nickel(0) and the strong back donation from the nickel(0) center to the carbonyl group even in a solution.



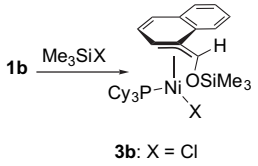
Scheme 3.

The reaction of $(\eta^2$-PhCHO)Ni$(PCy_3)_2$ (**1a**) with Me_3SiOTf gave the corresponding η^1:η^1-siloxybenzylnickel complex (**2a**) (Scheme 4).[4] Similarly, the reaction with Me_3SiCl gave the chloride analog (**3a**). Both resonances of benzyl proton and carbon in ^{1}H and ^{13}C NMR of **3a** are found in higher magnetic field than those for **1a** and were coupled with phosphorus. On the other hand, those of phenyl group are little different from the corresponding resonances of **1a** and free PhCHO in ^{1}H and ^{13}C NMR spectra. These spectral trends are similar to those of **2a**.

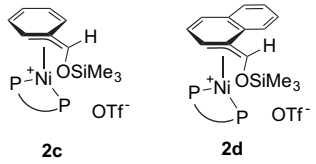


Scheme 4.

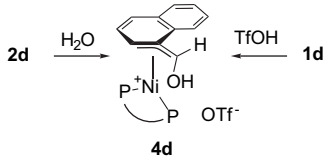
The reaction of $(\eta^2$-(1-NaphCHO))Ni$(PCy_3)_2$ (**1b**) with Me_3SiCl proceeded very rapidly to give $(\eta^3$-1-$Me_3SiOCHC_{10}H_7)$Ni(PCy_3)(Cl) (**3b**) quantitatively (Scheme 5), although **1a** was transformed into η^1:η^1-siloxybenzylnickel under the same condition. The corresponding complex having OTf (**2b**) was generated from **1b** and Me_3SiOTf, but could not be isolated due to the decomposition in the solution. In the spectra of **3b**, both proton and carbon at *ipso*- and β-position of naphthalene ring and Me_3SiOCH- were observed in much higher magnetic field than those in the spectra of **1b**, which indicates that these two carbons of aromatic ring participates in the coordination to nickel. The difference in the coordination mode between **2a**, **3a**, and **3b** might be due to the difference in the number of fused benzene ring. Thus, one benzene ring can remain intact on going from **1b** to **3b**, while **1a** has to lose all of its aromaticity upon forming the corresponding η^3-siloxybenzylnickel complex. The treatment of **1c** or **1d** with Me_3SiOTf led to the corresponding cationic η^3-siloxymethylarylnickel complexes (**2c**, **2d**), which also show higher magnetic field shift of proton and carbon at *ipso*- and β-position of naphthalene ring and Me_3SiOCH– (Scheme 6). These complexes could be the nickel analogs of the proposed intermediate in palladium/Me_3SiOTf-catalyzed bis-silylation of arylaldehyde.[1b] At this moment, we cannot rationalize the different reactivities toward Me_3SiOTf between **1a** and **1c** clearly. However, it may well account for a part of this observation that η^3-coordination of the benzyl ligand may require the softer nature of the nickel center than its η^1-coordination, and this requirement would be better fulfilled by the coordination of more the phosphorus ligands. A similar observation in the equilibrium between η^3-allenyl/propargylpalladium and η^1-propargylpalladium had been reported.[5] η^3-Siloxymethylarylnickel complex **2d** reacted with H_2O to give desilylated complex **4d** (Scheme 7). The X-ray structure analysis on **4d** shows η^3-coordination of hydroxymethylnaphthyl moiety. This complex was also formed by the reaction of **1d** with TfOH very rapidly and quantitatively. A similar reaction, the reaction of η^2-enonepalladium or platinum with TfOH to give η^3-1-hydroxyallylpalladium or platinum, had been reported.[1c]



Scheme 5.



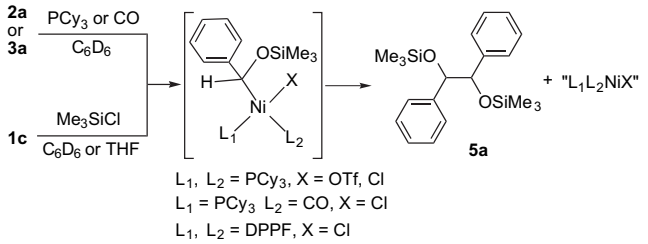
Scheme 6.



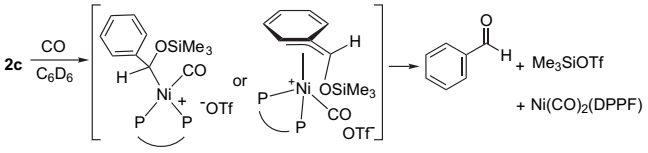
Scheme 7.

The addition of PCy_3 to a solution of **2a** or **3a** led to the formation of 1,2-bis(trimethylsiloxy)-1,2-diphenylethane (**5a**)[6] in 78 or 48% yield concomitant with an unidentified product, probably nickel(I) complex (Scheme 8). Similarly, the treatment of **3a** with carbon monoxide (5 atm) led to the formation of **5a** in 63%. This reaction might have proceeded via neutral nickel(II) intermediate as shown in Scheme 8, in which a radical coupling reaction might be involved. On the other hand, **2c** underwent the regeneration of PhCHO and Me_3SiOTf concomitant with the formation of Ni$(CO)_2$-(DPPF) under the same condition (Scheme 9). The reaction might have proceeded via cationic η^1- or five-coordinated η^3-benzylnickel(II) species generated by the coordination of carbon monoxide to nickel(II) center followed by the nucleophilic attack of TfO^- at Me_3Si group. Similarly, the reaction of **2c** with ^{n}Bu$_4$NCl generated $(\eta^2$-PhCHO)Ni(DPPF) (**1c**) and Me_3SiCl rapidly by the nucleophilic attack of Cl^- at Me_3Si group. The $(\eta^2$-PhCHO)Ni(DPPF) thus generated reacted with Me_3SiCl slowly in situ to give **5a** in

51% yield. In fact, the reaction of **1c** with Me_3SiCl gave **5a** as a sole organic product in 66% yield in C_6D_6 or quantitatively in THF.



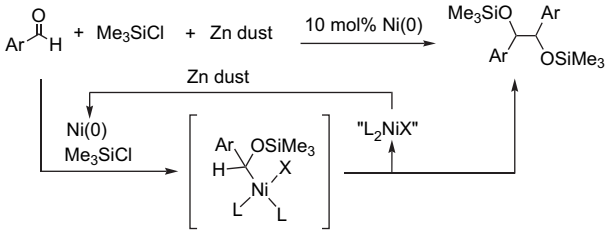
Scheme 8.



Scheme 9.

3. Catalytic reaction

The stoichiometric reaction of **1c** with Me_3SiCl depicted in Scheme 8 prompted us to test a possibility of a catalytic formation of **5a** and analogs by combining Scheme 8 with the reduction of L_1L_2NiX to Ni(0) species.[7] In the presence of 10 mol % of $Ni(cod)_2$ and DPPF or the corresponding (η^2-arylaldehyde)Ni(DPPF) and zinc dust as a reductant, the homocoupling reaction of arylaldehyde moiety proceeded catalytically to give pinacol type products as a mixture of two diastereomers (*threo*/*erythro*=50/50 for all products) (Scheme 10). The results are summarized in Scheme 11. Yields are determined for the diol compounds obtained by the hydrolysis of silylether.[7,8] The substituent group on phenyl group does not affect the yield so much (4-$MeOC_6H_4CHO$ (73%), PhCHO (88%), 4-$CF_3C_6H_4CHO$ (99%)). This reaction can be applied to naphthaldehydes as well (1-NaphCHO (70%), 2-NaphCHO (91%)).



Scheme 10.

4. Conclusion

The reaction of (η^2-PhCHO)$Ni(PCy_3)_2$ with Me_3SiOTf or Me_3SiCl gave neutral η^1:η^1-siloxybenzylnickel complex. This complex underwent the homocoupling reaction to give a pinacol derivative in the presence of PCy_3 or CO. The reaction of (η^2-NaphCHO)$Ni(PCy_3)_2$ with Me_3SiCl gave a neutral η^3-siloxynaphthylmethylnickel complex. Both (η^2-PhCHO)Ni(DPPF) and (η^2-NaphCHO)Ni(DPPF) reacted with Me_3SiOTf to give cationic η^3-siloxyarylmethylnickel complexes. The reaction of (η^2-PhCHO)Ni(DPPF) with Me_3SiCl gave the pinacol derivative and a nickel(I) species. In the presence of Zn dust, the reaction proceeded catalytically by the reduction of the nickel(I) to nickel(0).

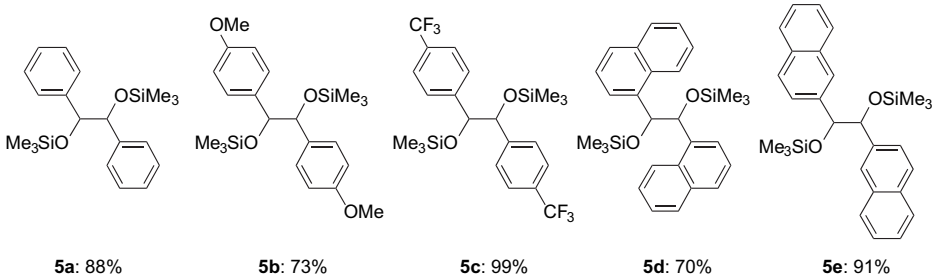
5. Experimental

5.1. General

All manipulations were conducted under a nitrogen atmosphere using standard Schlenk or dry box techniques. ^1H, ^{31}P, and ^{13}C nuclear magnetic resonance spectra were recorded on JEOL GSX-270S and JEOL AL-400 spectrometers. The chemical shifts in ^1H nuclear magnetic resonance spectra were recorded relative to Me_4Si or residual protonated solvent (C_6D_5H (δ 7.16), $CDHCl_2$ (δ 5.32)). The chemical shifts in the ^{13}C spectra were recorded relative to Me_4Si. The chemical shifts in the ^{31}P spectra were recorded using 85% H_3PO_4 as an external standard. Assignment of the resonances in ^1H and ^{13}C NMR spectra was based on ^1H–^1H COSY, HMQC, and HMBC experiments. HMQC and HMBC experiments are inverse detection hetero-correlated NMR experiments recorded at the ^1H frequency of the spectrometer, probing one-bond (CH) and multiple-bond (CCH and CCCH) connectivity. Elemental analyses were performed at Instrumental Analysis Center, Faculty of Engineering, Osaka University. For some compounds, accurate elemental analyses were precluded by extreme air or thermal sensitivity and/or systematic problems with elemental analysis of organometallic compounds. X-ray crystal data were collected by using a Rigaku RAXIS-RAPID Imaging Plate diffractometer.

5.2. Materials

The degassed and distilled solvents (THF, toluene, and hexane) used in this work were commercially available. C_6D_6 was distilled from sodium benzophenone ketyl. All commercially available reagents were distilled and degassed prior to use.



Scheme 11.

5.2.1. Isolation of (η^2-(1-NaphCHO))Ni(PCy_3)$_2$ (1b). To a solution of Ni(cod)$_2$ (177 mg, 0.64 mmol) and PCy_3 (362 mg, 0.64 mmol) in 5 mL of toluene was added 88 μL of 1-naphthaldehyde (101 mg, 1.28 mmol) at room temperature. The reaction mixture was concentrated in vacuo to give **1b** (450 mg, dark purple solids) in 95% yield. ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ 0.83–2.29 (m, 66H, *Cy*), 6.40 (t, *J*=5.0 Hz, 1H, –C*H*O), 7.27 (dd, *J*=7.2, 7.6 Hz, 1H, 7-*Ar*), 7.39 (dd, *J*=7.2, 8.7 Hz, 1H, 8-*Ar*), 7.44 (dd, *J*=6.9, 8.0 Hz, 1H, 3-*Ar*), 7.67 (d, *J*=8.0 Hz, 1H, 4-*Ar*), 7.75 (d, *J*=7.6 Hz, 1H, 6-*Ar*), 8.29 (d, *J*=6.9 Hz, 1H, 2-*Ar*), 8.81 (d, *J*=8.7 Hz, 1H, 9-*Ar*). ^{31}P NMR (109 MHz, C_6D_6, 25 °C): δ 36.75 (d, J_{PP}=43.3 Hz), 45.13 (d, J_{PP}=43.3 Hz). ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ 27.02–36.85 (*Cy*), 75.75 (d, J_{CP}=16.7 Hz, –*C*HO), 121.56 (d, J_{CP}=4.6 Hz, 2-*Ar*), 123.57 (d, J_{CP}=3.0 Hz, 4-*Ar*), 124.12 (s, 7-*Ar*), 125.03 (s, 8-*Ar*), 125.36 (s, 6-*Ar*), 126.72 (d, J_{CP}=3.0 Hz, 3-*Ar*), 128.63 (s, 5-*Ar*), 131.26 (d, J_{CP}=2.3 Hz, 9-*Ar*), 135.42 (s, 10-*Ar*), 147.47 (d, J_{CP}=4.6 Hz, 1-*Ar*). Anal. Calcd for $C_{47}H_{74}O_1P_2Ni_1$: C, 72.77; H, 9.62. Found: C, 72.98; H, 9.50.

5.2.2. Isolation of (η^2-PhCHO)Ni(DPPF) (1c). To a solution of Ni(cod)$_2$ (383 mg, 1.39 mmol) and DPPF (771 mg, 1.39 mmol) in 10 mL of toluene was added PhCHO (178 mg, 1.67 mmol) at room temperature. The solution changed from yellow to orange. The reaction mixture was concentrated in vacuo to give orange solids quantitatively. The solids were washed with hexane to give **1c** (988.7 mg, orange solids) in 99% yield. ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ 3.82–4.32 (m, 8H, *Cp*), 6.00 (t, *J*=6.1 Hz, 1H, –*CHO*), 7.28–7.35 (m, 15H), 7.28–7.35 (m, 2H), 7.48 (d, *J*=6.8 Hz, 2H), 7.85 (m, 2H), 8.30 (m, 4H). ^{31}P NMR (109 MHz, C_6D_6, 25 °C): δ 20.60 (d, J_{PP}=36.6 Hz), 32.20 (d, J_{PP}=36.6 Hz). ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ 71.38–86.40 (*Cp*), 86.48 (d, J_{CP}=16.7 Hz, –*C*HO), 124.37–137.49 (*Ph*-CHO), 148.95 (d, J_{CP}=4.6 Hz, *ipso-Ph*-CHO). Anal. Calcd for $C_{41}H_{34}O_1P_2Fe_1Ni_1$: C, 68.47; H, 4.77. Found: C, 67.48; H, 4.67.

5.2.3. Isolation of (η^2-(1-NaphCHO))Ni(DPPF) (1d). To a solution of Ni(cod)$_2$ (179 mg, 0.65 mmol) and DPPF (360 mg, 0.65 mmol) in 5 mL of toluene was added 1-naphthaldehyde (102 mg, 0.65 mmol) at room temperature. The reaction mixture was concentrated in vacuo to give orange solids quantitatively. The solids were washed with hexane to give **1d** (479.2 mg, orange solids) in 96% yield. ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ 3.70–4.25 (m, 8H, *Cp*), 6.58 (br s, 2H), 6.70 (s, 2H including –*CHO*), 6.91 (t, *J*=7.1 Hz, 2H), 7.10–7.20 (m, 12H), 7.52 (d, *J*=8.1 Hz, 1H), 7.58 (d, *J*=8.1 Hz, 1H), 7.83 (br s, 2H), 7.96 (d, *J*=6.2 Hz, 1H), 8.24 (br s, 4H), 8.53 (d, *J*=8.4 Hz, 1H). ^{31}P NMR (109 MHz, C_6D_6, 25 °C): δ 20.83 (d, J_{PP}= 35.4 Hz), 31.34 (d, J_{PP}=34.2 Hz). ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ 70.70–74.39 (*Cp*), 85.99 (d, J_{CP}=16.5 Hz, –*C*HO), 122.20–135.20 (*Ph*), 144.61 (d, J_{CP}=5.5 Hz). Anal. Calcd for $C_{45}H_{36}O_1P_2Fe_1Ni_1$: C, 70.26; H, 4.72. Found: C, 69.73; H, 4.65.

5.2.4. Isolation of (η^1:η^1-$Me_3SiOCHC_6H_5$)Ni(PCy_3)-(OTf) (2a). To a solution of Ni(cod)$_2$ (220 mg, 0.80 mmol), PCy_3 (224 mg, 0.80 mmol), and 81.3 μL of PhCHO (84.8 mg, 0.80 mmol) in 7 mL of THF was added 145 μL of Me_3SiOTf (178 mg, 0.80 mmol) at room temperature. The solution changed from orange to dark purple immediately. The reaction mixture was filtered through a short Celite column followed by concentration in vacuo to give **2a** (368 mg, purple solids) in 69% yield. ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ 0.31 (s, 9H, –Si*Me*$_3$), 0.95–1.95 (m, 33H, *Cy*), 4.34 (d, *J*=3.5 Hz, 1H, –C*H*O-SiMe$_3$), 7.02 (d, *J*=7.3, 7.4 Hz, 2H, *m-Ph*), 7.13 (t, *J*=7.4 Hz, 1H, *p-Ph*), 7.47 (d, J_{HP}=7.3 Hz, 2H, *o-Ph*). ^{31}P NMR (109 MHz, C_6D_6, 25 °C): δ 42.0 (s). ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ 0.5 (s, –Si*Me*$_3$), 27.1 (s, *Cy*), 28.4 (q, J_{CP}=9.9 Hz, *Cy*), 30.6 (d, J_{CP}=30.7 Hz, *Cy*), 33.6 (d, J_{CP}=21.5 Hz, *Cy*), 62.3 (d, J_{CP}=11.4 Hz, –*C*HOSiMe$_3$), 124.0 (s, *o-Ph*), 127.9 (s, *p-Ph*), 130.3 (s, *m-Ph*), 140.9 (s, *ipso-Ph*). Anal. Calcd for $C_{29}H_{48}F_3Ni_1O_4P_1S_1Si_1(H_2O)$: C, 52.18; H, 7.25. Found: C, 50.98; H, 6.71.

5.2.5. Isolation of (η^1:η^1-$Me_3SiOCHC_6H_5$)Ni(PCy_3)(Cl) (3a). To a solution of Ni(cod)$_2$ (220 mg, 0.80 mmol), PCy_3 (224 mg, 0.80 mmol), and 81.3 μL of PhCHO (84.8 mg, 0.80 mmol) in 7 mL of THF was added 101 μL of Me_3SiCl (86.9 mg, 0.80 mmol) at room temperature. The solution changed from orange to dark purple immediately. The reaction mixture was filtered through a short Celite column followed by concentration in vacuo to give **3a** (297 mg, purple solids) in 67% yield. ^{1}H NMR (270 MHz, C_6D_6, 25 °C): δ 0.41 (s, 9H, –Si*Me*$_3$), 0.89–2.20 (m, 33H, *Cy*), 4.54 (d, *J*=3.2 Hz, 1H, –C*H*OSiMe$_3$), 7.03 (m, 3H), 7.49 (d, *J*=6.5 Hz, 2H). ^{31}P NMR (109 MHz, C_6D_6, 25 °C): δ 46.4 (s). ^{13}C NMR (67.5 MHz, C_6D_6, 25 °C): δ 0.6 (s, –Si*Me*$_3$), 27.2 (s, *Cy*), 28.3 (q, J_{CP}=5.5 Hz, *Cy*), 30.4 (d, J_{CP}=17.6 Hz, *Cy*), 34.1 (d, J_{CP}=21.6 Hz, *Cy*), 63.6 (d, J_{CP}=11.5 Hz, –*C*HOSiMe$_3$), 124.1 (s), 126.6 (s), 129.7 (s), 143.2 (s). Anal. Calcd for $C_{28}H_{48}Cl_1Ni_1O_1P_1Si_1$: C, 60.72; H, 8.73. Found: C, 61.00; H, 8.51.

5.2.6. Isolation of (η^3-1-$Me_3SiOCHC_{10}H_7$)Ni(PCy_3)(Cl) (3b). To a solution of Ni(cod)$_2$ (271 mg, 1.0 mmol), PCy_3 (280 mg, 1.0 mmol), and 136 μL of 1-naphthaldehyde (156 mg, 1.0 mmol) in 5 mL of THF was added 127 μL of Me_3SiCl (108 mg, 0.80 mmol) at room temperature. The solution changed from orange to deep red. The reaction mixture was filtered through a short Celite column and reprecipitation from THF/pentane afforded **3b** (383 mg, brown solids) in 63% yield. ^{1}H NMR (400 MHz, toluene-d_8, −30 °C): δ 0.07 (s, 9H, –Si*Me*$_3$), 1.14–1.92 (m, 33H, *Cy*), 5.86 (d, *J*=8.0 Hz, 1H, –C*H*OSiMe$_3$), 6.58 (br s, 1H, 2-*Ar*), 7.29 (dd, *J*=7.4, 7.6 Hz, 1H, 7-*Ar*), 7.36 (dd, *J*=7.4, 8.0 Hz, 1H, 8-*Ar*), 7.48 (d, *J*=7.6 Hz, 1H, 6-*Ar*), 7.51 (dd, *J*=6.5, 8.7 Hz, 1H, 3-*Ar*), 7.62 (d, *J*=8.7 Hz, 1H, 4-*Ar*), 7.70 (d, *J*=8.0 Hz, 1H, 9-*Ar*). ^{31}P NMR (160 MHz, toluene-d_8, −30 °C): δ 37.1 (s). ^{13}C NMR (100 MHz, toluene-d_8, −30 °C): δ 0.10 (s, –Si*Me*$_3$), 14.9–35.0 (*Cy*), 69.7 (s, –*C*HOSiMe$_3$), 92.4 (s, 2-*Ar*), 108.6 (s, 1-*Ar*), 122.4 (s, 8-*Ar*), 126.7 (s, 9-*Ar*), 126.9 (s, 7-*Ar*), 127.60 (6-*Ar*, hidden by toluene-d_8), 127.85 (4-*Ar*, hidden by toluene-d_8), 129.9 (s, 5-*Ar*), 133.3 (s, 3-*Ar*), 136.1 (s, 10-*Ar*). Anal. Calcd for $C_{32}H_{50}Cl_1Ni_1O_1P_1Si_1$: C, 63.64; H, 8.34. Found: C, 63.43; H, 8.35.

