ELSEVIER

Tetrahedron

Tetrahedron Vol. 60, No. 6, 2004

Tetrahedron Symposium-in-Print Number 102