5.2.7. Isolation of [(η^3-$Me_3SiOCHC_6H_5$)Ni(DPPF)][OTf] (2c). To a suspension of (η^2-PhCHO)Ni(DPPF) (**1c**) (381 mg, 0.53 mmol) in 5 mL of THF was added 96 μL of Me_3SiOTf (118 mg, 0.53 mmol) at room temperature. The orange

suspension changed to deep red solution. The reaction mixture was concentrated in vacuo. The residue was washed with hexane to give **2c** (492.7 mg, orange solids) in 99% yield. ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C): δ −0.11 (s, 9H, –Si*Me*$_3$), 4.16–4.42 (m, 8H, *Cp*), 4.95 (s, 1H, –C*H*OSiMe$_3$), 6.65 (d, J=7.2 Hz, 2H, *o-Ph*), 6.97 (d, J=7.4 Hz, 2H, *m-Ph*), 7.12 (d, J=6.5 Hz, 1H, *p-Ph*), 7.40–7.70 (m, 20H). ^{31}P NMR (160 MHz, CD_2Cl_2, −80 °C): δ 22.66 (d, J_{PP}=2.4 Hz), 27.20 (s). ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ −0.35 (s, –Si*Me*$_3$), 74.03–75.68 (m, *Cp*), 86.16 (t, J_{CP}=11.4 Hz, –*C*HOSiMe$_3$), 113.37 (s, *o-PhCHOSiMe*$_3$), 116.67 (s, *ipso-PhCHOSiMe*$_3$), 129.51–134.24 (*Ph*). Anal. Calcd for $C_{45}H_{43}O_4F_3P_2S_1Si_1Fe_1Ni_1$: C, 57.41; H, 4.60. Found: C, 57.46; H, 4.74.

5.2.8. Generation of [(η^3-Me$_3$SiOCHC$_6$H$_5$)Ni(DPPF)][OTf] (2c). To a solution of **1c** (14.4 mg, 0.020 mmol) in 0.5 mL of CD_2Cl_2 was added Me_3SiOTf (4.4 mg, 0.020 mmol) at room temperature. The solution changed from orange to deep red and **2c** was generated quantitatively.

5.2.9. Isolation of [(η^3-1-Me$_3$SiOCHC$_{10}$H$_7$)Ni(DPPF)][OTf] (2d). To a solution of (η^2-(1-NaphCHO))Ni(DPPF) (**1d**) (155.2 mg, 0.20 mmol) in 10 mL of toluene was added 37 μL of Me_3SiOTf (44.8 mg, 0.20 mmol) at room temperature. The solution changed from orange to deep red solution. The reaction mixture was filtered through a short Celite column followed by concentration in vacuo. The residue was washed with hexane to give **2d** (192.4 mg, orange solids) in 96% yield. ^{1}H NMR (400 MHz, CD_2Cl_2, −20 °C): δ −0.02 (s, 9H, –Si*Me*$_3$), 4.00–4.50 (m, 8H, *Cp*), 5.28 (dd, J_{HH}=5.4 Hz, J_{HP}=9.8 Hz, 1H, 2-*Ar*), 6.20 (dd, J=5.4, 7.9 Hz, 1H, 3-*Ar*), 6.44 (dd, J_{HP}=2.9, 10.8 Hz, 1H, –C*H*OSiMe$_3$), 6.74 (d, J=8.3 Hz, 1H, 9-*Ar*), 6.80 (dd, J=7.6, 10.8 Hz, 2H), 7.23–7.90 (m, 22H). ^{31}P NMR (160 MHz, CD_2Cl_2, −20 °C): δ 24.24 (d, J_{PP}=10.3 Hz), 26.81 (d, J_{PP}=10.3 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2, −20 °C): δ −0.42 (s, –Si*Me*$_3$), 73.18–75.25 (m, *Cp*), 83.46 (d, J_{CP}=11.4 Hz, 2-*Ar*), 94.84 (dd, J_{CP}=1.5, 17.5 Hz, –*C*HOSiMe$_3$), 105.95 (s, 1-*Ar*), 121.61 (s, 9-*Ar*), 124.17 (s, 10-*Ar*), 126.15 (s), 126.6 (s), 128.5 (s), 128.82 (d, J_{CP}=3.8 Hz, 3-*Ar*), 129.17–134.71. Anal. Calcd for $C_{45}H_{43}O_4F_3P_2S_1Si_1Fe_1Ni_1$: C, 59.36; H, 4.57. Found: C, 59.70; H, 5.12.

5.2.10. Generation of [(η^3-1-Me$_3$SiOCHC$_{10}$H$_7$)Ni(DPPF)][OTf] (2d). To a suspension of **1d** (11.5 mg, 0.015 mmol) in 0.5 mL of C_6D_6 was added Me_3SiOTf (3.3 mg, 0.15 mmol) at room temperature. The orange suspension changed to deep red solution and **2d** was generated quantitatively.

5.2.11. Isolation of [(η^3-1-HOCHC$_{10}$H$_7$)Ni(DPPF)][OTf] (4d). To a solution of (η^2-(1-NaphCHO))Ni(DPPF) (**1d**) (167.4 mg, 0.22 mmol) in 10 mL of toluene was added 19 μL of HOTf (32.6 mg, 0.22 mmol) at room temperature. The orange solution changed to deep red suspension. The reaction mixture was concentrated in vacuo to give orange solids. The solids were washed with hexane to give **4d** (186.2 mg, orange solids) in 93% yield. ^{1}H NMR (400 MHz, CD_2Cl_2, −30 °C): δ 3.84–4.63 (m, 8H, *Cp*), 5.32 (1H, –C*H*OH, hidden by CD_2Cl_2), 6.38 (s, 1H), 6.49 (s, 1H), 7.12–8.30 (m), 9.34 (s, 1H). ^{31}P NMR (109 MHz, CD_2Cl_2, −80 °C): δ 25.63 (d, J_{PP}=5.0 Hz), 26.07 (d, J_{PP}=5.0 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2, −40 °C): δ 82.32–85.81 (*Cp*), 87.60 (br s), 110.49 (s), 113.02 (br s), 131.52 (s), 133.93 (s), 135.66 (s), 137.06–145.51 (*Ph*). Anal. Calcd for $C_{48}H_{41}O_4F_3P_2S_1Fe_1Ni_1(C_6H_6)$: C, 62.62; H, 4.35. Found: C, 63.18; H, 4.35. X-ray data for **4d**: M=1077.59, brown, triclinic, P-1 (no.2), a=12.448(1) Å, b=13.753(1) Å, c=16.815(1) Å, α=103.833(4)°, β=105.947(3)°, γ=104.314(2)°, V=2532.2(4) Å^3, Z=2, D_{calcd}=1.413 g/cm^3, T=0 °C, R=0.077.

5.2.12. Generation of [(η^3-1-HOCHC$_{10}$H$_7$)Ni(DPPF)][OTf] (4d). To a suspension of (η^2-(1-NaphCHO))Ni(DPPF) **1d** (11.5 mg, 0.015 mmol) in 0.5 mL of C_6D_6 was added Me_3SiOTf (3.3 mg, 0.015 mmol) at room temperature. The orange suspension changed to deep red solution and **2d** was generated quantitatively. To the solution was added 0.5 mg of H_2O (0.028 mmol, 0.5 μL) to give **4d** quantitatively.

5.2.13. Reaction of (η^1:η^1-Me$_3$SiOCHC$_6$H$_5$)Ni(PCy$_3$)(OTf) (2a) with PCy$_3$. To a solution of **2a** (13.4 mg, 0.02 mmol) in 0.5 mL of C_6D_6 was added PCy_3 (5.8 mg, 0.02 mmol) at room temperature and the reaction mixture was stirred for 2 days. The pinacol type product (**5a**) was generated in 78% yield.

5.2.14. Reaction of (η^1:η^1-Me$_3$SiOCHC$_6$H$_5$)Ni(PCy$_3$)(Cl) (3a) with PCy$_3$. To a solution of **3a** (11.6 mg, 0.02 mmol) in 0.5 mL of C_6D_6 was added PCy_3 (5.6 mg, 0.02 mmol) at room temperature and the reaction mixture was stirred for 2 days. Compound **5a** was obtained in 48% yield.

5.2.15. Reaction of (η^1:η^1-Me$_3$SiOCHC$_6$H$_5$)Ni(PCy$_3$)(Cl) (3a) with CO. A solution of **3a** (11.6 mg, 0.02 mmol) in 0.5 mL of C_6D_6 in a pressure tight NMR tube was treated with CO (5 atm). The solution changed from dark purple to pale blue immediately to give **5a** (63%).

5.2.16. Reaction of (η^1:η^1-Me$_3$SiOCHC$_6$H$_5$)Ni(PCy$_3$)(OTf) (2a) with CO. A solution of **2a** (11.6 mg, 0.02 mmol) in 0.5 mL of C_6D_6 in a pressure tight NMR tube was treated with CO (5 atm). The solution changed from dark purple to colorless solution immediately to give $Ni(PCy_3)(CO)_3$, PhCHO, and Me_3SiOTf quantitatively.

5.2.17. Reaction of [(η^3-Me$_3$SiOCHC$_6$H$_5$)Ni(DPPF)][OTf] (2c) with CO. A solution of **2c** (18.9 mg, 0.02 mmol) in 0.5 mL of C_6D_6 in a pressure tight NMR tube was treated with CO (5 atm). The solution changed from deep red to colorless solution immediately to give $Ni(DPPF)(CO)_2$, PhCHO, and Me_3SiOTf quantitatively.

5.2.18. Reaction of [(η^3-Me$_3$SiOCHC$_6$H$_5$)Ni(DPPF)][OTf] (2c) with Bu$_4$NCl. To a solution of **2c** (18.9 mg, 0.02 mmol) in 0.5 mL of C_6D_6 was added Bu_4NCl (5.4 mg, 0.02 mmol) at room temperature and the reaction mixture was stirred for 2 days. Compound **5a** was obtained in 51% yield.

5.2.19. Reaction of (η^2-PhCHO)Ni(DPPF) (1c) with Me$_3$SiCl. To a solution of **1c** (14.5 mg, 0.02 mmol) in 0.5 mL of C_6D_6 was added 2.5 μL of Me_3SiCl (2.3 mg, 0.02 mmol) at room temperature, and the reaction mixture was stirred for 2 days. Pinacol type product was obtained in 66% yield. When the reaction was carried out in THF, **5a** was obtained quantitatively.

5.2.20. Typical procedure for catalytic reaction (PhCHO). Under a nitrogen atmosphere, to a suspension of (η^2-PhCHO)Ni(DPPF) (1.5 mg, 0.002 mmol) and zinc dust (1.2 mg, 0.020 mmol) in 0.5 mL of THF were added 1.8 μL of PhCHO (2.0 mg, 0.018 mmol) and 2.5 μL of Me_3SiCl (2.3 mg, 0.020 mmol) at room temperature. The reaction mixture was stirred for 1 day to give **5a** in 88% yield. The yield was determined by GC as the corresponding diol obtained by the hydrolysis.

5.2.21. Reaction of 4-$MeOC_6H_4CHO$. $Ni(cod)_2$ (10 mol %) and DPPF were employed as a catalyst. Compound **5b** was obtained in 73% yield.

5.2.22. Reaction of 4-$CF_3C_6H_4CHO$. $Ni(cod)_2$ (10 mol %) and DPPF were employed as a catalyst. Compound **5c** was obtained in 99% yield.

5.2.23. Reaction of 1-naphthaldehyde. Compound **2d** (10 mol %) was employed as a catalyst. Compound **5d** was obtained in 70% yield.

5.2.24. Reaction of 2-naphthaldehyde. $Ni(cod)_2$ (10 mol %) and DPPF were employed as a catalyst. Compound **5e** was obtained in 91% yield.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.03.124.

References and notes

1. (a) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 1944–1950; (b) Ogoshi, S.; Tomiyasu, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2002**, *124*, 11598–11599; (c) Ogoshi, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2003**, *125*, 9020–9021; (d) Morita, M.; Inoue, K.; Ogoshi, S.; Kurosawa, H. *Organometallics* **2003**, *22*, 5468–5472; (e) Morita, M.; Inoue, K.; Yoshida, T.; Ogoshi, S.; Kurosawa, H. *J. Organomet. Chem.* **2004**, *689*, 894–898.
2. Walther, D. *J. Organomet. Chem.* **1980**, *190*, 393–401.
3. Bennett, M. A. *Pure Appl. Chem.* **1989**, *61*, 1695–1700; Kim, Y.-J.; Osakada, K.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 964–966; Ashley-Smith, J.; Green, M.; Stone, F. G. A. *J. Chem. Soc. A* **1969**, 3019–3023.
4. Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11082–11083.
5. Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. *J. Am. Chem. Soc.* **1998**, *129*, 1938–1939.
6. Johnson, D. L.; Gladysz, J. A. *Inorg. Chem.* **1981**, *20*, 2508–2515.
7. Metal-catalyzed reductive homocoupling reaction of arylaldehyde. For *Cr* see: Svatoš, A.; Boland, W. *Synlett* **1998**, 549–551; For *V* see: Hirao, T.; Hasegawa, T.; Muguruma, Y.; Ikeda, S. *J. Org. Chem.* **1996**, *61*, 366–367; For *Sm* see: Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666–11667; For *Ce* see: Groth, U.; Jeske, M. *Synlett* **2001**, 129–131.
8. For diols see: Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198–13199.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 7589–7597

Nickel-mediated cyclization of enynes under an atmosphere of carbon dioxide

Masanori Takimoto,[c] Takashi Mizuno,[a] Miwako Mori[b,*] and Yoshihiro Sato[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan*
[b]*Health Sciences University of Hokkaido, Ishikari-tobetsu, Hokkaido 061-0293, Japan*
[c]*Organometallic Chemistry Laboratory, RIKEN (The Institute of Physical and Chemical Research), Hirosawa 2-1, Wako, Saitama 351-0198, Japan*

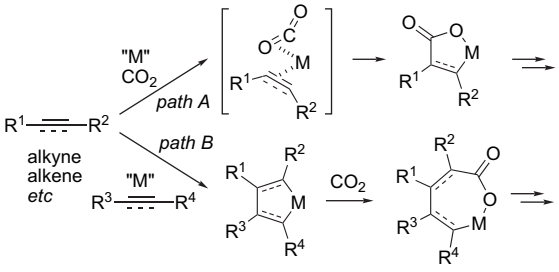
Received 7 December 2005; revised 3 March 2006; accepted 3 March 2006
Available online 12 June 2006

Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry

Abstract—Nickel-mediated carboxylation of α,ω-enyne was investigated. In the presence of a stoichiometric amount of zero-valent nickel complex, enynes having an electron-withdrawing group on alkene reacted with carbon dioxide via intramolecular cyclization to afford cyclic carboxylic acids in good yields. Various heterocyclic compounds were prepared by this carboxylative cyclization protocol. The reaction seems to proceed through oxidative cycloaddition of the α,ω-enyne moiety to a zero-valent nickel complex, regioselective insertion of carbon dioxide at the Csp^3-nickel bond, and hydrolysis of the resulting oxanickelacycle intermediate.

1. Introduction

Development of the carbon dioxide (CO_2) incorporation reaction into organic molecules is regarded as an important subject in synthetic organic chemistry. However, despite its abundant reserve and lower toxicity, the utility in synthetic organic chemistry has been limited because of its high thermodynamic stability and kinetic inertness. To overcome this disadvantage, various methods using transition metal complexes as promoters or catalysts have been explored.[1] The oxidative cycloaddition of CO_2 and unsaturated hydrocarbons to low-valent transition metal complexes is one of the most extensively studied CO_2 incorporation processes (Scheme 1, path A) and much interest has been shown in nickel-mediated processes.[2,3] Another potentially useful process is the insertion of CO_2 into metallacycle intermediates, which are readily prepared by oxidative cycloaddition of two unsaturated hydrocarbon components to low-valent transition metals (Scheme 1, path B). This process is also highly attractive because multiple carbon–carbon bond formations are accomplished during the process; however, synthetic reactions that utilize such a process have rarely been explored except for palladium- or nickel-catalyzed co-oligomerization of 1,3-dienes with CO_2, which proceeds through insertion of CO_2 into a bis-allylmetal intermediate.[4–9]

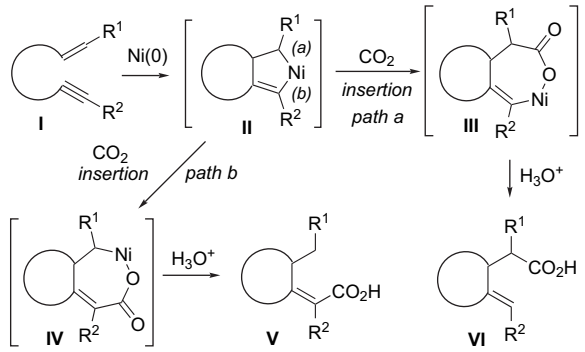


Scheme 1.

To fill this void in CO_2 incorporation chemistry, a nickel-mediated reaction using α,ω-enynes as metallacycle precursors have been explored. It was envisioned that α,ω-enyne **I** will readily react with a zero-valent nickel complex to form oxanickelacyclopentene **II** (Scheme 2).[10–13] There are two possible pathways by which CO_2 is inserted into **II**. If complex **II** undergoes insertion of CO_2 at the Csp^3-nickel bond (path a), oxanickelacycloheptene **III** would be formed, and this would be hydrolyzed to provide carboxylic acid **VI**. The other possible pathway, i.e., insertion of CO_2 into the Csp^2–nickel bond (path b), would provide α,β-unsaturated carboxylic acid **V** through the formation of oxanickelacycloheptene **IV**. Herein, we described the results of our investigation of a nickel-mediated cyclization–carboxylation cascade of α,ω-enynes.[14]

* Corresponding authors. Tel.: +81 11 706 4982; fax: +81 11 706 4982 (Y.S.); tel.: +81 11 787 6045; fax: +81 11 787 6045 (M.M.); e-mail addresses: mori@pharm.hokudai.ac.jp; biyo@pharm.hokudai.ac.jp

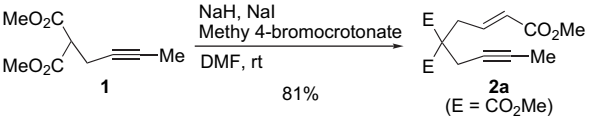
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.121



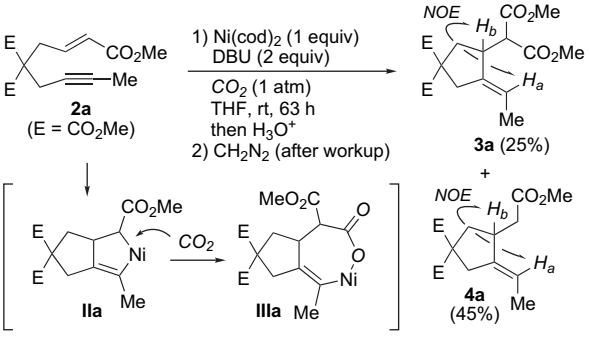
Scheme 2.

2. Results and discussion

To examine the feasibility of the above-described process, a reaction of 1,6-enyne **2a**, which was readily prepared from **1** (Scheme 3), was first carried out under conditions developed for carboxylation of unsaturated hydrocarbons.[2d,3] To a THF solution of $Ni(cod)_2$ (1 equiv) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 2 equiv to nickel) was slowly added a solution of enyne **2a** in THF at 0 °C under an atmosphere of CO_2, and the solution was stirred at room temperature for 63 h (Scheme 4). Hydrolysis of the resulting mixture followed by treatment with diazomethane afforded carboxylative cyclization product **3a** in 25% yield along with 45% of **4a**. The configurations of each double bond in **3a** and **4a** were determined to be (*E*) by the results of NOE experiments for **3a** and **4a**. The formation of **4a** was rationalized by protonolysis of nickelacycle **IIa**, and these results strongly suggested that the carboxylation proceeds through CO_2 insertion into the Csp^3–nickel bond of nickelacycle **IIa** giving oxanickelacycle **IIIa**.



Scheme 3.



Scheme 4.

To improve the yield of carboxylation product **3a**, enyne **2a** was submitted to various reaction conditions (Table 1). When the reaction was carried out in THF at 40 °C, the yield of **3a** was improved to 48% (entry 1). However, when the reaction was carried out under reflux conditions, only 9% of **3a** was obtained (entry 2). Formation of a significant amount of **4a** suggests the thermal instability of nickelacycle **IIa**. In addition, it seemed that the stability of **IIIa** was not so high at an elevated temperature because a shorter reaction period resulted in better yield of **3a** when the reactions were conducted at 40 °C (entry 3 vs entry 1). Although this carboxylative cyclization reaction could be carried out in toluene, the yield of **3a** slightly decreased (entry 4). Gratifyingly, the use of dioxane significantly improved the yield of the carboxylation product (entry 5). Interestingly, the yield of **3a** increased to 70% when the reaction was carried out in the presence of molecular sieves 4Å (entry 6).[15] The use of other ligands instead of DBU reduced the yields of **3a** (entries 7–9). The low combined yields of **3a** and **4a** in these reactions indicated that these ligands did not promote the formation of nickelacycle **IIa**. On the basis of these results, the reaction conditions employed in entry 6 were chosen as the standard reaction conditions for further investigations.

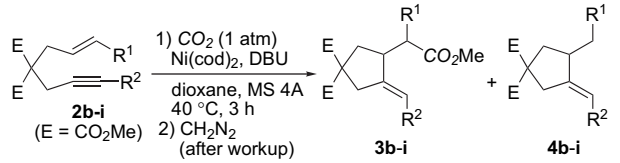
Table 1. Carboxylative cyclization of **2a** under various conditions[a]

Entry	Solvent	Ligand	Additive	Temp (°C)	Time (h)	Yields (%)	
						3a	**4a**
1	THF	DBU[b]	—	40	18	48	38
2	THF	DBU[b]	—	Reflux	13	9	77
3	THF	DBU[b]	—	40	3	55	30
4	Toluene	DBU[b]	—	40	18	41	15
5	Dioxane	DBU[b]	—	40	3	60	25
6	Dioxane	DBU[b]	MS 4Å	40	3	70	9
7	THF	PPh_3[b]	—	40	12	8	15
8	Dioxane	DPPE[c]	MS 4Å	40	4	0	0
9	Dioxane	TMEDA[c]	MS 4Å	40	3	22	0

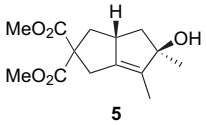
[a] All reactions were carried out using 1 equiv of $Ni(cod)_2$ under an atmosphere of CO_2 (1 atm). The obtained crude materials were treated with CH_2N_2 before isolation.
[b] 1 equiv.
[c] 2 equiv.

Carboxylative cyclizations of enynes having various substituents on the alkene or alkyne moiety were examined (Table 2). First, enynes **2b**–**2e**, whose alkene moieties were

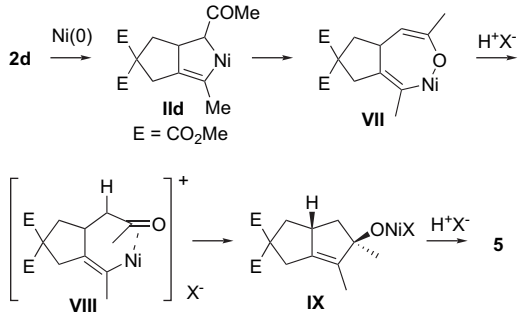
Table 2. Substituent effects of enynes



Entry	Enyne	R^1	R^2	Yields (%)		
				3	**4**	**3+4**
1	**2b**	H	Me	0	0	0
2	**2c**	Me	Me	0	0	0
3	**2d**	COMe	Me	0	54	54
4	**2e**	CN	Me	44	2	46
5	**2f**	CO_2Me	CH_2OMe	56	16	72
6	**2g**	CO_2Me	Ph	51	24	75
7	**2h**	CO_2Me	CO_2Me	27	61	88
8	**2i**	CO_2Me	$SiMe_3$	0	61	61



modified from enyne **2a**, were submitted to the carboxylation reaction. Reaction of enyne **2b**, which had no substituent at the terminus of alkyne, provided neither carboxylation product **3b** nor simply cyclized compound **4b** (entry 1). The reaction of **2c** having a methyl group on its alkene moiety also gave the same result. The fact that cyclized compounds **3** and **4** were not obtained in these two reactions indicated that oxidative cycloaddition of **2b** and **2c** did not proceed under these conditions. The reaction of enyne **2d** having an electron-withdrawing keto-carbonyl group on alkene afforded no carboxylation product (entry 3). However, in this reaction, cyclized product **4d** and bicyclic alcohol **5** were obtained in 54 and 39% yields, respectively. It was speculated that **5** was formed via the formal [3+2] cycloaddition pathway proposed by Montgomery.[12i,k,m] The reaction involves tautomerization of oxanickelacycle **IId** to nickel enolate **VII** and selective mono-protonation of **VII** followed by carbonyl insertion into the nickel–carbon bond of **VIII** to give **5** (Scheme 5). Thus, the formation **5** also indicated that oxidative cycloaddition of **2d** took place. In contrast to these results (entries 1–3), enyne **2e**, having a cyano group on alkene as an electron-withdrawing group, underwent carboxylative cyclization to give **3e** in 44% yield (entry 4).

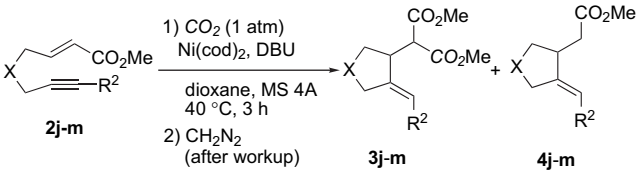


Scheme 5.

Next, the effects of substituents on the alkyne moiety were investigated using enynes **2f**–**2i**. Reaction of enynes **2f** or **2g** having an alkyl or aryl group on alkyne provided carboxylative cyclization product **3f** or **3g** in 56 or 51% yields, respectively (entries 5 and 6). In contrast to these results, the reaction of **2h** having a methoxycarbonyl group on alkyne gave **3h** in only 27% yield (entry 7) and that of **2i** afforded no carboxylation product. However, since the combined yields of **3** and **4** were relatively high in these reactions (entries 5–8), oxidative cycloaddition of enyne to Ni(0) might proceed. From the results shown in Table 2, the effects of substituents on alkene or alkyne are summarized as follows: (i) an electron-withdrawing substituent on alkene is necessary for oxidative cycloaddition of enynes to a Ni(0) complex and (ii) the carboxylation step, which would proceed through insertion of CO_2 into the nickelacyclopentenes, is greatly affected by substituents on both alkene and alkyne moieties (entries 3–8).

To explore the utility of this novel method for synthesis of cyclic compounds, reactions of enynes with various tethers were next examined (Table 3). In cyclization of enyne **2j** having no substituent on its tether, the desired carboxylation product **3j** was obtained in only 31% yield (Table 3, entry 1). In contrast to this result, carboxylative cyclizations of enynes **2k**, **2l**, and **2m**, which had a heteroatom in those

Table 3. Carboxylative cyclizations of various 1,6-enynes

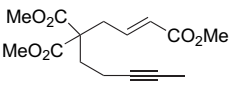
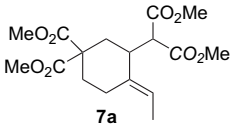
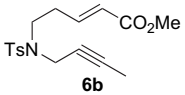
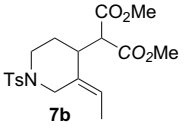
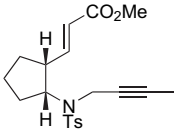
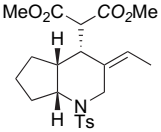
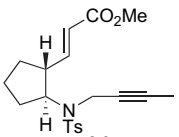
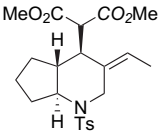


Entry	Enyne	X	R^2	Yields (%)		Recovery of **2** (%)
				3	**4**	
1	**2j**	CH_2	Me	31	22	39
2	**2k**	TsN	Me	54	25	0
3	**2l**	TsN	CH_2OMe	55	34	0
4	**2m**	O	Me	68	12	0

tethers, proceeded smoothly to afforded desired heterocyclic products **3** in good yields (entries 2–4).

Carboxylative cyclizations of 1,7-enynes **6** were then examined to apply this method for construction of a six-membered ring skeleton (Table 4). When reaction of **6a** was carried out under standard conditions for 8 h, the desired compound **7a** was obtained in 47% yield. Carboxylative cyclization of **6b**, which had a nitrogen atom in the tether chain, proceeded smoothly to afford compound **7b** with a piperidine skeleton in 80% yield. It was noteworthy that substrates **6c** and **6d**, in which a pre-existing five-membered ring was present in the tether chain, also underwent carboxylative cyclization to provide **7c** and **7d**, which have a bicyclic skeletal framework, in 55 and 75% yields, respectively, in a stereospecific manner.

Table 4. Carboxylative cyclizations of various 1,7-enynes

Enyne	Product	Yield (%)
 **6a**	 **7a**	47
 **6b**	 **7b**	80
 **6c**	 **7c**	55
 **6d**	 **7d**	75

All reactions were carried out in dioxane at 40 °C for 8 h in the presence of MS 4Å under an atmosphere of CO_2 (1 atm). All products were isolated as methyl esters by treating crude products with diazomethane.

3. Conclusion

In summary, nickel-mediated carboxylative cyclization of enynes was investigated. The effects of substituents on alkene and alkyne were investigated, and it was revealed that an electron-withdrawing group on alkene is necessary for this process. The utility of this novel method was demonstrated by application to the synthesis of various carboxylic acid derivatives having five- to six-membered ring skeletons, involving bicyclic skeletal frameworks.

4. Experimental

4.1. General

All manipulations were performed under an argon atmosphere unless otherwise stated. $Ni(cod)_2$ was prepared according to the previously reported procedure.[16] DMF and DBU were distilled from CaH_2. THF (dehydrated, stabilizer-free) was purchased from Kanto Kagaku Co. and used as received. Toluene and dioxane were distilled from sodium benzophenone ketyl. CO_2 (UHP grade, >99.995%) was purchased from Sumitomo Seika Chemicals Co., Ltd and used without further purification. All other reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (70–230 mesh or 230–400 mesh). Enyne **2b** was prepared by the procedure reported in the literature.[17] Methods for preparing enynes **2c**–**2m** and **6a**–**6d** are described in the electronic Supplementary data.

4.2. Preparation of enynes

4.2.1. Trimethyl (*E*)-Oct-1-en-6-yne-1,4,4,-tricarboxylate (2a). To a suspension of NaH (60% dispersion in oil, 240 mg, 6.0 mmol) in DMF (15 mL) was added **1**[18] (1.1 g, 6.6 mmol) in DMF (10 mL) at 0 °C, and then the mixture had been stirred at room temperature for 1 h. The resulting mixture was cooled to 0 °C, and then methyl 4-bromocrotonate (1.1 mL, 9.0 mmol) and NaI (90 mg, 0.6 mmol) were added. After the mixture had been stirred at room temperature for 3 h, saturated aqueous solution of NH_4Cl was added at 0 °C. The aqueous layer was extracted with AcOEt. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8/1) to afford **1a** (1.4 g, 81%) as a colorless crystal. Mp 53.0–55.0 °C; IR (neat) 2954, 1738, 1279 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (dt, J=8.0, 15.6 Hz, 1H), 5.93 (d, J=15.6 Hz, 1H), 3.75 (s, 6H), 3.72 (s, 3H), 2.93 (dd, J=1.5, 8.0 Hz, 2H), 2.75 (q, J=2.6 Hz, 1H), 1.76 (t, J=2.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.7, 166.1, 142.2, 124.9, 79.5, 72.7, 56.9, 52.9, 52.9, 51.5, 35.1, 23.5, 3.5; LRMS (EI, *m/z*) 281 (M^+−H), 251, 223, 191, 163; HRMS (EI, *m/z*) calcd for $C_{14}H_{18}O_6$: 282.1103. Found: 282.1107; Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.44; H, 6.38.

4.2.2. Dimethyl non-2-en-7-yne-5,5-dicarboxylate (2c). IR (neat) 2954, 1736, 1284 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63–5.53 (m, 1H), 5.26–5.19 (m, 1H), 3.72 (s, 3H), 2.81 (d, J=7.6 Hz, 0.5H), 2.73–2.69 (m, 3.5H), 1.75 (t, J=2.3 Hz, 3H), 1.65 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.4, 130.1, 124.1, 78.6, 73.3, 57.4, 52.5, 52.5, 35.3, 22.9, 18.0, 3.5; LRMS (EI, *m/z*) 239 (M^+), 207, 178, 147; HRMS (EI, *m/z*) calcd for $C_{12}H_{15}O_3$ (M^+−OMe): 207.1021. Found: 207.1027.

4.2.3. Dimethyl 2-(but-2-ynyl)-2-{(*E*)-4-oxopent-2-enyl}-malonate (2d). IR (neat) 2955, 1738, 1677, 1267 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.64 (dt, J=7.5, 14.5 Hz, 1H), 6.14 (d, J=14.5 Hz, 1H), 3.75 (s, 6H), 2.93 (d, J=7.5 Hz, 2H), 2.76 (q, J=2.5 Hz, 2H), 2.36 (s, 3H), 1.77 (t, J=2.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 170.6, 170.6, 141.9, 135.3, 80.1, 73.0, 57.3, 53.1, 53.1, 35.7, 27.0, 23.9, 3.5; LRMS (EI, *m/z*) 266 (M^+), 251, 235, 207, 175, 147; HRMS (EI, *m/z*) calcd for $C_{14}H_{17}O_5$ (M^+−H): 265.1076. Found: 265.1079.

4.2.4. Dimethyl 2-(but-2-ynyl)-2-(3-cyanoallyl)malonate (2e). IR (neat) 2956, 2225, 1733, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (dt, J=7.7, 15.4 Hz, 0.83H), 6.48 (dt, J=7.9, 10.9 Hz, 0.17H), 5.48 (d, J=15.4 Hz, 0.83H), 5.47 (d, J=10.9 Hz, 0.17H), 3.76 (s, 6H), 3.14 (d, J=7.9 Hz, 0.34H), 2.92 (d, J=7.7 Hz, 1.66H), 2.76–2.73 (m, 2H), 1.77 (t, J=2.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.4, 149.5, 148.4, 116.6, 115.1, 103.5, 102.7, 80.2, 80.0, 72.3, 72.2, 56.7, 56.7, 53.0, 53.0, 53.0, 53.0, 36.4, 34.8, 24.0, 23.9, 3.5, 3.4; LRMS (EI, *m/z*) 249 (M^+), 218, 189, 158; HRMS (EI, *m/z*) calcd for $C_{13}H_{15}NO_4$: 249.1001. Found: 240.1002.

4.2.5. Trimethyl (*E*)-8-methoxyoct-1-en-6-yne-1,4,4-tricarboxylate (2f). IR (neat) 2954, 1737, 1268 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (dt, J=7.6, 15.5 Hz, 1H), 5.93 (d, J=15.5 Hz, 1H), 4.06 (t, J=2.1 Hz, 2H), 3.75 (s, 6H), 3.72 (s, 3H), 3.34 (s, 3H), 2.94 (d, J=7.6 Hz, 2H), 2.86 (t, J=2.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.5, 166.0, 141.9, 125.2, 80.5, 79.7, 59.8, 57.4, 56.7, 53.0, 53.0, 51.6, 35.1, 23.5; LRMS (EI, *m/z*) 311 (M^+), 280, 253, 221, 193, 161; HRMS (EI, *m/z*) calcd for $C_{15}H_{20}O_7$: 311.1131. Found: 311.1128.

4.2.6. Trimethyl (*E*)-7-phenylhept-1-en-6-yne-1,4,4-tricarboxylate (2g). IR (neat) 2954, 1737, 1278 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.36 (m, 2H), 7.31–7.29 (m, 3H), 6.83 (dt, J=7.8, 15.5 Hz, 1H), 5.97 (d, J=15.5 Hz, 1H), 3.78 (s, 6H), 3.72 (s, 3H), 3.03 (s, 2H), 3.01 (d, J=7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.4, 165.9, 141.9, 131.4, 131.4, 128.0, 128.0, 127.9, 125.0, 122.7, 84.0, 83.4, 56.8, 53.4, 52.9, 51.4, 35.2, 24.0; LRMS (EI, *m/z*) 344 (M^+), 329, 312, 285, 253, 225; HRMS (EI, *m/z*) calcd for $C_{19}H_{20}O_6$: 344.1260. Found: 344.1259.

4.2.7. Tetramethyl (*E*)-hept-1-en-6-yne-1,4,4,7-tetracarboxylate (2h). IR (neat) 2955, 1723, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (dt, J=7.6, 15.2 Hz, 1H), 5.97 (d, J=15.2 Hz, 1H), 3.78 (s, 6H), 3.76 (s, 3H), 3.73 (s, 3H), 2.96 (s, 2H), 2.95 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.7, 166.6, 154.0, 141.7, 126.2, 83.0, 76.1, 56.4, 53.3, 53.3, 52.9, 51.8, 35.3, 23.4; LRMS (EI, *m/z*) 326 (M^+), 311, 295, 267, 235; HRMS (EI, *m/z*) calcd for $C_{15}H_{18}O_8$: 326.1001. Found: 326.1005.

4.2.8. Trimethyl (*E*)-7-(trimethylsilyl)hept-1-en-6-yne-1,4,4-tricarboxylate (2i). IR (neat) 2956, 1736, 1279 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (dt, J=7.9, 15.5 Hz, 1H), 5.93 (d, J=15.5 Hz, 1H), 3.74 (s, 6H), 3.72 (s, 3H), 2.93 (dd, J=0.8, 8.0 Hz, 2H), 2.81 (s, 2H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.5, 166.0, 142.0, 125.2, 100.5, 89.0, 56.8, 53.0, 53.0, 51.6, 35.1, 24.6, 0.0, 0.0, 0.0; LRMS (EI, *m/z*) 340 (M^+), 325, 309, 281; HRMS (EI, *m/z*) calcd for $C_{16}H_{24}O_6Si$: 340.1342. Found: 340.1345.

4.2.9. Methyl (*E*)-non-2-en-7-ynoate (2j). IR (neat) 2950, 1724, 1268 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (dt, J=7.0, 14.0 Hz, 1H), 5.86 (d, J=14.0 Hz, 1H), 3.73 (s, 3H), 2.31 (dt, J=8.5, 8.5 Hz, 2H), 2.19–2.15 (m, 2H), 1.78 (t, J=2.5 Hz, 3H), 1.64 (tt, J=7.1, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 148.6, 121.3, 78.1, 76.3, 51.4, 31.2, 27.3, 18.2, 3.5; LRMS (EI, *m/z*) 165 (M^+−H), 151, 134, 107; HRMS (EI, *m/z*) calcd for $C_{10}H_{13}O_2$ (M^+−H): 165.0915. Found: 165.0915.

4.2.10. Methyl (*E*)-4-{*N*-(but-2-ynyl)-*N*-tosylamino}but-2-enoate (2k). IR (neat) 3055, 1724, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=8.3 Hz, 2H), 7.31 (d, J=8.3 Hz, 2H), 6.82 (dt, J=5.8, 15.7 Hz, 1H), 6.03 (d, J=15.7 Hz, 1H), 4.02 (q, J=2.3 Hz, 2H), 3.96 (d, J=5.8 Hz, 2H), 3.74 (s, 3H), 2.43 (s, 3H), 1.55 (t, J=2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 143.5, 141.9, 135.5, 129.2, 129.2, 127.6, 127.6, 123.6, 82.2, 71.0, 51.6, 47.0, 37.2, 21.4, 3.2; LRMS (EI, *m/z*) 321 (M^+), 290, 262, 166; HRMS (EI, *m/z*) calcd for $C_{16}H_{19}NO_4S$: 321.1035. Found: 321.1039.

4.2.11. Methyl (*E*)-4-{*N*-(4-methoxybut-2-ynyl)-*N*-tosylamino}but-2-enoate (2l). IR (neat) 2951, 2255, 1725, 1279 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.72 (m, 2H), 7.32–7.30 (m, 2H), 6.82 (dt, J=5.6, 15.6 Hz, 1H), 6.04 (d, J=15.6 Hz, 1H), 4.13 (s, 2H), 3.98 (d, J=5.6 Hz, 2H), 3.85 (s, 2H), 3.74 (s, 3H), 3.20 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 144.4, 142.2, 136.2, 130.0, 130.0, 128.1, 128.1, 124.4, 82.3, 78.8, 59.6, 57.5, 51.8, 47.4, 37.1, 21.5; LRMS (EI, *m/z*) 351 (M^+), 335, 196, 155; HRMS (EI, *m/z*) calcd for $C_{17}H_{21}NO_5S$: 351.1140. Found: 351.1128.

4.2.12. Methyl (*E*)-4-(but-2-ynyloxy)but-2-enoate (2m). IR (neat) 2952, 1724, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (dt, J=4.0, 15.6 Hz, 1H), 6.09 (d, J=15.6 Hz, 1H), 4.21 (dd, J=2.4, 4.0 Hz, 2H), 4.15 (q, J=2.4 Hz, 2H), 3.74 (s, 3H), 1.86 (t, J=2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 143.9, 121.1, 83.1, 74.5, 67.9, 58.5, 51.6, 3.6; LRMS (EI, *m/z*) 167 (M^+−H), 153, 138, 109; HRMS (EI, *m/z*) calcd for $C_9H_{11}O_3$ (M^+−H): 167.0708. Found: 167.0706.

4.2.13. Trimethyl (*E*)-non-1-en-7-yne-1,4,4-tricarboxylate (6a). IR (neat) 3054, 1734, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (dt, J=7.8, 15.5 Hz, 1H), 5.89 (d, J=15.5 Hz, 1H), 3.74 (s, 6H), 3.72 (s, 3H), 2.81 (d, J=7.8 Hz, 2H), 2.12 (s, 4H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.8, 166.3, 142.7, 125.2, 77.6, 76.8, 57.1, 52.9, 52.9, 51.7, 35.8, 32.4, 14.4, 3.6; LRMS (EI, *m/z*) 295 (M^+−H), 281, 264, 230, 198; HRMS (EI, *m/z*) calcd for $C_{15}H_{20}O_6$: 296.1260. Found: 296.1256.

4.2.14. Methyl (*E*)-5-{*N*-(but-2-ynyl)-*N*-tosylamino}pent-2-enoate (6b). IR (neat) 2951, 1722, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73–7.71 (m, 2H), 7.30–7.29 (m, 2H), 6.90 (dt, J=6.9, 15.5 Hz, 1H), 5.89 (d, J=15.5 Hz, 1H), 4.05 (q, J=1.9 Hz, 2H), 3.73 (s, 3H), 3.29 (t, J=7.4 Hz, 2H), 2.50 (dt, J=6.9, 7.4 Hz, 2H), 2.42 (s, 3H), 1.58 (t, J=1.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 144.6, 143.2, 135.3, 129.1, 129.0, 127.5, 127.4, 122.7, 81.7, 71.3, 51.3, 44.8, 37.1, 30.7, 21.4, 3.1; LRMS (EI, *m/z*) 335 (M^+), 304, 236, 184, 155, 91; HRMS (EI, *m/z*) calcd for $C_{17}H_{21}O_4NS$: 335.1191. Found: 335.196.

4.2.15. Methyl (*E*)-3-[(1*R,2*R**)-2-{*N*-(but-2-ynyl)-*N*-tosylamino}cyclopentyl]acrylate (6c).** IR (neat) 2954, 1720, 1653, 1261 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79–7.77 (m, 2H), 7.28–7.26 (m, 2H), 6.97 (dd, J=8.3, 15.6 Hz, 1H), 5.77 (d, J=15.6 Hz, 1H), 4.19 (dq, J=2.1, 18.4 Hz, 1H), 4.11 (dt, J=8.5, 8.5 Hz, 1H), 3.75 (dq, J=2.3, 18.4 Hz, 1H), 3.72 (s, 3H), 2.99–2.92 (m, 1H), 2.42 (s, 3H), 1.93–1.81 (m, 4H), 1.65–1.48 (m, 2H), 1.64 (t, J=2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 148.0, 143.0, 137.2, 129.1, 129.1, 127.6, 127.7, 121.8, 80.8, 74.6, 61.5, 51.5, 45.4, 36.2, 29.0, 27.7, 21.7, 21.5, 3.4; LRMS (EI, *m/z*) 375 (M^+), 344, 290, 220; HRMS (EI, *m/z*) calcd for $C_{20}H_{25}O_4NS$: 375.1504. Found: 375.1503.

4.2.16. Methyl (*E*)-3-[(1*R,2*S**)-2-{*N*-(but-2-ynyl)-*N*-tosylamino}cyclopentyl]acrylate (6d).** IR (neat) 2952, 1722, 1656, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74–7.73 (m, 2H), 7.24–7.22 (m, 2H), 6.64 (dd, J=8.5, 16.0 Hz, 1H), 5.71 (d, J=16.0 Hz, 1H), 4.15 (dq, J=1.9, 18.1 Hz, 1 H), 4.02 (dt, J=8.1, 8.1 Hz, 1H), 3.93 (dq, J=2.5, 18.1 Hz, 1H), 3.70 (s, 3H), 2.84 (ddt, J=8.7, 8.7, 8.7 Hz, 1H), 2.40 (s, 3H), 1.90–1.83 (m, 2H), 1.77–1.65 (m, 3H), 1.71 (t, J=2.5 Hz, 3H), 1.48–1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.3, 143.0, 137.5, 129.0, 129.0, 127.4, 127.4, 121.5, 80.6, 75.1, 63.8, 51.3, 44.9, 33.1, 30.1, 28.7, 22.0, 21.5, 3.4; LRMS (EI, *m/z*) 375 (M^+), 344, 316, 220; HRMS (EI, *m/z*) calcd for $C_{20}H_{25}O_4NS$: 375.1504. Found: 375.1504.

4.3. Typical procedure for nickel-mediated carboxylative cyclization (Table 1, entry 4)

A flame-dried round bottom flask was charged with $Ni(cod)_2$ (49 mg, 0.18 mmol), MS 4Å (500 mg), and degassed dioxane (1.5 mL). To this was added DBU (0.055 mL, 0.35 mmol), and the flask was immersed in a liquid nitrogen bath. After the mixture had been frozen, the flask was evacuated to 0.05 mmHg. The flask was backfilled with CO_2 in a plastic balloon and the frozen mixture was slowly thawed at ambient temperature. To this suspension was slowly added **2a** (50 mg, 0.18 mmol) in degassed dioxane (2 mL) over a period of 1 h. The resulting mixture was stirred at 40 °C for 3 h and then quenched with 10% aqueous HCl at 0 °C. The mixture was extracted with AcOEt and the combined organic layers were extracted with saturated aqueous $NaHCO_3$ (base extraction). The basic aqueous layers were acidified with 10% HCl and then extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was treated with diazomethane according to the standard procedure. The obtained crude material was purified by silica gel

column chromatography (hexane/AcOEt = 5/1) to afford **3a** (42.4 mg, 70%) as a colorless oil. From the residual organic layer of the base extraction, **4a** (4.5 mg, 9%) was obtained as a colorless oil after standard workup and purification by a silica gel column chromatography (hexane/AcOEt = 5/1).

4.3.1. Dimethyl (*E*)-3-{di(methoxycarbonyl)methyl}-4-ethylidenecyclopentane-1,1-dicarboxylate (3a). IR (neat) 2955, 1736, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27–5.21 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.58 (d, J=8.0 Hz, 1H), 3.32–3.25 (m, 1H), 3.02 (d, J=16.8 Hz, 1H), 2.84 (d, J=16.8 Hz, 1H), 2.57 (dd, J=7.6, 13.1 Hz, 1H), 2.27 (dd, J=9.5, 13.1 Hz, 1H), 1.59 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.8, 168.7, 168.3, 139.3, 118.0, 58.3, 54.9, 52.9, 52.8, 52.5, 52.4, 41.9, 36.9, 36.8, 14.8; LRMS (EI, *m*/*z*) 342 (M^+), 311, 282, 250, 222, 191; HRMS (EI, *m*/*z*) calcd for $C_{16}H_{22}O_8$: 342.1315. Found: 342.1308.

4.3.2. Dimethyl (*E*)-3-{(methoxycarbonyl)methyl}-4-ethylidenecyclopentane-1,1-dicarboxylate (4a). IR (neat) 2954, 1736, 1258 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.26–5.20 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.02 (d, J=17.4 Hz, 1H), 2.94–2.92 (m, 1H), 2.84 (d, J=17.4 Hz, 1H), 2.63 (dd, J=7.4, 13.0 Hz, 1H), 2.59 (dd, J=5.4, 15.5 Hz, 1H), 2.28 (dd, J=8.7, 15.5 Hz, 1H), 1.89 (dd, J=10.6, 13.0 Hz, 1H), 1.60 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 172.9, 172.8, 141.9, 117.0, 58.5, 53.1, 53.0, 51.8, 40.2, 38.9, 38.7, 37.2, 14.7; LRMS (EI, *m*/*z*) 284 (M^+), 253, 224, 192; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}O_6$: 284.1260. Found: 284.1267.

4.3.3. Dimethyl (*E*)-3-ethylidene-4-(2-oxopropyl)cyclopentane-1,1-dicarboxylate (4d). IR (neat) 2955, 1733, 1267 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.20–5.15 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.01 (d, J=17.0 Hz, 1H), 2.99–2.93 (m, 1H), 2.82 (d, J=17.0 Hz, 1H), 2.70 (dd, J=5.3, 17.0 Hz, 1H), 2.62 (dd, J=7.4, 12.6 Hz, 1H), 2.45 (dd, J=8.3, 17.0 Hz, 1H), 2.15 (s, 3H), 1.78 (dd, J=10.5, 12.9 Hz, 1H), 1.59 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 172.2, 172.0, 141.7, 116.1, 58.3, 52.8, 52.8, 48.3, 40.1, 37.8, 37.0, 30.3, 14.6; LRMS (EI, *m*/*z*) 268 (M^+), 237, 208, 176, 151; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}O_5$: 268.1310. Found: 268.1313.

4.3.4. (3a*R,5*R**)-Dimethyl 2-(methyl)bicyclo[3,3,0]oct-1-en-3-ol-7,7-dicarboxylate (5).** IR (neat) 3507, 2952, 1732, 1262 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.69 (s, 3H), 2.67 (dd, J=1.7, 13.1 Hz, 1H), 2.65 (dd, J=1.7, 13.2 Hz, 1H), 2.51 (d, J=14.0 Hz, 1H), 2.44 (br s, 1H), 2.43–2.37 (m, 1H), 2.25 (d, J=14.0 Hz, 1H), 1.89 (d, J=13.1 Hz, 1H), 1.86 (dd, J=9.0, 13.2 Hz, 1H), 1.62 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 171.3, 134.0, 133.2, 96.4, 60.9, 53.0, 52.6, 47.8, 45.4, 42.1, 42.0, 14.3, 9.3; LRMS (EI, *m*/*z*) 268 (M^+), 250, 237, 190, 131; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}O_5$: 268.1310. Found: 268.1313.

4.3.5. Dimethyl (*E*)-3-{(methoxycarbonyl)(cyano)methyl}-4-ethylidenecyclopentane-1,1-dicarboxylate (3e). IR (neat) 3520, 2954, 1731, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.50–5.43 (m, 0.33H), 5.41–5.34 (m, 0.67H), 3.83 (s, 3H), 3.80 (d, J=4.8 Hz, 0.67H), 3.76 (s, 3H), 3.74 (s, 3H), 3.63 (d, J=6.0 Hz, 0.33H), 3.30–3.25 (m, 1H), 3.05 (d, J=17.2 Hz, 1H), 2.90 (d, J=17.2 Hz, 1H), 2.65 (dd, J=3.6, 11.2 Hz, 0.33H), 2.61 (dd, J=6.8, 11.6 Hz, 0.66H), 2.17 (dd, J=11.6, 13.2 Hz, 0.66H), 2.14 (dd, J=3.6, 9.6 Hz, 0.33H), 1.68 (d, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.1, 148.1, 145.2, 132.7, 127.9, 127.9, 126.4, 125.5, 125.5, 93.9, 63.3, 53.0, 52.9, 49.8, 46.6, 40.0, 32.1, 10.4; LRMS (EI, *m*/*z*) 330 (M^+), 312, 299, 280, 253; HRMS (EI, *m*/*z*) calcd for $C_{19}H_{22}O_5$: 330.1467. Found: 330.1470.

4.3.6. Dimethyl (*E*)-3-{di(methoxycarbonyl)methyl}-4-(2-methoxyethylidene)cyclopentane-1,1-dicarboxylate (3f). IR (neat) 2955, 1735, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.36–5.33 (m, 1H), 3.91 (dq, J=6.6, 13.1 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.65 (d, J=7.5 Hz, 1H), 3.36–3.30 (m, 1H), 3.28 (t, J=11.5 Hz, 3H), 3.07 (d, J=16.9 Hz, 1H), 2.92 (d, J=16.9 Hz, 1H), 2.59 (dd, J=8.2, 13.1 Hz, 1H), 2.32 (dd, J=9.9, 13.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 171.5, 168.5, 168.1, 143.0, 120.3, 69.6, 58.4, 57.7, 54.4, 53.0, 52.9, 52.6, 52.4, 42.1, 37.1, 36.3; LRMS (EI, *m*/*z*) 341 (M^+−OMe), 309, 280, 249, 240, 221, 180; HRMS (EI, *m*/*z*) calcd for $C_{16}H_{21}O_8$ (M^+−OMe): 341.1236. Found: 341.1234.

4.3.7. Dimethyl (*E*)-3-{(methoxycarbonyl)methyl}-4-(2-methoxyethylidene)cyclopentane-1,1-dicarboxylate (4f). IR (neat) 2953, 1734, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.37–5.33 (m, 1H), 3.93 (d, J=6.3 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.31(s, 3H), 3.08 (d, J=17.3 Hz, 1H), 3.02–2.95 (m, 1H), 2.92 (d, J=17.3 Hz, 1H), 2.68–2.62 (m, 2H), 2.34 (dd, J=8.7, 15.7 Hz, 1H), 1.92 (dd, J=10.7, 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.7, 171.7, 145.0, 118.7, 69.8, 58.4, 57.9, 53.0, 52.9, 51.7, 39.5, 39.1, 38.2, 37.1; LRMS (EI, *m*/*z*) 314 (M^+), 282, 250, 222, 191; HRMS (EI, *m*/*z*) calcd for $C_{15}H_{22}O_7$: 314.1365. Found: 314.1361.

4.3.8. Dimethyl (*E*)-3-{di(methoxycarbonyl)methyl}-4-benzylidenecyclopentane-1,1-dicarboxylate (3g). IR (neat) 2955, 1732, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5H), 6.29 (s, 0.77H), 3.82–3.68 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.56–3.51 (m, 1H), 3.29 (d, J=17.5 Hz, 1H), 3.25 (d, J=17.5 Hz, 1H), 2.65 (dd, J=8.0, 13.0 Hz, 1H), 2.37 (dd, J=9.5, 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.5, 169.5, 169.1, 142.1, 142.0, 137.9, 137.8, 129.1, 128.9, 127.3, 124.8, 59.5, 55.3, 53.2, 53.2, 52.9, 52.8, 44.0, 38.9, 36.1; LRMS (EI, *m*/*z*) 404 (M^+), 373, 344, 312, 284, 253, 225; HRMS (EI, *m*/*z*) calcd for $C_{21}H_{24}O_8$: 404.1471. Found: 404.1477.

4.3.9. Dimethyl (*E*)-3-{(methoxycarbonyl)methyl}-4-benzylidenecyclopentane-1,1-dicarboxylate (4g). IR (neat) 2954, 1732, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.19 (m, 5H), 6.25 (s, 0.86H), 3.73 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.36 (d, J=17.5 Hz, 1H), 3.23–3.19 (m, 1H), 3.21 (d, J=17.5 Hz, 1H), 2.75 (dd, J=5.3, 15.6 Hz, 1H), 2.71 (dd, J=8.5, 13.0 Hz, 1H), 2.45 (dd, J=9.0, 15.6 Hz, 0.76H), 1.98 (dd, J=10.5, 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.8, 171.7, 143.3, 143.2, 137.2, 131.6, 128.3, 128.2, 126.5, 122.7, 59.1, 52.9, 52.9, 51.7, 40.6, 40.5, 39.1, 39.0; LRMS (EI, *m*/*z*) 346

(M^+), 315, 286, 256, 226; HRMS (EI, *m/z*) calcd for $C_{19}H_{22}O_6$: 345.1416. Found: 346.1417.

4.3.10. Dimethyl (*E*)-3-{di(methoxycarbonyl)methyl}-4-{(methoxycarbonyl)methylene}cyclopentane-1,1-dicarboxylate (3h). IR (neat) 2955, 1735, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68–5.66 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.74–3.66 (m, 2H), 3.73 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.48–3.42 (m, 1H), 3.34 (d, *J*=19.2 Hz, 1H), 2.59 (dd, *J*=8.4, 13.2 Hz, 1H), 2.40 (dd, *J*=10.8, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.0, 168.0, 167.5, 166.2, 162.4, 113.4, 58.4, 53.3, 52.9, 52.9, 52.8, 52.6, 51.2, 43.5, 40.3, 35.6; LRMS (EI, *m/z*) 386 (M^+), 354, 322, 294, 262, 235, 207; HRMS (EI, *m/z*) calcd for $C_{17}H_{22}O_{10}$: 386.1212. Found: 386.1203.

4.3.11. Dimethyl (*E*)-3-{(methoxycarbonyl)methyl}-4-{(methoxycarbonyl)methylene}cyclopentane-1,1-dicarboxylate (4h). IR (neat) 2954, 1735, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (br s, 1H), 3.74 (s, 6H), 3.71 (s, 3H), 3.70 (s, 3H), 3.72–3.67 (m, 1H), 3.36 (d, *J*=19.6 Hz, 1H), 3.19–3.11 (m, 1H), 2.70–2.65 (m, 1H), 2.65 (dd, *J*=5.2, 16.4 Hz, 1H), 2.41 (dd, *J*=8.4, 16.4 Hz, 1H), 2.00 (dd, *J*=11.2, 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.5, 171.3, 166.5, 164.5, 112.7, 58.4, 53.0, 52.9, 51.8, 51.2, 40.8, 40.4, 38.8, 37.5; LRMS (EI, *m/z*) 328 (M^+), 296, 268, 236, 209; HRMS (EI, *m/z*) calcd for $C_{15}H_{20}O_8$: 328.1158. Found: 328.1165.

4.3.12. Dimethyl (*E*)-3-{(methoxycarbonyl)methyl}-4-{(trimethylsilyl)methylene}cyclopentane-1,1-dicarboxylate (4i). IR (neat) 2985, 1741, 1243 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (s, 0.16H), 3.74 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.08 (d, *J*=16.5 Hz, 1H), 2.94–2.89 (m, 1H), 2.91 (d, *J*=16.5 Hz, 1H), 2.68–2.61 (m, 2H), 2.29 (dd, *J*=9.2, 15.9 Hz, 0.34H), 1.92 (dd, *J*=10.4, 13.2 Hz, 1H), 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.3, 172.2, 159.0, 120.9, 59.0, 53.3, 53.2, 52.0, 41.6, 40.8, 39.4, 39.1, 0.0, 0.0, 0.0; LRMS (EI, *m/z*) 342 (M^+), 327, 311, 283, 251; HRMS (EI, *m/z*) calcd for $C_{16}H_{26}O_6Si$: 342.1498. Found: 342.1496.

4.3.13. Dimethyl 2-{(*E*)-2-ethylidenecyclopentyl}malonate (3j). IR (neat) 2962, 1735, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.23–5.21 (m, 1H), 3.72 (s, 3H), 3.72 (s, 3H), 3.45 (d, *J*=9.0 Hz, 1H), 3.12–3.09 (m, 1H), 2.35–2.16 (m, 2H), 1.84–1.71 (m, 2H), 1.65–1.54 (m, 2H), 1.56 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.8, 143.2, 116.3, 55.3, 52.2, 44.0, 30.5, 28.3, 23.4, 14.8, 1.0; LRMS (EI, *m/z*) 226 (M^+), 195, 166; HRMS (EI, *m/z*) calcd for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1204.

4.3.14. Methyl 2-{(*E*)-2-ethylidenecyclopentyl}acetate (4j). IR (neat) 2954, 1733, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24–5.18 (m, 1H), 3.67 (s, 3H), 2.79–2.69 (m, 1H), 2.52 (dd, *J*=5.2, 14.8 Hz, 1H), 2.31–2.12 (m, 3H), 2.22 (dd, *J*=8.8, 14.8 Hz, 1H), 1.91 (dt, *J*=7.2, 19.2 Hz, 1H), 1.79–1.70 (m, 1H), 1.61–1.54 (m, 1H), 1.58 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 145.6, 114.4, 51.3, 40.6, 39.2, 33.1, 28.7, 23.8, 14.6; LRMS (EI, *m/z*) 168 (M^+), 108, 95, 79; HRMS (EI, *m/z*) calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1156.

4.3.15. Dimethyl 2-{(*Z*)-4-ethylidene-1-tosylpyrrolidin-3-yl}malonate (3k). IR (neat) 2953, 1737, 1347, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75–7.70 (m, 2H), 7.38–7.32 (m, 2H), 7.35–7.31 (m, 1H), 3.88 (d, *J*=15.2 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.61 (d, *J*=15.2 Hz, 1H), 3.52 (d, *J*=9.0 Hz, 1H), 3.42 (dd, *J*=2.7, 9.7 Hz, 1H), 3.29–3.24 (m, 1H), 3.18 (dd, *J*=6.5, 9.7 Hz, 1H), 2.44 (s, 3H), 1.51 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 168.0, 143.7, 135.3, 132.0, 129.6, 129.6, 127.8, 127.8, 120.2, 54.5, 52.7, 52.5, 51.7, 49.0, 42.7, 21.6, 14.7; LRMS (EI, *m/z*) 381 (M^+), 350, 250, 226; HRMS (EI, *m/z*) calcd for $C_{18}H_{23}NO_6S$: 381.1246. Found: 381.1266.

4.3.16. Methyl 2-{(*Z*)-4-ethylidene-1-tosylpyrrolidin-3-yl}acetate (4k). IR (neat) 2953, 1736, 1346, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75–7.70 (m, 2H), 7.38–7.32 (m, 2H), 5.31–5.26 (m, 1H), 3.81 (d, *J*=14.2 Hz, 1H), 3.74 (d, *J*=14.2 Hz, 1H), 3.67 (s, 3H), 3.47–3.43 (m, 1H), 2.98 (d, *J*=6.0 Hz, 2H), 2.49 (dd, *J*=9.3, 16.1 Hz, 1H), 2.44 (s, 3H), 2.32 (dd, *J*=8.7, 16.1 Hz, 1H), 1.61 (d, *J*=5.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 143.6, 137.8, 132.3, 129.6, 129.6, 127.8, 127.8, 117.8, 53.3, 51.8, 49.4, 39.0, 37.6, 21.6, 14.6; LRMS (EI, *m/z*) 323 (M^+), 292, 250, 168; HRMS (EI, *m/z*) calcd for $C_{16}H_{21}NO_4S$: 323.1191. Found: 323.1188.

4.3.17. Dimethyl 2-{(*Z*)-4-(2-methoxyethylidene)-1-tosylpyrrolidin-3-yl}malonate (3l). IR (neat) 2953, 1736, 1347, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.69 (m, 2H), 7.35–7.34 (m, 2H), 5.44–5.42 (m, 1H), 3.93 (d, *J*=14.3 Hz, 1H), 3.80–3.77 (m, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 3.68 (d, *J*=14.3 Hz, 1H), 3.56 (d, *J*=8.8 Hz, 1H), 3.43 (dd, *J*=3.2, 9.9 Hz, 1H), 3.33–3.29 (m, 1H), 3.26 (s, 3H), 3.21 (dd, *J*=6.4, 9.9 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 167.6, 143.7, 138.0, 131.8, 129.6, 129.6, 127.6, 121.8, 121.8, 69.3, 58.2, 54.3, 52.9, 52.7, 51.2, 49.0, 43.0, 21.7; LRMS (EI, *m/z*) 411 (M^+), 379, 366, 348; HRMS (EI, *m/z*) calcd for $C_{19}H_{25}NO_7S$: 411.1352. Found: 411.1345.

4.3.18. Methyl 2-{(*Z*)-4-(2-methoxyethylidene)-1-tosylpyrrolidin-3-yl}acetate (4l). IR (neat) 2927, 1735, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.70 (m, 2H), 7.35–7.33 (m, 2H), 5.40–5.39 (m, 1H), 3.86 (d, *J*=15.0 Hz, 1H), 3.81 (d, *J*=7.1 Hz, 2H), 3.67 (s, 3H), 3.48 (dd, *J*=7.1, 9.3 Hz, 1H), 3.33 (d, *J*=15.0 Hz, 1H), 3.28 (s, 3H), 3.07–3.05 (m, 1H), 2.98 (dd, *J*=6.2, 9.3 Hz, 1H), 2.53 (dd, *J*=5.2, 16.3 Hz, 1H), 2.44 (s, 3H), 2.38 (dd, *J*=8.7, 16.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 143.8, 141.0, 132.4, 129.7, 129.7, 127.8, 127.8, 119.6, 69.5, 58.2, 52.8, 51.8, 49.4, 39.4, 37.3, 21.6; LRMS (EI, *m/z*) 353 (M^+), 321, 308, 248, 198, 155; HRMS (EI, *m/z*) calcd for $C_{17}H_{23}NO_5S$: 353.1297. Found: 353.1291.

4.3.19. Dimethyl 2-{(*Z*)-4-ethylidene-tetrahydrofuran-3-yl}malonate (3m). IR (neat) 2954, 1737, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.41–5.38 (m, 1H), 4.36 (d, *J*=13.5 Hz, 1H), 4.28 (d, *J*=13.5 Hz, 1H), 3.90 (dd, *J*=5.6, 9.3 Hz, 1H), 3.85 (dd, *J*=3.0, 9.3 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.55 (dd, *J*=9.6 Hz, 1H), 3.32–3.29 (m, 1H), 1.56 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 168.4, 139.1, 117.3, 71.8, 68.7, 54.5, 52.6, 52.3, 43.7, 14.8; LRMS (EI, *m/z*) 228 (M^+), 197, 132,

97; HRMS (EI, *m/z*) calcd for $C_{11}H_{16}O_5$: 228.0998. Found: 228.0997.

4.3.20. Methyl 2-{(*Z*)-4-ethylidene-tetrahydrofuran-3-yl}acetate (4m). IR (neat) 2952, 1735, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35–5.32 (m, 1H), 4.35 (d, *J*=15.8 Hz, 1H), 4.32 (d, *J*=15.8 Hz, 1H), 4.05 (dd, *J*=6.6, 8.6 Hz, 1H), 3.69 (s, 3H), 3.56 (dd, *J*=5.9, 8.6 Hz, 1H), 3.06–2.99 (m, 1H), 2.54 (dd, *J*=5.6, 16.1 Hz, 1H), 2.39 (dd, *J*=9.2, 16.1 Hz, 1H), 1.57 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 141.7, 114.9, 73.7, 69.1, 51.6, 40.0, 37.5, 14.7; LRMS (EI, *m/z*) 170 (M^+), 139, 110, 97; HRMS (EI, *m/z*) calcd for $C_9H_{14}O_3$: 170.0943. Found: 170.0939.

4.3.21. Dimethyl (*E*)-3-{di(methoxycarbonyl)methyl}-4-ethylidenecyclohexane-1,1-dicarboxylate (7a). IR (neat) 2955, 1734, 1240 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (q, *J*=6.7 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H), 3.56 (d, *J*=10.8 Hz, 1H), 2.97–2.93 (m, 1H), 2.45–2.40 (m, 1H), 2.28 (dd, *J*=4.6, 13.6 Hz, 1H), 2.17–1.98 (m, 4H), 1.57 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.3, 168.4, 168.3, 136.9, 116.8, 54.5, 54.3, 52.7, 52.7, 52.5, 52.4, 41.3, 35.0, 32.0, 23.6, 12.9; LRMS (EI, *m/z*) 356 (M^+), 325, 264, 237, 205; HRMS (EI, *m/z*) calcd for $C_{17}H_{24}O_8$: 356.1471. Found: 356.1475.

4.3.22. Dimethyl 2-{(*Z*)-3-ethylidene-1-tosylpiperidin-4-yl}malonate (7b). IR (neat) 2954, 1736, 1268 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67–7.66 (m, 2H), 7.34–7.33 (m, 2H), 5.38 (q, *J*=6.8 Hz, 1H), 3.88 (d, *J*=13.0 Hz, 1H), 3.71 (s, 3H), 3.63 (s, 3H), 3.55 (d, *J*=11.2 Hz, 1H), 3.39 (d, *J*=13.0 Hz, 1H), 3.31–3.27 (m, 1H), 3.00–2.91 (m, 2H), 2.45 (s, 3H), 1.88–1.81 (m, 1H), 1.66 (d, *J*=6.8 Hz, 3H), 1.64–1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.8, 143.4, 133.1, 130.7, 129.5, 129.5, 127.5, 127.4, 122.8, 52.9, 52.7, 52.5, 43.9, 43.3, 41.4, 28.8, 21.7, 13.2; LRMS (EI, *m/z*) 395 (M^+), 364, 304, 264, 240; HRMS (EI, *m/z*) calcd for $C_{19}H_{25}O_6NS$: 395.1395. Found: 395.1399.

4.3.23. Dimethyl 2-{(*Z*,4*R,4a*R**,7a*S**)-3-ethylidene-octahydro-1-tosyl-1*H*-cyclopenta[*b*]pyridin-4-yl}malonate (7c).** IR (neat) 2953, 1736, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75–7.74 (m, 2H), 7.32–7.31 (m, 2H), 5.42–5.40 (m, 1H), 4.31 (dd, *J*=8.1, 18.7 Hz, 1H), 4.21 (d, *J*=15.6 Hz, 1H), 3.82 (d, *J*=11.8 Hz, 1H), 3.72 (s, 3H), 3.66 (d, *J*=15.6 Hz, 1H), 3.60 (s, 3H), 2.76 (d, *J*=11.8 Hz, 1H), 2.44 (s, 3H), 2.30–2.25 (m, 1H), 1.84–1.80 (m, 1H), 1.60–1.52 (m, 3H), 1.53 (t, *J*=6.9 Hz, 3H), 1.27–1.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.7, 143.2, 136.2, 129.6, 129.6, 129.4, 129.4, 127.3, 124.4, 55.2, 54.7, 52.5, 52.1, 46.3, 40.7, 39.1, 31.6, 28.0, 24.2, 21.6, 12.9; LRMS (EI, *m/z*) 435 (M^+), 404, 304, 280; HRMS (EI, *m/z*) calcd for $C_{22}H_{29}O_6NS$: 435.1715. Found: 435.1707.

4.3.24. Dimethyl 2-{(*Z*,4*S,4a*R**,7a*S**)-3-ethylidene-octahydro-1-tosyl-1*H*-cyclopenta[*b*]pyridine-4-yl}malonate (7d).** IR (neat) 2953, 1736, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.24–7.22 (m, 2H), 5.28 (q, *J*=7.0 Hz, 1H), 4.13 (d, *J*=13.5 Hz, 1H), 3.64 (s, 3H), 3.60 (s, 3H), 3.57 (d, *J*=13.5 Hz, 1H), 3.56 (d, *J*=6.9 Hz, 1H), 2.66 (dd, *J*=6.9, 10.9 Hz, 1H), 2.48 (ddd, *J*=6.9, 10.9, 10.9 Hz, 1H), 2.43 (s, 3H), 2.30–2.25 (m, 1H), 2.02–1.99 (m, 1H), 1.85–1.62 (m, 4H), 1.60 (d, *J*=7.0 Hz, 3H), 1.16–1.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.6, 143.3, 134.3, 132.5, 129.5, 129.4, 127.6, 127.6, 122.6, 62.8, 54.7, 52.5, 47.2, 46.7, 46.1, 31.1, 26.5, 21.5, 20.8, 13.9, 13.9; LRMS (EI, *m/z*) 435 (M^+), 404, 304, 280; HRMS (EI, *m/z*) calcd for $C_{22}H_{29}O_6NS$: 435.1715. Found: 435.1707.

Acknowledgements

This work was supported by Grant-in-Aids for Scientific Research (No. 14771235) and Scientific Research on Priority Area (A): 'Creation of Biologically Functional Molecules' (No. 17035003) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan, which are gratefully acknowledged.

Supplementary data

Information on procedures for preparation of enynes **2c**–**2n** and **6a**–**6d**, spectral data for all synthetic intermediates of those enynes, and determination of the stereochemistry of **7c** and **7d** are described. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.03.121.

References and notes

1. Reviews: (a) Behr, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 661; (b) Braunstein, P.; Matt, D.; Nobel, D. *Chem. Rev.* **1988**, *88*, 747; (c) Leitner, W. *Coord. Chem. Rev.* **1996**, *153*, 257; (d) Yin, X.; Moss, J. R. *Coord. Chem. Rev.* **1999**, *181*, 27; (e) Walther, D.; Ruben, M.; Rau, S. *Coord. Chem. Rev.* **1999**, *182*, 67; (f) Mori, M.; Takimoto, M. *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH: Weinheim, 2005; pp 205–223.
2. Selected recent reports: (a) Tsuda, T.; Morikawa, S.; Hasegawa, N.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2978; (b) Tsuda, T.; Yamamoto, T.; Saegusa, T. *J. Organomet. Chem.* **1992**, *429*, C46; (c) Dérien, S.; Clinet, J.-C.; Duñach, E.; Périchon, J. *J. Org. Chem.* **1993**, *58*, 2578; (d) Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* **1998**, *64*, 3975; (e) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188; (f) Tekavec, T. N.; Arif, A. M.; Louie, J. *Tetrahedron* **2004**, *60*, 7431. See also references cited in Refs 1.
3. (a) Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2001**, *123*, 2895; (b) Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* **2001**, *3*, 3345; (c) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323; (d) Takimoto, M.; Kawamura, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2599; (e) Takimoto, M.; Kawamura, M.; Mori, M. *Synthesis* **2004**, 791; (f) Shimizu, K.; Takimoto, M.; Sato, Y.; Mori, M. *Org. Lett.* **2005**, *7*, 195; (g) Takimoto, M.; Kawamura, M.; Mori, M.; Sato, Y. *Synlett* **2005**, 2019.
4. (a) Sasaki, Y.; Inoue, Y.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1976**, 605; (b) Inoue, Y.; Sasaki, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2375.

5. (a) Musco, A.; Perego, C.; Tartiari, V. *Inorg. Chim. Acta* **1978**, *28*, L147; (b) Musco, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 693.
6. (a) Behr, A.; Juszak, K.-D.; Keim, W. *Synthesis* **1983**, 574; (b) Behr, A.; Juszak, K.-D. *J. Organomet. Chem.* **1983**, *255*, 263; (c) Behr, A.; He, R. *J. Organomet. Chem.* **1984**, *276*, C69; (d) Behr, A. *Bull. Soc. Chim. Belg.* **1985**, *94*, 671; (e) Behr, A.; He, R.; Juszak, K.-D.; Krüger, C.; Tsay, Y.-H. *Chem. Ber.* **1986**, *119*, 991; (f) Behr, A.; Kanne, U. *J. Organomet. Chem.* **1986**, *309*, 215.
7. Braunstein, P.; Matt, D.; Nobel, D. *J. Am. Chem. Soc.* **1988**, *110*, 3207.
8. (a) Hoberg, H.; Gross, S.; Milchereit, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 571; (b) Hoberg, H.; Peres, Y.; Milchereit, A.; Gross, S. *J. Organomet. Chem.* **1988**, *345*, C17; (c) Hoberg, H.; Minato, M. *J. Organomet. Chem.* **1991**, *406*, C25.
9. (a) Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2002**, *124*, 10008; (b) Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* **2004**, *126*, 5956.
10. (a) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286; (b) Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539.
11. Zhang, M.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 4498.
12. (a) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099; (b) Montgomery, J.; Seo, J.; Chui, H. M. P. *Tetrahedron Lett.* **1996**, *37*, 6839; (c) Montgomery, J.; Chevliakov, M. V.; Brielmann, H. L. *Tetrahedron* **1997**, *53*, 16449; (d) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911; (e) Montgomery, J.; Seo, J. *Tetrahedron* **1998**, *54*, 1131; (f) Chevliakov, M. V.; Montgomery, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 3144; (g) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139; (h) Seo, J.; Chui, H. M. P.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 476; (i) Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6775; (j) Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370; (k) Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 13481; (l) Ni, Y.; Amarasinghe, K. K. D.; Ksebati, B.; Montgomery, J. *Org. Lett.* **2003**, *5*, 3771; (m) Hrant, H. P.; Chowdhury, S. K.; Gutiérrez-García, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636.
13. (a) Ikeda, S.-i.; Miyashita, H.; Taniguchi, M.; Kondo, H.; Okano, M.; Sato, Y.; Odashima, K. *J. Am. Chem. Soc.* **2002**, *124*, 12060; (b) Ikeda, S.-i.; Sanuki, R.; Miyachi, H.; Miyashita, H.; Taniguchi, M.; Odashima, K. *J. Am. Chem. Soc.* **2004**, *126*, 10331.
14. Portion of this work have previously been communicated: Takimoto, M.; Mizuno, T.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **2005**, *46*, 5173.
15. The role of MS 4Å has not been clear yet. One speculation is that MS 4Å prevents nickelacycle **II** from hydrolysis by removing a trace amount of water in the reaction system.
16. Schunn, R. A. *Inorg. Synth.* **1974**, *15*, 5.
17. Park, K. H.; Son, S. U.; Chung, Y. K. *Org. Lett.* **2002**, *4*, 4361.
18. Atkinson, R. S.; Grimshire, M. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1215.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7598–7610
Tetrahedron

Directing effects of tethered alkenes in nickel-catalyzed coupling reactions of 1,6-enynes and aldehydes

Ryan M. Moslin,[a] Karen M. Miller[b] and Timothy F. Jamison[a,*]

[a]*Massachusetts Institute of Technology, Department of Chemistry, Cambridge, MA 02139, USA*
[b]*Novartis Institute for Biomedical Research, Inc., 250 Massachusetts Ave., Cambridge, MA 02139, USA*

Received 7 December 2005; revised 1 March 2006; accepted 1 March 2006
Available online 15 June 2006

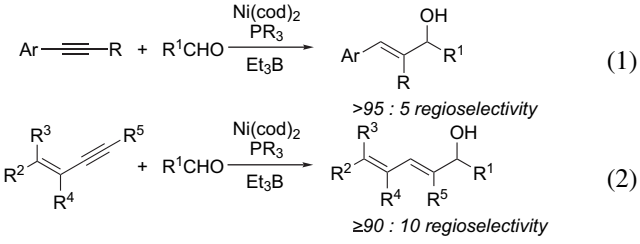
Dedicated to Professor Günther Wilke in honor of his groundbreaking contributions to organonickel chemistry

Abstract—Nickel-catalyzed reductive coupling reactions of aldehydes and 1,6-enynes proceed in excellent regioselectivity in the absence of a phosphine, and the use of a monodentate phosphine additive leads to the formation of the opposite regioisomer with equally high selectivity. Both products are the result of the same fundamental mechanism, with the inversion of regioselectivity being the result of stereospecific ligand substitution at the metal center.

1. Introduction

Substrate-directable reactions are an important class of selective organic transformations, and understanding their mechanism of direction is paramount to their utility.[1] Recently, we reported a substrate-directed, nickel-catalyzed reductive coupling of 1,6-enynes and aldehydes in which the regioselectivity of the reaction was controlled by a tethered olefin.[2] Herein we report a full account of this class of coupling reactions, as well as a description of the likely mechanism by which regioselectivity is controlled.

The nickel-catalyzed coupling of alkynes and aldehydes has emerged as a powerful method for the efficient and selective preparation of allylic alcohols.[3,4] In most cases, the regioselectivity of these coupling reactions is determined by a steric or electronic difference in the alkyne substituents. For example, previous investigations in our laboratory have shown that alkynes conjugated to either an aryl or alkenyl substituent undergo nickel-catalyzed reductive coupling with aldehydes in high regioselectivity (Scheme 1, Eqs. 1 and 2).[4b,d,f]



Scheme 1.

The high degree of regioselectivity observed with certain classes of 1,3-enynes led us to hypothesize that an interaction between the alkene and the metal center has an influence on selectivity (Fig. 1).[4f] Assuming that the reaction proceeds through an oxametallacyclopentene intermediate, interaction of the conjugated alkene with the metal center could result in a stabilizing interaction, thus favoring formation of the regioisomer shown.[5] These results led us to conduct a thorough investigation of the directing effects of tethered alkenes in reductive coupling reactions of alkynes and aldehydes.[6]

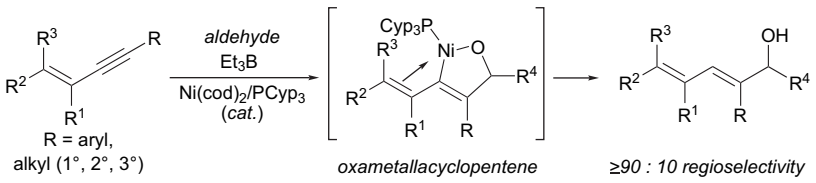


Figure 1.

* Corresponding author. Tel.: +1 617 253 2135; fax: +1 617 324 0253; e-mail: tfj@mit.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.122

2. Results and discussion

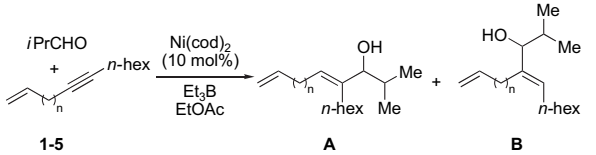
2.1. Discovery of ligand-switchable nickel-catalyzed couplings of aldehydes and 1,6-enynes

A study of nickel-catalyzed reductive coupling reactions of isobutraldehyde with enynes of different tether lengths revealed a marked difference in reactivity and selectivity when the alkyne and alkene were separated by three methylene units (Table 1, entry 4). As it is very unlikely that **4** is significantly different sterically or electronically than alkynes **2**, **3**, or **5**, it seems that involvement of the olefin in the reaction occurs uniquely in the case of the 1,6-enyne. Also interesting is that conjugated enynes do not couple effectively in the absence of a phosphine additive (entry 1), suggesting that the origin of the high regioselectivity observed with 1,3-enynes is different than that observed with 1,6-enynes.

Reductive coupling reactions of 1,6-enynes and aldehydes in the absence of phosphine additive proved remarkably general, considering that previous systems had all required the addition of a phosphine (Table 2).[2,4,7] Also noteworthy is that the presence of an olefin tether is sufficient to overcome an inherent steric preference for the **B** regioisomer (entry 4).[4c] Heteroatoms, which could conceivably compete with the olefin for binding, are well tolerated and augment the versatility of the directed transformation (entries 6–8).

The effect of different phosphine additives on the regioselectivity of reductive coupling reactions of enyne **4** and isobutyraldehyde was also investigated and provided valuable insight into the mechanism of these transformations (Table 3).[8] Electron-rich phosphines afforded superior yields and, remarkably, with very large phosphines (cone angle >160°), the sense of regioselectivity was completely reversed, giving >95:5 of regioisomer **B** (Table 3, entries 1–3).[9] The use of smaller phosphines, even those marginally so ferrocenyldiphenylphosphine ($PFcPh_2$) (cone angle ~155°),[10] resulted in a significant loss of regioselectivity (entries 4–6, Table 3). Since no regioselectivity was observed when 1,2-dihydro-**4** was coupled to isobutyraldehyde in the presence of tricyclopentylphosphine ($PCyp_3$) (77%, 50:50 regioselectivity) it is likely that the tethered olefin is responsible for the regioselectivity both in the presence and absence of a phosphine additive.

Table 1. Directing effects of tethered alkenes[a]



	Alkyne	*n*	Yield	Regioselectivity[b]
1	**1**	0	<5	n.d.
2	**2**	1	<5	n.d.
3	**3**	2	<5	n.d.
4	**4**	3	53[c]	>95:5
5	**5**	4	<5	n.d.
6	*n*-Pentyl–C≡C–*n*-hexyl	n.a.	28[c]	50:50

[a] Standard procedure: The alkyne (0.50 mmol) was added to a 0 °C solution of $Ni(cod)_2$ (0.05 mmol), *i*-PrCHO (1.00 mmol), and Et_3B (1.00 mmol) in EtOAc (0.5 mL), and the solution was allowed to stir 15 h at room temperature.

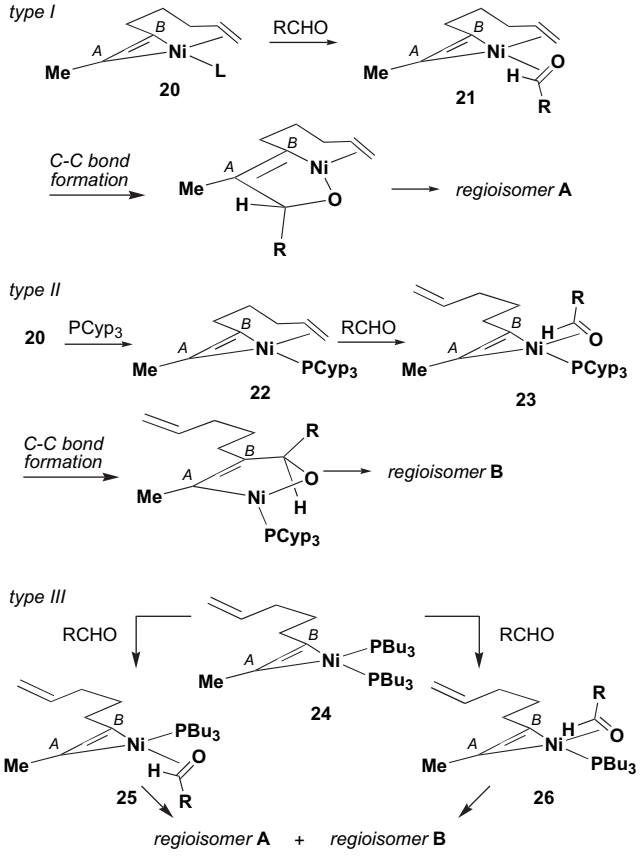
[b] Determined by ^1H NMR and/or GC.

[c] Some alkylative coupling (transfer of Et from Et_3B) also observed.

Although directing effects of tethered alkenes have been demonstrated in other metal-mediated reactions,[11] the only other examples in which the sense of the effect was reversed by an additive are Pd-catalyzed enyne isomerizations reported by Trost.[12] However, in this case high regioselectivity was observed in only one direction (≥15:1 vs 1:2.5), while we observe equal and opposite regioselectivity in the presence or absence of an additive.

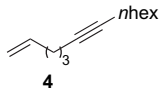
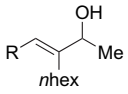
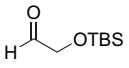
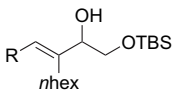
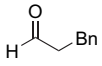
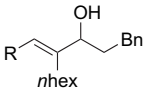
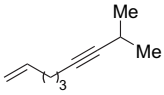
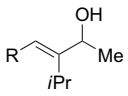
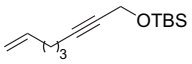
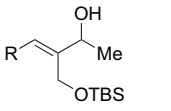
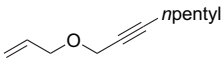
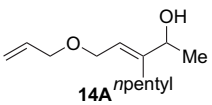
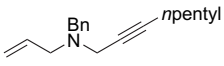
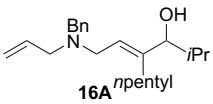
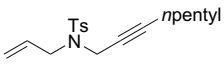
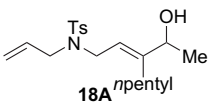
2.2. Origin of regioselectivity in the nickel-catalyzed reductive coupling of aldehydes and 1,6-enynes

Our investigation of additive effects (Table 3) led us to propose that three different pathways could be operating in these reactions depending upon which phosphine is used: one that exclusively forms **A** (Scheme 2, type I), one that exclusively forms **B** (type II), and one that gives a mixture of regioisomers **A** and **B** (type III). We propose a mechanistic rationale for each of the observed regiochemical outcomes, each of which is based on the assumption that the active catalyst involves a trisubstituted, planar, d^8 metal center undergoing stereospecific ligand substitution.[13]



Scheme 2.

Table 2. Highly regioselective, catalytic reductive coupling reactions directed by a remote alkene[a]

Entry	Enyne	Aldehyde	Product	Yield, regioselectivity (**A**:**B**)
1	 **4**		 **6A**	69% (>95:5)
2	**4**		 **7A**	58% (>95:5)
3	**4**		 **8A**	60% (>95:5)
4	 **9**		 **10A**	64% (>95:5)
5	 **11**		 **12A**	62% (>95:5)
6	 **13**		 **14A**	60% (>95:5)
7	 **15**		 **16A**	62% (>95:5)
8	 **17**		 **18A**	68% (>95:5)

[a] See Eq. 3, Table 1. R=$(CH_2)_3CH{=}CH_2$. Regioselectivity determined by ^{1}H NMR and/or GC.

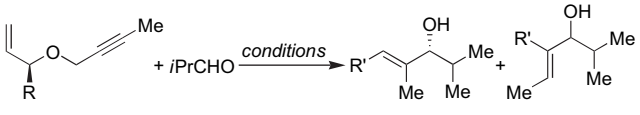
In all cases, C–C bond formation is believed to occur through an oxanickellacyclopentene.[2,4] Also, in all cases the third ligand (L) is assumed to be an olefin[14] and, as it is not part of a bidentate chelate, is considered to be the most weakly bound ligand. Therefore, in substitution reactions of **20**, L is the ligand that is preferentially displaced from the metal center.

Table 3. Effect of phosphine ligand on regioselectivity in reductive couplings of **4** and isobutyraldehyde[a,b]

Entry	PR_3	PR_3 cone angle	**19A**	**19B**	Yield[c]
1	$PCyp_3$	ND[d]	5	>95	50
2	PCy_3	170	5	>95	30
3	$PiPr_3$	161	5	>95	25
4	$PFcPh_2$	155[e]	40	60	20
5	$PCyPh_2$	152	42	58	30
6	PBu_3	132	42	58	75
7	None	—	>95	5	50

[a] Conditions (see Eq. 3): 0.5 mmol scale, 10 mol % $Ni(cod)_2$, 20 mol % ligand, 100 mol % alkyne, 200 mol % *i*-PrCHO, 200 mol % Et_3B, EtOAc, 0 °C to rt, 15 h. Regioselectivity determined by GC analysis.
[b] Ref. 8.
[c] 10–15% reductive cyclization product observed in all cases (cf. 2.4); yields are approximated based on ^{1}H NMR integration of the mixture.
[d] A value for the cone angle of $PCyp_3$ has not been reported.
[e] Ref. 9.

Table 4. Coupling reactions of chiral 1,6-enynes



27 R = Et
28 R = *t*Bu

29A, **30A** **29B**, **30B**

Entry	Enyne	Reaction conditions[a]	Products	**A**:**B**[b]	dr **A**[c]	dr **B**[c]
1	**27** (R=Et)	I	**29A**, **B**	>95:5	95:5	—
2		II		<5:95	—	45:55
3		III		55:45	50:50	45:55
4	**28** (R=*t*Bu)	I	**30A**, **B**	>95:5	>95:5	—
5		II		<5:95	—	42:58
6		III		51:49	45:55	42:58

[a] I: $Ni(cod)_2$ (10 mol %), Et_3B (200 mol %). II: Reaction conditions I+$PCyp_3$ (20 mol %). III: Reaction conditions I+PBu_3 (20 mol %).
[b] Based on isolated yields.
[c] Determined by ^{1}H NMR.

In the absence of a phosphine ligand (Scheme 2, type I), ligand substitution places the aldehyde cis to the alkyne carbon that is distal to the alkene (C(*A*)) and cis to the bound olefin, giving **21**. C–C bond formation occurs at C(*A*) while the olefin tether is coordinated to the nickel, resulting in exclusive formation of regioisomer **A**. In the presence of a large, electron-rich phosphine (e.g., $PCyp_3$), L is again displaced, but in this case by the phosphine, giving complex **22** (Scheme 2, type II). As the phosphine is coordinated more strongly to the metal center than the tethered alkene, the latter is preferentially displaced by the aldehyde in a stereospecific fashion, ultimately leading to regioisomer **B** by way of **23**. Thus, despite not being bound during the C–C bond formation, the olefin nevertheless determines regioselectivity. When the smaller tri-*n*-butylphosphine (PBu_3) is employed (type III), two equivalents of phosphine are bound to the metal center, displacing both the olefin tether and L to give **24**. In this case, regioselectivity is not determined by the olefin, and a non-selective displacement of either phosphine by the aldehyde leads to a mixture of **25** and **26**, which in turn affords a mixture of regioisomers **A** and **B**.

In order to test these mechanistic hypotheses and the overriding assumption of a planar, three-coordinate nickel complex, we evaluated the effect of a stereogenic center in the olefin tether. We hypothesized that in the absence of a phosphine (type I), coordination of the olefin to the metal center should enhance diastereoselection, while conditions employing achiral phosphines (types II and III) should lead to lower diastereoselectivity since the olefin would be dissociated during the C–C bond-forming step.

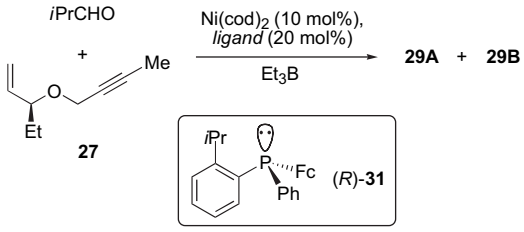
Thus, chiral 1,6-enynes **27** and **28** were synthesized and coupled with isobutyraldehyde under three distinct sets of catalytic conditions (Table 4): (I) $Ni(cod)_2$ with no additive; (II) $Ni(cod)_2$+$PCyp_3$; and (III) $Ni(cod)_2$+PBu_3.

As predicted, under type I reaction conditions (no phosphine) both enynes gave exclusively regioisomer **A** (Table 4, entries 1 and 4). In addition, both allylic alcohols were formed in excellent diastereoselectivity, indicating a strong influence of the stereogenic center in the tether, despite being separated from the site of C–C bond formation by five atoms (1,6-induction).

Conversely, under type II reaction conditions, regioisomer **B** is formed exclusively, but diastereoselection is negligible (entries 2 and 5). Type III reaction conditions are neither regioselective nor diastereoselective (entries 3 and 6).

Taken together, these experiments strongly support the notion that, in the absence of phosphine (type I), the alkene is coordinated to Ni during the C–C bond-forming step and that, in the presence of phosphine (type II or III), the alkene is not coordinated to Ni during the C–C bond-forming step. In other words, the critical aspect of the type II and type III mechanisms is that the phosphine is bound to the Ni during the C–C bond-forming step. We reasoned that since the influence of the chiral center in the tether in these cases is minimal, any diastereoselectivity induced by a chiral phosphine could be attributed to the phosphine alone, a result that would be consistent with phosphine being bound to Ni as the C–C bond is formed.

Table 5. Coupling reactions of chiral, enantiomerically enriched 1,6-enynes[a] with ferrocenyl-containing phosphines



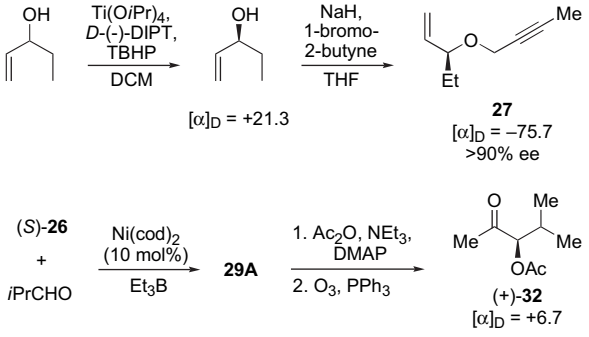
Ligand	**A**:**B**[b]	dr **29A** (*R*:*S*)[c]	dr **29B**[d]
(*R*)-**31**	48:52	30:70	28:72
(*S*)-**31**	55:45	66:34	68:32
$FcPPh_2$	54:46	56:44	48:52

[a] Enantiomerically enriched (>90% ee) **27** was used (Scheme 3).
[b] Based on isolated yields.
[c] Configuration of allylic alcohol stereogenic center.
[d] Relative stereochemistry not determined.

To this end, we subjected enyne **27** and isobutyraldehyde to reductive coupling conditions in the presence of an achiral or chiral ferrocenyl-containing phosphine (Table 5).[4c,15] Nearly equimolar amounts of regioisomers **A** and **B** were obtained in all cases, suggesting that the reaction occurs via a type III mechanistic pathway (cf. Scheme 2). Both the *R* and *S* phosphine ligands afforded modest diastereoinduction. These results demonstrate that the enyne stereocenter exerts little to no influence on the diastereoselectivity and clearly indicate that phosphine is bound to nickel during the C–C bond-forming step.

2.3. Origin of diastereoselectivity in the coupling of chiral 1,6-enynes

The high levels of diastereoselectivity afforded by enynes **27** and **28** in the absence of phosphine (Table 4, entries 1 and 4), prompted us to investigate coupling reactions of these chiral enynes further. In order to determine the sense of induction in the formation of regioisomer **A**, enantiomerically enriched enyne **27** was prepared (Scheme 3). 1-Penten-3-ol was resolved using a Sharpless asymmetric epoxidation,[16,17] and Williamson ether synthesis using the (*S*) enantiomer afforded enyne **27**.



Scheme 3.

Nickel-catalyzed reductive coupling of (*S*)-**27** and *i*-PrCHO in the absence of a phosphine (type I reaction conditions) afforded **29A** in >95:5 regioselectivity and 95:5 diastereoselectivity. Conversion to the corresponding acetate followed

by ozonolysis afforded ketone (+)-**32**. The sign of the specific rotation of this compound was opposite that of (−)-**32** prepared from commercially available (*S*)-2-hydroxy-3-methylbutyric acid,[18] thus establishing the allylic alcohol configuration in **29A** as *R*.

One possible explanation for the high diastereoselectivity was that the oxygen in the ethereal tether was binding to the aldehyde via the boron (Fig. 2), thus directing the aldehyde to the top face due to the conformation of the ring chelate.

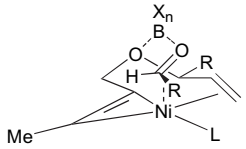
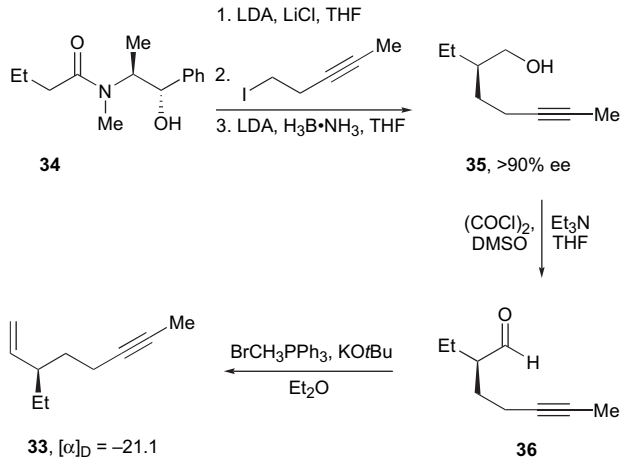


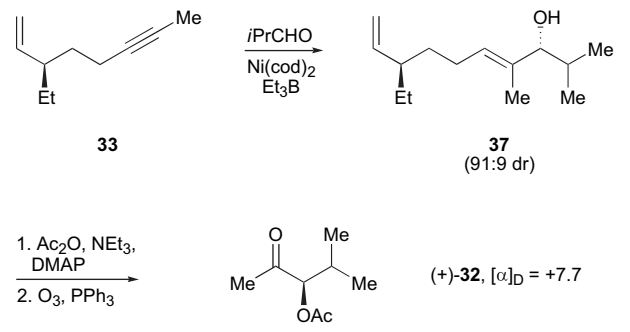
Figure 2.

To evaluate whether the oxygen atom of the tether plays a significant role in the reaction, we synthesized a 1,6-enyne (**33**) in which the oxygen was replaced with a methylene group, by way of a highly diastereoselective Myers alkylation, followed by Swern oxidation and Wittig olefination (Scheme 4)[19].



Scheme 4.

Under type I coupling conditions, enyne **33** gave results similar to those obtained with the enynes possessing an ethereal tether between the alkene and the alkyne. Nickel-catalyzed reductive coupling of **33** and *i*-PrCHO afforded allylic alcohol **37** in very high regioselectivity and in slightly reduced but nevertheless high diastereoselectivity (Scheme 5). The



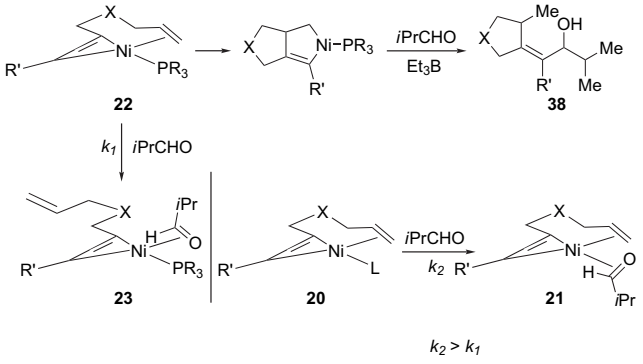
Scheme 5.

sense of induction, determined to be *R* using the same sequence of operations shown in Scheme 3, was also the same as that observed with enynes **27** and **28**. Thus, an oxygen atom and a CH_2 group at this position in the tether have similar (albeit measurably different) effects in type I coupling reactions.

The exact mode of diastereoinduction is unknown. However, since the size of the alkyl substituent of the chiral center has very little effect on the diastereoinduction (Table 4, entries 1 and 4), and since the oxygen of the ethereal tether does not appear to be involved, therefore, it is likely that the alkyl substituent controls the conformation of the ring chelate and it is the conformation of the ring chelate rather than the chiral center itself that interacts with the aldehyde and determines the stereochemical outcome of the reaction.

2.4. Carbocyclization

In the presence of a phosphine additive, **38** is observed as a minor product of nickel-catalyzed couplings of 1,6-enynes and aldehydes (Scheme 6).[2] This compound is thought to arise from complex **22** in a manner analogous to the nickel(0)-promoted enyne cyclizations previously reported by Tamao et al.[20] We propose that this side reaction is seen only in the presence of a phosphine additive because the formation of **23** (from **22**) will be slow relative to the formation of **21** (from **20**), since L is presumed to be more weakly bound than the tethered olefin.



Scheme 6.

3. Conclusion

In summary, alkene-directed, nickel-catalyzed reductive coupling of 1,6-enynes and aldehydes is a versatile tool for organic synthesis. The chelation-controlled, highly diastereoselective transformations possible in the absence of a phosphine additive have clear synthetic utility, while in the presence of a well-suited chiral phosphine, an enantioselective method for the production of regioisomer **B** might also be achieved.

Three distinct mechanistic pathways and their associated reaction conditions have been described, and our observations support the hypothesis that nickel-catalyzed reductive coupling reactions of alkynes and aldehydes proceed through an approximately planar, three-coordinate d^8 nickel complex. The mechanistic insight gained through this investigation should facilitate the development of other selective, nickel-catalyzed transformations.

4. Experimental

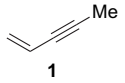
4.1. General methods

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of argon using standard Schlenk-line techniques. Bis(cyclooctadienyl)nickel(0) ($Ni(cod)_2$) and tricyclopentylphosphine ($PCyp_3$) were purchased from Strem Chemicals, Inc. and used without further purification. Triethylborane (Et_3B), triethylamine, methylsulfoxide, tributylphosphine (PBu_3), and penten-3-ol were purchased from Aldrich Chemical Co. and, unless otherwise stated, used as received. Isobutyraldehyde (Alfa Aeser) was distilled from anhydrous magnesium sulfate ($MgSO_4$) prior to use. (±)-4,4-Dimethyl-penten-3-ol was synthesized according to the literature procedure, and distilled prior to use.[21] Tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium/benzophenone ketyl, and dichloromethane (DCM) was freshly distilled from calcium hydride. Toluene was distilled from sodium metal, ethyl acetate was distilled from anhydrous magnesium sulfate, both toluene and ethyl acetate were sparged for 10 min with argon prior to use in coupling experiments.

4.2. Preparation of starting materials

The synthesis of 6-tridecyne, **2**–**5**, **9**, **11**, **13**, **15**, and **17** have been reported previously.[2]

4.2.1. 1-Decen-3-yne[22] (1).



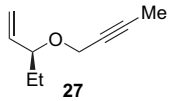
1

1-Octyne (2.21 mL, 15 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. Then *n*-BuLi (15 mmol, 6 mL of 2.5 M solution in hexanes) was added dropwise, and the mixture was stirred at 0 °C for 30 min. A solution of dry $ZnCl_2$ (2.04 g, 15 mmol) in THF (10 mL) was added via cannula and the mixture was allowed to warm to room temperature. In a 250 mL round-bottom flask, vinyl bromide (25 mmol, 25 mL of a 1 M solution in THF) and $Pd(PPh_3)_4$ (0.69 g, 0.6 mmol) were combined. The alkynyl zinc solution was transferred to the palladium solution via cannula. The bright yellow solution was stirred for 2 h, and then quenched with 1 M HCl (75 mL). The organics were extracted with pentanes (2×75 mL), washed with saturated NaCl, dried over $MgSO_4$, and filtered. Pentanes were removed via distillation, and the residue was then distilled under reduced pressure to provide **1** (0.95 g, 7.0 mmol, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddt, J=17.4, 10.8, 2.1 Hz, 1H); 5.54 (dd, J=17.4, 2.3 Hz, 1H); 5.37 (dd, J=10.8, 2.3 Hz, 1H); 2.29 (dt, J=10.2, 2.1 Hz, 2H); 1.48–1.57 (m, 2H); 1.25–1.44 (m, 6H); 0.89 (t, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.6, 117.9, 91.5, 76.5, 31.6, 28.9, 28.8, 22.8, 19.6, 14.3.

4.2.2. (+)-Penten-3-ol.

Synthesized according to a literature procedure.[23] Flame-dried molecular sieves 4 Å (ca. 5 g) were loaded into a 100 mL round-bottomed flask filled with DCM (25 mL). To this suspension was added diisopropyl D-tartrate (352 μL, 2.1 mmol) and racemic penten-3-ol (3 g, 34 mmol). The suspension was cooled to −5 °C and $Ti(OiPr)_4$ (414 μL, 1.4 mmol) was added. The reaction was stirred for 30 min, and then *t*-BuOOH (5.5 M in decanes, 6 mL, 33 mmol) was added. The reaction was warmed to 0 °C and stirred for 7 h. The slurry was added to a solution of iron(II) sulfate (11 g) and citric acid (3.5 g) in water (30 mL) and diluted with ether (80 mL). The layers were separated and the aqueous layer extracted once with diethyl ether. The combined organics were washed with brine, dried over magnesium sulfate, and filtered. Solvent was removed under atmospheric pressure via distillation through a Vigereux column (10 cm). Fractional distillation (20 Torr, 50 °C) of the residue then provided (+)-penten-3-ol as a clear oil (1 g, 33% yield). $[\alpha]_D^{22}$ +21.6 (*c* 0.37, $CHCl_3$). The optical rotation was compared to literature values,[17] and the stereocenter was determined to be (*S*).

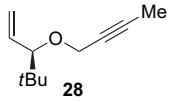
4.2.3. (−)-3-But-2-ynyloxy-pent-1-ene (27).



27

Sodium hydride (7.5 g, ~58%, ~180 mmol) was loaded into a round-bottom flask and rinsed with anhydrous pentanes (3×50 mL) and dried in vacuo. THF (200 mL) was added followed by addition of (+)-penten-3-ol (3.08 mL, 30 mmol), and the mixture was stirred for 3 h at room temperature prior to addition of 1-bromo-2-butyne (5.25 mL, 60 mmol). After stirring overnight, the reaction was quenched by careful addition of saturated aqueous ammonium chloride. The organics were extracted with diethyl ether (3×150 mL), washed with brine, dried over magnesium sulfate, filtered, and concentrated (0 °C, 50 Torr). The product (as a solution in THF) was loaded directly onto silica (7 cm×5 cm) and chromatographed (10:1 pentanes/diethyl ether). Removal of the solvent (0 °C, 50 Torr) followed by distillation through a short-path apparatus (35 °C, 1 Torr) yielded (−)-**27** as a clear oil (3.83 g, 92%, >90% ee). Compound (−)-**27**: $[\alpha]_D^{22}$ −75.7 (*c* 3.09, $CHCl_3$); chiral GC analysis (Varian CP-3800, G-TA column, 50 °C, 0.7 mL/min H_2 carrier) t_R (*S*) 14.4 min, t_R (*R*) 14.9 min; IR 2964 (m), 2924 (s), 2856 (m), 2248 (w), 1457 (b, w), 1057 (s), 910 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (ddd, J=17.0, 11.0, 8.5 Hz, 1H), 5.23 (dd, J=8.5, 2.0 Hz, 1H), 5.22 (dd, J=17.0, 2.0 Hz, 1H), 4.15 (dq, J_d=15.0 Hz, J_q=2.0 Hz, 1H), 3.97 (dq, J_d=15.0 Hz, J_q=2.0 Hz, 1H), 3.73 (q, J=7.0 Hz, 1H), 1.86 (t, J=2.0 Hz, 3H), 1.66 (apparent septet, J=7.0 Hz, 1H), 1.52 (apparent septet, J=7.0 Hz, 1H), 0.91 (t, J=7.5 Hz, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 138.3, 118.1, 81.9, 81.8, 75.8, 56.1, 28.3, 9.9, 3.9.

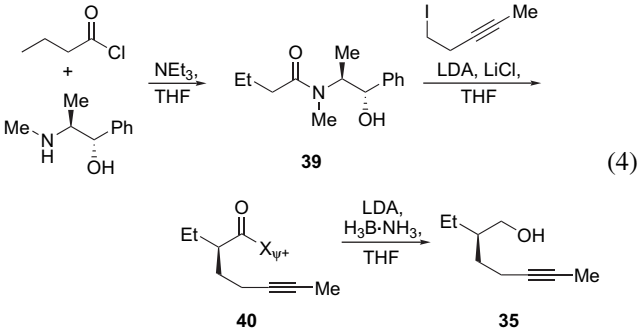
4.2.4. (±)-3-But-2-ynyloxy-4,4-pent-1-ene (28).



28

According to the procedure for **27**, (±)-4,4-dimethyl-penten-3-ol (1.71 g, 15 mmol) was reacted with 600 mol % NaH and 300 mol % 1-bromo-2-butyne to give 2 g (80%)

of a clear oil after chromatography (25:1 pentanes/diethyl ether) and distillation (65 °C, 1 Torr). Compound **28**: IR 2956 (s), 2870 (m), 2361 (w), 1464 (b, w), 1363 (m), 1136 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (ddd, J=17.0, 10.5, 8.5 Hz, 1H), 5.27 (dd, J=10.5, 1.5 Hz, 1H), 5.19 (dd, J=17.0, 1.5 Hz, 1H), 4.14 (dq, J_d=15.0 Hz, J_q=2.0 Hz, 1H), 3.92 (dq, J_d=15.0 Hz, J_q=2.0 Hz, 1H), 3.42 (d, J=8.5 Hz, 1H), 1.86 (t, J=2.0 Hz, 3H), 0.91 (s, 9H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 135.4, 119.2, 88.0, 81.5, 76.1, 56.4, 34.4, 26.3, 3.9; HRMS m/z (ESI, M+Na^+) calcd 189.1250 found 189.1256.



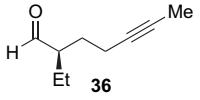
(4)

4.2.5. 2-Ethyl-hept-5-yn-1-ol (35). The synthesis of **35** was accomplished following the work of Myers and co-workers.[19] Butyryl chloride (3.1 mL, 30 mmol) was added dropwise to a chilled (0 °C) solution of (+)-(*S*, *S*)-pseudoephedrine (4.95 g, 30 mmol) and NEt_3 (5.4 mL, 39 mmol) in THF (10 mL). The reaction was stirred for 30 min and then quenched by the addition of water. The product mixture was partitioned between ethyl acetate and brine, the organic layer was separated, washed two times with brine, and then dried over sodium sulfate. The solvent was removed in vacuo and the crude solid recrystallized from toluene (20 mL) to give **39** as white crystals (5.15 g, 74%). NMR matched known values.[24]

n-Butyllithium (2.5 M in hexanes, 9.8 mL, 24.5 mmol) was added dropwise to a cold (−78 °C) slurry of *i*-Pr_2NH (3.7 mL, 26 mmol) and LiCl (flame dried under vacuum prior to use) (3.23 g, 77 mmol) in THF (17 mL). The suspension was warmed to 0 °C for 5 min then cooled to −78 °C. Compound **39** (2.96 g, 12.6 mmol) was added dropwise as a solution in cold (0 °C) THF (37 mL) and the reaction stirred at −78 °C for 1 h, 0 °C for 15 min and then room temperature for 5 min before being re-cooled to 0 °C. 5-Iodo-2-pentyne (1.16 g, 6.0 mmol), available in two steps from the corresponding alcohol,[25] was added in a single portion and the reaction was stirred at 0 °C for 2 h before being allowed to gradually warm to room temperature overnight. The reaction was quenched via the addition of saturated aqueous ammonium chloride and the product extracted with ethyl acetate. The combined organics were dried over sodium sulfate, filtered, concentrated, and then chromatographed (3:2 hexanes/ethyl acetate) to give **40** as a viscous pale yellow oil (1.34 g, 73%). The relative stereochemistry of **40** was assigned by analogy to Myers' work.[19]

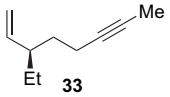
Compound **40** was reduced using LDA and $H_3B\cdot NH_3$ (LAB) prepared as follows: *n*-Butyllithium (2.5 M in hexanes, 5.3 mL, 13.2 mmol) was added dropwise to a cold (−78 °C) solution of *i*-Pr_2NH (2.0 mL, 13.9 mmol) in THF (14 mL). The solution was warmed to 0 °C and stirred for 10 min, then $H_3B\cdot NH_3$ (407 mg, 13.2 mmol) was added in a single portion. The reaction was stirred at 0 °C for an additional 15 min and then warmed to room temperature for 15 min. The reaction was re-cooled (0 °C) for the dropwise addition of **40** (1.0 g, 3.3 mmol) in THF (8.3 mL), and then warmed back up to room temperature until the reaction was determined to be complete by TLC (2 h). The system was cooled to 0 °C and 33 mL of 3 N HCl was added carefully. The slurry was stirred for 30 min at 0 °C, the product was extracted with ether, and the combined organics washed with 1 N HCl, 1 N NaOH, and brine. The crude product was dried over magnesium sulfate, filtered, concentrated, and chromatographed (5:2 hexanes/diethyl ether) to give **35** as a clear oil (267 mg, 81%). The enantiomeric excess was approximated by formation of the Mosher ester of this sample and of racemic material[26] and then comparing their respective ^1H NMR spectra. $[\alpha]_D^{22}$ −4.6, (*c* 3.37, $CHCl_3$); IR 3348 (b, m), 2961 (s), 2921 (s), 2876 (s), 2361 (m), 2341 (m), 1461 (m), 1380 (w), 1043 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.60 (m, 2H), 2.19 (m, 2H), 1.79 (t, J=2.5 Hz, 3H), 1.55 (m, 2H), 1.39 (m, 3H), 0.92 (t, J=7.5 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 79.5, 75.9, 64.9, 41.3, 30.1, 23.4, 16.6, 11.3, 3.7.

4.2.6. 2-Ethyl-hept-5-ynal (36).



DMSO (298 μL, 4.2 mmol) was added to oxalyl chloride (262 μL, 3 mmol) in cold (−78 °C) dichloromethane (20 mL), and the mixture was stirred for 10 min before **35** (280 mg, 2 mmol) was added. After stirring for an additional 20 min, NEt_3 (836 μL, 6 mmol) was added in a single portion, and the cold bath subsequently removed. The reaction was allowed to warm for 30 min before being quenched via the addition of water. The product was extracted with ether and the combined organics dried over magnesium sulfate. The solvent was removed under reduced pressure (80 Torr, 0 °C, rotary evaporator), and the crude mixture was flushed through a silica plug eluting with 10:1 pentanes/diethyl ether and then concentrated to give a clear oil (274 mg, 99%). IR 2964 (m), 2923 (m), 2361 (s), 2341 (s), 1726 (m), 1380 (b, m), 1261 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.64 (d, J=2.5 Hz, 1H), 2.39 (dtt, J_d=2.5, J_t=7.5, 5.5 Hz, 1H), 2.18 (m, 2H), 1.87 (m, 1H), 1.77 (t, J=2.5 Hz, 3H), 1.70 (m, 1H), 1.66–1.52 (m, 4H), 0.94 (t, J=7.5 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.2, 78.3, 76.9, 52.4, 27.7, 21.7, 16.8, 11.5, 3.6; HRMS m/z (ESI, M+Na^+) calcd 161.0937 found 161.0944.

4.2.7. 3-Ethyl-oct-1-en-6-yne (33).



Freshly dried methyltriphenylphosphonium bromide (1.02 g, 2.86 mmol) was added in one portion to a cooled (0 °C) suspension of KO*t*Bu (355 mg, 2.86 mmol) in ether (4 mL), resulting in the suspension turning bright yellow. The suspension was warmed to room temperature and stirred

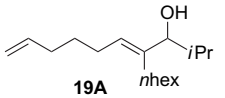
for 40 min, **36** (274 mg, 2 mmol) was added from a 10 mL pear-shaped flask, rinsing with ether (total volume 2 mL). Stirring was continued for 45 min at room temperature and then the reaction was quenched with water (200 μL). The suspension was stirred until all of the precipitate collected at the bottom of the flask (5 min) leaving a clear liquid phase. The flask was equipped with a short-path distillation apparatus and heated to 50 °C to remove most of the diethyl ether. The receiving flask was then cooled to −78 °C and the system was placed under vacuum resulting in the instantaneous transfer of all remaining liquid materials (a mixture of diethyl ether, *t*-BuOH, water, and **33**) to the cooled receiving flask. Sodium sulfate was added to the biphasic mixture and then the material was passed through a plug of silica eluting with pentanes. The solvent was removed (0 °C, 140 Torr) to give **33** as a clear oil (175 mg, 64%). $[\alpha]_D^{22}$ −21.1 (*c* 0.41, DCM); IR 3077 (w), 2964 (s), 2921 (s), 2875 (m), 2361 (w), 1640 (w), 1455 (m), 997 (m), 914 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (ddd, J=17.0, 10.0, 9.5 Hz, 1H), 5.00 (m, 2H), 2.16 (m, 1H), 2.06 (m, 1H), 1.98 (m, 1H), 1.79 (t, J=2.5 Hz, 3H), 1.60 (m, 1H), 1.40 (m, 2H), 1.26 (m, 1H), 0.86 (t, J=7.5 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 142.3, 115.3, 79.5, 75.5, 45.2, 34.1, 27.7, 16.8, 11.8, 3.7; HRMS *m/z* (EI, M^+) calcd 136.1248 found 136.1247.

4.3. Alkene-directed reductive coupling of alkynes and aldehydes

4.3.1. General procedure A. In a glove box, $Ni(cod)_2$ (14 mg, 0.05 mmol) was placed into an oven-dried, single-necked round-bottom flask, and the flask was then sealed with a rubber septum. The flask was removed from the glove box, placed under argon, and degassed ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et_3B (0.15 mL, 1.0 mmol). The reaction could also be run in the absence of any additional solvent with no detrimental effect. The resulting solution was then cooled to 0 °C, and isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe. After stirring for 5 min, the enyne (0.5 mmol) was added. The reaction was allowed to gradually warm to room temperature and stirred for 15 h. The septa was then removed and the reaction opened to air for 30 min to promote quenching of the catalyst. Reactions, which were run neat, were first diluted with 2 mL of reagent grade ethyl acetate prior to being opened to the air. The crude mixture was concentrated and purified by flash chromatography.

4.3.2. General procedure B (with phosphine additive). In a glove box, $Ni(cod)_2$ (14 mg, 0.05 mmol) and PR_3 (0.1 mmol) were placed into an oven-dried, single-necked round-bottom flask, and the flask was then sealed with a rubber septum. The flask was removed from the glove box, placed under argon, and degassed ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et_3B (0.15 mL, 1.0 mmol). The reaction could also be run in the absence of any additional solvent with no detrimental effect. The resulting solution was then cooled to 0 °C, and isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe. After stirring for 5 min, the enyne (0.5 mmol) was added. The reaction was allowed to gradually warm to room temperature and stirred for 15 h. The septa was then removed and the reaction opened to air for 30 min to promote quenching of the catalyst. Reactions, which were run neat, were first diluted with 2 mL of reagent grade ethyl acetate prior to being opened to the air. The crude mixture was concentrated and purified by flash chromatography.

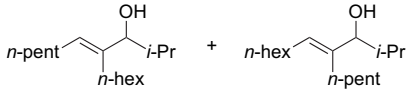
4.3.2.1. 4-Hexyl-2-methyl-deca-4,9-dien-3-ol (19A).



19A

Procedure A (no additive) (half-scale): Reaction of isobutyraldehyde (45 μL, 0.5 mmol) and **4** (45 mg, 0.25 mmol) in the presence of $Ni(cod)_2$ (7 mg, 0.025 mmol) and Et_3B (75 μL, 0.5 mmol) in EtOAc (0.25 mL) afforded an 85:15 mixture of the title compound and the corresponding alkylative coupling product (transfer of an ethyl group instead of a hydrogen from Et_3B) (34 mg, 53% yield (46% reductive), >95:5 regioselectivity). An analytically pure sample of **19A** was obtained via flash chromatography on silica gel impregnated with 5% silver nitrate. R_f=0.40 (10:1 hexanes/ethyl acetate). ^1H NMR (500 MHz, $CDCl_3$) δ 5.78–5.87 (m, 1H); 5.35 (t, J=7.5 Hz, 1H); 4.99–5.04 (m, 1H); 4.95–4.98 (m, 1H); 3.66 (d, J=7.5 Hz, 1H); 1.92–2.10 (m, 6H); 1.78 (oct., J=7 Hz, 1H); 1.44–1.51 (m, 2H); 1.24–1.43 (m, 8H); 0.96 (d, J=7 Hz, 3H); 0.89 (t, J=7 Hz, 3H); 0.84 (d, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 139.0, 127.4, 114.7, 82.9, 33.7, 31.9, 31.9, 31.8, 30.3, 30.2, 29.3, 28.2, 27.2, 22.9, 20.1, 18.3, 14.3. IR (thin film NaCl): 3623, 3428, 3078, 2956, 2929, 2871, 2859, 1823, 1641, 1468, 1379, 1365, 1295, 1246, 1169, 1130, 1116, 1007. HRMS (ESI) *m/z* 275.235 [(M+Na)$^+$; calcd for $C_{17}H_{32}O$: 275.235]. Regioselectivity confirmed by GC analysis (chiral B-PH, 125 °C, 2.5 mL/min): 21.30, 22.06 min.

4.3.2.2. 4-Hexyl-2-methyl-dec-4-en-3-ol (41A) and 2-methyl-4-pentyl-undec-4-en-3-ol (41B).



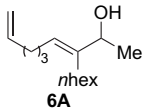
41A **41B**

Procedure A (no additive): Reaction of isobutyraldehyde and 6-tridecyne (90 mg, 0.5 mmol) afforded an 85:15 mixture of the title compounds and the corresponding alkylative coupling products (transfer of an ethyl group instead of a hydrogen from Et_3B) as a clear oil (36 mg, 28% yield (24% reductive), 51:49 mixture of regioisomers **41A** and **41B**).

Procedure B ($PCyp_3$): Reaction of isobutyraldehyde and 6-tridecyne (90 mg, 0.5 mmol) afforded a 51:49 mixture of regioisomers **41A** and **41B** as a clear oil (98 mg, 77% yield). R_f=0.39 (10:1 hexanes/ethyl acetate). ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (t, J=7 Hz, 1H); 3.65 (d, J=7.5 Hz, 1H); 1.92–2.07 (m, 4H); 1.78 (oct., J=7 Hz, 1H); 1.24–1.44 (m, 14H); 0.96 (d, J=6 Hz, 3H); 0.87–0.92 (m, 6H); 0.84 (d, J=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 128.0, 83.0, 83.0, 32.7, 32.0, 31.9, 31.8, 31.8, 30.3, 30.2, 30.0, 30.0, 29.7, 29.3, 28.2, 28.1, 27.8, 27.7, 22.9, 22.9, 22.8, 22.7, 20.1, 18.3, 14.3, 14.3, 14.3,

14.3. IR (thin film NaCl): 3624, 3423, 2957, 2927, 2872, 2859, 1713, 1661, 1467, 1379, 1366, 1297, 1244, 1169, 1105, 1008. HRMS (ESI) *m/z* 277.251 [(M+Na)$^+$; calcd for $C_{17}H_{34}O$: 277.250]. Regioselectivity determined by GC analysis (chiral B-PH, 110 °C, 2.0 mL/min): 51.08, 52.04 min.

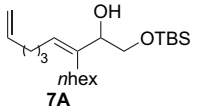
4.3.2.3. 3-Hexyl-nona-3,8-dien-2-ol (6A).



6A

Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of acetaldehyde (100 μL, 2 mmol) and **4** (89 mg, 0.5 mmol) afforded the title compound as a clear oil (77 mg, 69% yield, >95:5 regioselectivity). R_f=0.19 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78–5.86 (m, 1H); 5.41 (t, *J*=7 Hz, 1H); 4.99–5.05 (m, 1H); 4.94–4.98 (m, 1H); 4.23 (q, *J*=6.5 Hz, 1H); 1.95–2.12 (m, 6H); 1.46 (quin., *J*=7.5 Hz, 2H); 1.28–1.42 (m, 8H); 1.27 (d, *J*=6.5 Hz, 3H); 0.90 (t, *J*=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 139.0, 125.2, 114.7, 72.3, 33.6, 31.9, 30.1, 30.0, 29.2, 27.8, 27.1, 22.9, 22.6, 14.3. IR (thin film NaCl): 3349, 3078, 2957, 2928, 2858, 1641, 1458, 1415, 1378, 1366, 1283, 1116, 1062. HRMS (ESI) *m/z* 247.203 [(M+Na)$^+$; calcd for $C_{15}H_{28}O$: 247.203].

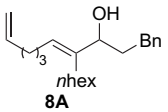
4.3.2.4. 1-(*tert*-Butyl-dimethyl-silanyloxy)-3-hexyl-nona-3,8-dien-2-ol (7A).



7A

Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of (*tert*-butyldimethylsilyloxy)acetaldehyde (190 μL, 1 mmol) and **4** (89 mg, 0.5 mmol) afforded the title compound as a clear oil (102 mg, 58% yield, >95:5 regioselectivity). R_f=0.42 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.86 (m, 1H); 5.48 (t, *J*=7 Hz, 1H); 5.10 (dd, *J*=17, 1 Hz, 1H); 4.96 (dt, *J*=10, 1 Hz, 1H); 4.08 (dd, *J*=8.5, 3 Hz, 1H); 3.64 (dd, *J*=10, 3 Hz, 1H); 3.42 (dd, *J*=10, 8.5 Hz, 1H); 2.03–2.12 (m, 5H); 1.87–1.94 (m, 1H); 1.47 (quin., *J*=7.5 Hz, 2H); 1.24–1.40 (m, 8H); 0.91 (s, 9H); 0.89 (t, *J*=7 Hz, 3H); 0.09 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 138.4, 127.2, 114.7, 75.7, 67.3, 33.7, 31.9, 29.9, 29.8, 29.2, 28.6, 27.2, 26.1, 22.9, 18.5, 14.3, −5.1, −5.1. IR (thin film NaCl): 3572, 3472, 3078, 2956, 2929, 2858, 1824, 1730, 1641, 1471, 1464, 1390, 1362, 1316, 1255, 1223, 1099, 1057, 1006, 992. HRMS (ESI) *m/z* 377.284 [(M+Na)$^+$; calcd for $C_{21}H_{42}O_2Si$: 377.285].

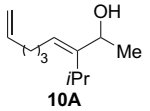
4.3.2.5. 4-Hexyl-1-phenyl-deca-4,9-dien-3-ol (8A).



8A

Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of 3-phenylpropionaldehyde (132 μL, 1 mmol) and **4** (89 mg, 0.5 mmol) afforded the title compound as a clear oil (95 mg, 60% yield, >95:5 regioselectivity). R_f=0.23 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.31 (m, 2H); 7.17–7.22 (m, 3H); 5.78–5.87 (m, 1H); 5.41 (t, *J*=7 Hz, 1H); 5.00–5.04 (m, 1H); 4.95–4.98 (m, 1H); 4.05 (t, *J*=6.5 Hz, 1H); 2.70–2.76 (m, 1H); 2.60–2.66 (m, 1H); 1.96–2.11 (m, 6H); 1.84–1.89 (m, 2H); 1.47 (quin., *J*=7.5 Hz, 2H); 1.24–1.42 (m, 8H); 0.89 (t, *J*=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 142.4, 138.9, 128.6, 128.6, 126.8, 126.0, 114.8, 76.3, 37.6, 33.6, 32.5, 31.9, 30.2, 30.1, 29.9, 27.8, 27.2, 22.9, 14.3. IR (thin film NaCl): 3360, 3077, 3064, 3027, 2954, 2928, 2858, 1940, 1821, 1727, 1641, 1604, 1496, 1455, 1415, 1378, 1301, 1154, 1048, 1031, 992. HRMS (ESI) *m/z* 337.250 [(M+Na)$^+$; calcd for $C_{22}H_{34}O$: 337.250].

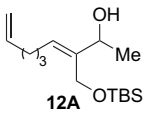
4.3.2.6. 3-Isopropyl-nona-3,8-dien-2-ol (10A).



10A

Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of acetaldehyde (100 μL, 1.8 mmol) and **9** (68 mg, 0.5 mmol) afforded the title compound as a clear oil (58 mg, 64% yield, >95:5 regioselectivity). R_f=0.20 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78–5.86 (m, 1H); 5.47 (t, *J*=7 Hz, 1H); 4.99–5.04 (m, 1H); 4.95–4.98 (m, 1H); 4.30 (q, *J*=6.5 Hz, 1H); 2.76 (septet, *J*=7 Hz, 1H); 2.05–2.13 (m, 4H); 1.47 (quin., *J*=7 Hz, 2H); 1.29 (d, *J*=6.5 Hz, 3H); 1.11 (d, *J*=7 Hz, 3H); 1.05 (d, *J*=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 139.0, 124.2, 114.7, 68.4, 33.6, 29.4, 28.2, 27.0, 24.2, 22.0, 21.7. IR (thin film NaCl): 3361, 3078, 2962, 2929, 2872, 1824, 1641, 1460, 1415, 1365, 1304, 1282, 1217, 1150, 1111, 1060. HRMS (ESI) *m/z* 205.156 [(M+Na)$^+$; calcd for $C_{12}H_{22}O$: 205.156].

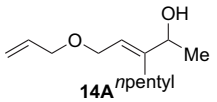
4.3.2.7. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-nona-3,8-dien-2-ol (12A).



12A

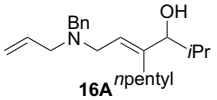
Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of acetaldehyde (100 μL, 1.8 mmol) and **11** (119 mg, 0.5 mmol) afforded the title compound as a clear oil (88 mg, 62% yield, >95:5 regioselectivity). R_f=0.40 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76–5.85 (m, 1H); 5.49 (t, *J*=7.5 Hz, 1H); 4.99–5.04 (m, 1H); 4.95–4.98 (m, 1H); 4.31–4.40 (m, 3H); 2.00–2.10 (m, 4H); 1.48 (quin., *J*=7.5 Hz, 2H); 1.34 (d, *J*=6 Hz, 3H); 0.92 (s, 9H); 0.12 (s, 3H); 0.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 138.7, 127.7, 114.9, 72.4, 60.2, 33.4, 28.9, 26.9, 26.1, 22.2, 18.4, −5.3. IR (thin film NaCl): 3421, 3078, 2956, 2929, 2886, 2858, 1668, 1641, 1472, 1463, 1442, 1406, 1390, 1362, 1255, 1072. HRMS (ESI) *m/z* 307.206 [(M+Na)$^+$; calcd for $C_{16}H_{32}O_2Si$: 307.206].

4.3.2.8. 5-Allyloxy-3-pentyl-pent-3-en-2-ol (14A).



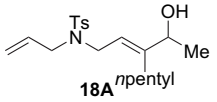
Procedure A (no additive) (modifications: toluene used in place of EtOAc as the reaction solvent, and slow addition of the enyne over 3 h via syringe pump): reductive coupling of acetaldehyde (100 μL, 1.8 mmol) and **13** (83 mg, 0.5 mmol) afforded the title compound as a clear oil (64 mg, 60% yield, >95:5 regioselectivity). R_f=0.17 (5:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90–5.97 (m, 1H); 5.64 (t, J=6.5 Hz, 1H); 5.27–5.32 (m, 1H); 5.19–5.22 (m, 1H); 4.27 (q, J=6.5 Hz, 1H); 4.05 (d, J=6.5 Hz, 2H); 3.99 (dt, J=6, 1.5 Hz, 2H); 2.09–2.16 (m, 1H); 1.98–2.04 (m, 1H); 1.20–1.42 (m, 11H); 0.90 (t, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 135.0, 121.2, 117.4, 71.6, 71.6, 66.5, 32.4, 30.0, 28.2, 22.7, 22.4, 14.2. IR (thin film NaCl): 3392, 2957, 2932, 2861, 1647, 1459, 1367, 1212, 1065. HRMS (ESI) m/z 235.166 [(M+Na)$^+$; calcd for $C_{13}H_{24}O_2$: 235.167].

4.3.2.9. 6-(Allyl-benzyl-amino)-2-methyl-4-pentyl-hex-4-en-3-ol (16A).



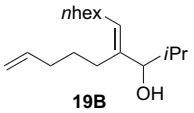
Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of isobutyraldehyde (90 μL, 1.0 mmol) and **15** (128 mg, 0.5 mmol) afforded the title compound as a clear oil (102 mg, 62% yield, >95:5 regioselectivity). R_f=0.22 (5:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.36 (m, 4H); 5.86–5.95 (m, 1H); 5.52 (t, J=6.5 Hz, 1H); 5.20 (dd, J=17.5, 2 Hz, 1H); 5.16 (d, J=10 Hz, 1H); 3.69 (d, J=7 Hz, 1H); 3.57 (s, 2H); 3.12 (d, J=7 Hz, 2H); 3.09 (d, J=6.5 Hz, 2H); 1.97–2.04 (m, 1H); 1.89–1.95 (m, 1H); 1.79 (octet, J=7 Hz, 1H); 1.22–1.38 (m, 6H); 0.95 (d, J=6.5 Hz, 3H); 0.88 (t, J=7 Hz, 3H); 0.86 (d, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 139.7, 136.2, 129.2, 128.4, 127.0, 124.7, 117.7, 82.4, 58.3, 57.1, 50.9, 32.6, 31.7, 29.9, 28.4, 22.7, 20.1, 18.1, 14.3. IR (thin film NaCl): 3423, 3065, 3028, 2956, 2930, 2870, 1643, 1495, 1455, 1366, 1255, 1118, 1073, 1012. HRMS (ESI) m/z 330.279 [(M+Na)$^+$; calcd for $C_{22}H_{35}NO$: 330.279].

4.3.2.10. *N*-allyl-*N*-[3-(1-hydroxyethyl)-oct-2-enyl]-benzenesulfonamide (18A).



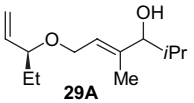
Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of acetaldehyde (200 μL, 3.6 mmol) and **17** (160 mg, 0.5 mmol) afforded the title compound as a clear oil (125 mg, 68% yield, >95:5 regioselectivity). R_f=0.29 (3:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J=8.5 Hz, 2H); 7.30 (d, J=8.5 Hz, 2H); 5.64–5.73 (m, 1H); 5.26 (t, J=7 Hz, 1H); 5.14–5.18 (m, 2H); 4.16 (q, J=6.5 Hz, 1H); 3.86 (d, J=6.5 Hz, 2H); 3.79–3.81 (m, 2H); 2.44 (s, 3H); 2.02–2.08 (m, 1H); 1.89–1.96 (m, 1H); 1.22–1.36 (m, 6H); 1.20 (d, J=6.5 Hz, 3H); 0.89 (t, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 143.4, 137.7, 133.4, 129.8, 127.4, 119.0, 118.9, 71.3, 49.9, 44.2, 32.4, 29.7, 28.0, 22.6, 22.4, 21.7, 14.2. IR (thin film NaCl): 3521, 2957, 2931, 2870, 1644, 1598, 1495, 1446, 1418, 1402, 1343, 1305, 1289, 1264, 1213, 1159, 1119, 1092, 1059. HRMS (ESI) m/z 388.192 [(M+Na)$^+$; calcd for $C_{20}H_{31}NO_3S$: 388.192].

4.3.2.11. 2-Methyl-4-pent-4-enyl-undec-4-en-3-ol (19B).



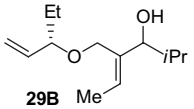
Procedure B (general for all phosphines listed in Table 3) (modification: aldehyde added over 3 h via syringe pump): Reaction of isobutyraldehyde and **4** (89 mg, 0.5 mmol) provided **19B** as a clear oil (57 mg, 45% yield). Following initial purification, flash chromatography on silica gel impregnated with 5% silver nitrate was required to remove minor impurities. R_f=0.40 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79–5.87 (m, 1H); 5.36 (t, J=7 Hz, 1H); 5.01–5.05 (m, 1H); 4.96–4.99 (m, 1H); 3.65 (d, J=7 Hz, 1H); 1.95–2.13 (m, 6H); 1.78 (oct., J=7 Hz, 1H); 1.46–1.56 (m, 2H); 1.24–1.40 (m, 8H); 0.96 (d, J=7 Hz, 3H); 0.89 (t, J=7 Hz, 3H); 0.83 (d, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 138.9, 128.4, 114.9, 83.0, 34.6, 32.0, 31.8, 30.0, 29.5, 29.3, 27.8, 27.5, 22.8, 20.08, 18.4, 14.3. IR (thin film NaCl): 3415, 3077, 2956, 2928, 2858, 1823, 1722, 1641, 1467, 1379, 1366, 1297, 1249, 1168, 1113, 1010. HRMS (ESI) m/z 275.235 [(M+Na)$^+$; calcd for $C_{17}H_{32}O$: 275.235]. Regioselectivity confirmed by GC analysis (chiral B-PH, 125 °C, 2.5 mL/min): 21.30, 22.06 min.

4.3.2.12. 6-(1-Ethyl-allyloxy)-2,4-dimethyl-hex-4-en-3-ol (29A).



Procedure A (no additive) (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of Ni(cod)$_2$ (14 mg, 0.05 mmol) and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether → 7:1 hexanes/ethyl acetate to give 59 mg (56%) of **29A** as a clear oil. R_f=0.30 (6:1 hexanes/EtOAc, $KMnO_4$) (single regioisomer, 95:5 mixture of *S*, *R* and *S*, *S*).

4.3.2.13. 4-(1-Ethyl-allyloxymethyl)-2-methyl-hex-4-en-3-ol (29B).



Procedure B ($PCyp_3$) (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of

$Ni(cod)_2$ (14 mg, 0.05 mmol), $PCyp_3$ (28 μL, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 25 mg (24%) of **29B** as a clear oil R_f=0.46 (6:1 hexanes/EtOAc, $KMnO_4$) (single regioisomer, 55:45 mixture of diastereomers).

Compounds **29A+29B**. Procedure B (PBu_3) (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol), PBu_3 (25 μL, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 19.3 mg (18%) of **29A** and 16 mg (15%) of **29B** as clear oils (**29A**: 50:50 mixture of diastereomers; **29B**: 55:45 mixture of diastereomers).

Compounds **29A+29B**. Procedure B ((*R*)-**31**)[27] (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol) (*R*)-**31** (41 mg, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 9 mg (8%) of **29A** and 10 mg (9%) of **29B** as clear oils (**29A**: 30:70 mixture of *S*, *R*:*S*, *S*; **29B**: 72:28 mixture of diastereomers).

Compounds **29A+29B**. Procedure B ((*S*)-**31**)[27] (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol) (*S*)-**31** (41 mg, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 10.6 mg (10%) of **29A** and 8.9 mg (9%) of **29B** as clear oils (**29A**: 66:34 mixture of *S*, *R*:*S*, *S*; **29B**: 32:68 mixture of diastereomers).

Compounds **29A+29B**. Procedure B ($FcPPh_2$) (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol), $FcPPh_2$ (37 mg, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 8.2 mg (7%) of **29A** and 7.2 mg (6%) of **29B** as clear oils (**29A**: 56:44 mixture of *S*, *R*:*S*, *S*; **29B**: 52:48 mixture of diastereomers).

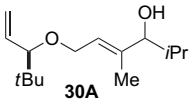
Compound **29A**: $[\alpha]_D^{22}$ −23.4 (*c* 0.86, $CHCl_3$); IR 3429 (b, m), 2962 (s), 2934 (s), 2872 (s), 1465 (m), 1094 (s), 1017 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)—data are for (*S*,*R*) diastereomer—δ 5.68 (ddd, *J*=17.0, 10.5, 8.0 Hz, 1H), 5.55 (t, *J*=6.0 Hz, 1H), 5.20 (dd, *J*=10.5, 1.0 Hz, 1H), 5.18 (dd, *J*=17.0, 1.0 Hz, 1H), 4.10 (dd, *J*=12.0, 6.5 Hz, 1H), 3.90 (dd, *J*=12.0 Hz, 6.5 Hz, 1H), 3.64 (dd, *J*=8.0, 3.0 Hz, 1H), 3.56 (q, *J*=6.5 Hz, 1H), 1.78 (apparent hex, *J*=6.5 Hz, 1H), 1.62 (m, 1H), 1.60 (s, 3H), 1.55 (OH) (br s, 1H), 1.49 (apparent sept, *J*=7.0 Hz, 1H), 0.98 (d, *J*=6.5 Hz, 3H), 0.90 (t, *J*=7.5 Hz, 3H), 0.81 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 140.3, 139.3, 124.5, 117.2, 83.6, 82.4, 64.5, 31.0, 28.5, 19.6, 18.5, 11.9, 10.0; HRMS *m*/*z* (ESI, M+Na^+) calcd 235.1669 found 235.1670.

The (*S*,*S*) diastereomer was not independently synthesized; however, those peaks, which were resolvable from the (*S*,*R*) diastereomer were ^1H NMR (500 MHz, $CDCl_3$) δ 4.06 (dd, *J*=12.0, 5.5 Hz, 1H), 3.94 (dd, *J*=12.0, 7.0 Hz, 1H).

Compound **29B**: IR 3454 (b, m), 2962 (s), 2934 (s), 2872 (s), 1669 (w), 1466 (m), 1319 (m), 1056 (s) cm^{-1}; the diastereomers were not separated, peaks belonging to a specific diastereomer are indicated by subscript A or B, those peaks labeled A were favored with achiral phosphines and (*R*)-**31**. ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (m, 1H), 5.64 (m, 1H), 5.24 (m, 2H), 4.30_A (d, *J*=11.0 Hz, 1H), 4.09_B (d, *J*=11.0 Hz, 1H), 4.04_B (d, *J*=11.0 Hz, 1H), 3.80_A (d, *J*=11.0 Hz, 1H), 3.58 (m, 2H), 2.86 (OH) (d, *J*=7.0 Hz, 1H), 1.80 (m, 1H), 1.69 (apparent t, *J*=7.0 Hz, 3H), 1.63 (M, 1H), 1.52 (m, 1H), 1.03_A (d, *J*=6.0 Hz, 3H), 1.03_B (d, *J*=6.0 Hz, 3H), 0.91_A (t, *J*=7.5 Hz, 3H), 0.89_B (t, *J*=7.5 Hz, 3H), 0.77_A (d, *J*=6.0 Hz, 3H), 0.75_B (d, *J*=6.0 Hz, 3H); no attempt was made to specify which carbon signals belonged to each diastereomer, there are exactly double the number of expected signals for a single compound. ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 138.7, 138.7, 127.2, 127.0, 118.0, 117.8, 84.3, 84.0, 83.6, 83.3, 64.5, 64.2, 32.6, 32.5, 28.6, 28.5, 19.8, 19.8, 19.3, 19.2, 13.4, 13.4, 10.1, 9.9; HRMS *m*/*z* (ESI, M+Na^+) calcd 235.1669 found 235.1672.

The relative stereochemistry of **30A** was assigned based on analogy to **29A**.

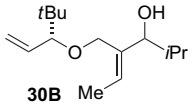
4.3.2.14. 6-(1-*tert*-Butyl-allyloxy)-2,4-dimethyl-hex-4-en-3-ol (30A).



30A

Procedure A (no additive) (no EtOAc): **28** (83 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol) and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→8:1 hexanes/ethyl acetate to give 33 mg (28%) of **30A** as a clear oil R_f=0.43 (6:1 hexanes/EtOAc, $KMnO_4$) (single regioisomer, >95:5 (±) *S*,*S*:*S*,*R*).

4.3.2.15. 4-(1-*tert*-Butyl-allyloxymethyl)-2-methyl-hex-4-en-3-ol (30B).



30B

Procedure B ($PCyp_3$) (no EtOAc): **28** (83 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol), $PCyp_3$ (28 μL, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 22 mg (18%) of **30B** as a clear oil R_f=0.55 (6:1 hexanes/EtOAc, $KMnO_4$) (single regioisomer, 42:58 mixture of diastereomers).

Compounds **30A+30B**. Procedure B (PBu_3) (no EtOAc): **28** (83 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL,

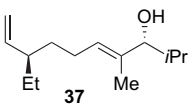
1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol), PBu_3 (25 μL, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 15.6 mg (13%) of **30A** and 14.8 mg (12%) of **30B** as clear oils (**30A**: 45:55 mixture of diastereomers; **30B**: 42:58 mixture of diastereomers).

Compound **30A**: IR 3411 (b, m), 2962 (s), 2956 (s), 2872 (s), 2870 (s), 2361 (w), 1465 (m), 1363 (s), 1016 (b, s), 925 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)—data are for (±)-(*R*,*R*) diastereomer—δ 5.72 (ddd, *J*=17.5, 10.0, 8.5 Hz, 1H), 5.52 (t, *J*=6.0 Hz, 1H), 5.25 (dd, *J*=10.0, 1.5 Hz, 1H), 5.14 (dd, *J*=17.5, 1.5 Hz, 1H), 4.08 (dd, *J*=12.5, 6.0 Hz, 1H), 3.86 (dd, *J*=12.5 Hz, 7.0 Hz, 1H), 3.64 (dd, *J*=8.5, 3.0 Hz, 1H), 3.21 (d, *J*=8.5 Hz, 1H), 1.78 (apparent hex, *J*=7.0 Hz, 1H), 1.60 (s, 3H), 1.54 (OH) (d, *J*=3.0 Hz, 1H), 0.99 (d, *J*=7.0 Hz, 3H), 0.88 (s, 9H), 0.82 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 140.3, 139.3, 124.5, 117.2, 83.6, 82.4, 64.5, 31.0, 28.5, 19.6, 18.5, 11.9, 10.0; HRMS *m*/*z* (ESI, M+Na^+) calcd 263.1982 found 263.1982.

The (±)-(*R*,*S*) diastereomer was not independently synthesized; however, those peaks that were resolvable from the (±)-(*R*,*R*) diastereomer were ^1H NMR (500 MHz, $CDCl_3$) δ 4.05 (dd, *J*=12.5, 5.5 Hz, 1H), 3.23 (d, *J*=8.5 Hz, 1H), 0.97 (d, *J*=6.5 Hz, 3H), 0.89 (s, 9H).

Compound **30B**: IR 3462 (b, m), 2956 (s), 2870 (s), 2361 (w), 1670 (b, w), 1465 (m), 1364 (m), 1068 (s) cm^{-1}; the diastereomers were not separated, peaks belonging to a specific diastereomer are indicated by subscript A or B, with achiral phosphines A was the major product. ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.61 (apparent q, *J*=6.5 Hz, 1H), 5.32_A (dd, *J*=10.5, 2.0 Hz, 1H), 5.31_B (dd, *J*=10.5, 2.0 Hz, 1H), 5.21 (d, *J*=17.5 Hz, 1H), 4.29_B (d, *J*=11.0 Hz, 1H), 4.08_A (d, *J*=11.0 Hz, 1H), 3.94_A (d, *J*=11.0 Hz, 1H), 3.74_B (d, *J*=11.0 Hz, 1H), 3.56 (q, *J*=7.0 Hz, 1H), 3.27_B (d, *J*=8.0 Hz, 1H), 3.23_A (d, *J*=8.0 Hz, 1H), 2.85_B (OH) (d, *J*=7.0 Hz, 1H), 2.82_A (OH) (d, *J*=7.0 Hz, 1H), 1.80 (m, 1H), 1.66 (m, 3H), 1.63 (M, 1H), 1.03 (apparent t, *J*=6.5 Hz, 3H), 0.90_B (s, 9H), 0.89_A (s, 9H), 0.76 (apparent t, *J*=6.0 Hz, 3H); no attempt was made to specify which carbon signals belonged to each diastereomer, there are exactly double the number of expected signals for a single compound. ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 137.3, 137.1, 135.9, 135.8, 126.8, 126.7, 119.5, 119.3, 90.6, 90.6, 84.4, 84.3, 65.0, 64.8, 34.6, 34.6, 32.5, 32.4, 26.4, 26.3, 19.9, 19.8, 19.3, 19.3, 13.4, 13.4; HRMS *m*/*z* (ESI, M+Na^+) calcd 263.1982 found 263.1986.

4.3.2.16. 8-Ethyl-2,4-dimethyl-deca-4,9-dien-3-ol (37).

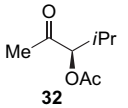


37

Procedure A (no additive) (no EtOAc): **33** (68 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol) and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→8:1 hexanes/ethyl acetate to give 82 mg (78%) of **37** as a single regioisomer and as a mixture of diastereomers (91:1 *R*, *R*, to *R*, *S*). R_f=0.48 (6:1 hexanes/EtOAc, $KMnO_4$) $[\alpha]_D^{22}$ −0.45 (*c* 0.84, DCM); IR 3391 (b, m), 2959 (s), 2922 (s), 2872 (s), 1640 (w), 1460 (m), 1121 (w), 1010 (s), 911 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)—data are for (*R*,*R*) diastereomer—δ 5.52 (ddd, *J*=17.0, 10.0, 9.0 Hz, 1H), 5.34 (t, *J*=7.0 Hz, 1H), 5.00 (dd, *J*=10.0, 2.0 Hz, 1H), 4.95 (dd, *J*=17.0, 2.0 Hz, 1H), 3.57 (dd, *J*=9.0, 3.0 Hz, 1H), 2.01 (m, 2H), 1.86 (m, 1H), 1.76 (m, 1H), 1.58 (s, 3H), 1.43 (m, 2H), 1.39 (OH) (d, *J*=3.0 Hz, 1H), 1.28 (m, 2H), 0.99 (d, *J*=7.0 Hz, 3H), 0.85 (t, *J*=7.0 Hz, 3H), 0.78 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 143.1, 136.5, 128.2, 114.8, 84.5, 45.7, 34.6, 31.3, 28.0, 25.4, 19.7, 18.9, 11.9, 11.4.

The (*R*,*S*) diastereomer was not independently synthesized; however, those peaks which were resolvable from the (*R*,*R*) diastereomer were ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 (ddd, *J*=17.0, 10.0, 9.0 Hz, 1H), 4.10 (dd, *J*=9.0, 3.0 Hz, 1H), 1.07 (d, *J*=6.0 Hz, 3H), 0.72 (d, *J*=6.0 Hz, 3H).

4.3.2.17. (+)-Acetic acid 1-isopropyl-2-oxo-propyl ester ((+)-32).



32

To a cold (0 °C) solution of (−)-**29A** (35 mg, 0.165 mmol) in DCM (1.5 ml) was added NEt_3 (71 μL, 0.51 mmol), Ac_2O (24 μL, 0.25 mmol), and DMAP (2 mg, 0.016 mmol). The mixture was warmed to room temperature and stirred for 1.5 h. At this point it was concentrated in vacuo and filtered through silica eluting with 10:1 hexanes/ethyl acetate. This afforded the crude acetate-protected product, which was carried on to the ozonolysis without purification. The intermediate was dissolved in DCM (3 mL) cooled to −78 °C and exposed to O_3 until the reaction was dark blue. The solution was then degassed with argon and PPh_3 (600 mg) was added. The reaction was allowed to warm to 0 °C over 4 h, and then concentrated in vacuo. The crude material was loaded onto a column (15:1 pentanes/DCM) with a minimal amount of DCM and then eluted with 15:1 pentanes/DCM until separation of PPh_3 and byproducts was complete, then column was flushed with 1:1 pentanes/diethyl ether to give (+)-**32** as a clear oil (15.1 mg, 58% over two steps). $[\alpha]_D^{22}$ +6.7 (*c* 1.01, DCM); ^1H NMR (500 MHz, $CDCl_3$) δ 4.87 (d, *J*=4.0 Hz, 1H), 2.24 (m, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 1.01 (d, *J*=7.0 Hz, 3H), 0.93 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.6, 171.0, 83.0, 29.6, 27.2, 20.8, 19.4, 17.0.

Compound (+)-**32**: Following the above procedure, **37** (42 mg, 0.2 mmol) was converted to (+)-**32** (20.5 mg, 66%) over two steps. $[\alpha]_D^{22}$ +7.7 (*c* 1.4, DCM).

Acknowledgements

This work was supported by the National Institute of General Medical Science (GM-063755). We thank Dr. Li Li (MIT Department of Chemistry Instrumentation Facility) for

obtaining mass spectrometry data. The MIT DCIF is supported in part by the NSF (CHE-9809061 and DBI-9729592) and the NIH (1S10RR13886-01).

References and notes

1. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
2. Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342.
3. Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890.
4. (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065; (b) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221; (c) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156; (d) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442; (e) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698; (f) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130.
5. Crystallographic evidence for a similar interaction in a Pt complex: Benyunes, S. A.; Brandt, L.; Fries, A.; Green, M.; Mahon, M. F.; Papworth, T. M. T. *J. Chem. Soc., Dalton Trans.* **1993**, 3785.
6. A preliminary account of this work has been reported: Moslin, R. M.; Miller, K. M.; Jamison, T. F. *Org. Lett.* **2006**, *8*, 455.
7. Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130.
8. Miller, K. M. Selective, Nickel-Catalyzed Carbon–Carbon Bond-Forming Reactions of Alkynes, Ph.D. Thesis, Massachusetts Institute of Technology: Cambridge, MA, June 2005.
9. Phosphine properties taken from: Tamaru, Y. *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH: Weinheim, 2005; pp 1–37 and references therein.
10. Otto, S.; Roodt, A.; Smith, J. *Inorg. Chim. Acta* **2000**, *303*, 295.
11. Ni-catalyzed sp^3–sp^3 cross coupling: (a) Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2723; (b) Krafft, M. E.; Sugiura, M.; Abboud, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 9174; (c) Nomura, N.; Tsurugi, K.; RaganBabu, T. V.; Kondo, T. *J. Am. Chem. Soc.* **2004**, *124*, 5354.
12. Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255.
13. In d^8, square-planar complexes ligand substitution generally occurs through an associative pathway with retention of stereochemistry. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, California, CA, 1987; pp 241–244.
14. Ethylene, 1,5-cyclooctadiene, or another equivalent of **8** or **9** are all possible.
15. Miller, K. M.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 3077.
16. Hill, M. L.; Raphael, R. A. *Tetrahedron* **1990**, *46*, 4487.
17. Kagan, H. B. *Stereochemistry*; George Thieme: Stuttgart, 1977; Vol. 4, p 224.
18. Bach, J.; Berenguer, R.; Farràs, J.; Garcia, J.; Meseguer, J.; Vilarrasa, J. *Tetrahedron: Asymmetry* **1995**, *6*, 2683.
19. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.
20. Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286.
21. Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1990**, *55*, 5058.
22. Negishi, E.-I.; Okukado, M.; Lovich, S. F.; Luo, F.-T. *J. Org. Chem.* **1984**, *49*, 2629.
23. Hill, M. L.; Raphael, R. A. *Tetrahedron* **1990**, *46*, 4487.
24. Meyers, M. J.; Sun, J.; Carlson, K. E.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **1999**, *42*, 2456.
25. Ansell, M. F.; Emmett, J. C.; Coombs, R. V. *J. Chem. Soc. C* **1968**, 217.
26. Racemic material was available using the chemistry of Hodgson and co-workers. Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *J. Am. Chem. Soc.* **2004**, *126*, 6870.
27. Miller, K. M.; Colby, E. A.; Woodin, K. S.; Jamison, T. F. *Adv. Synth. Catal.* **2005**, *347*, 1533.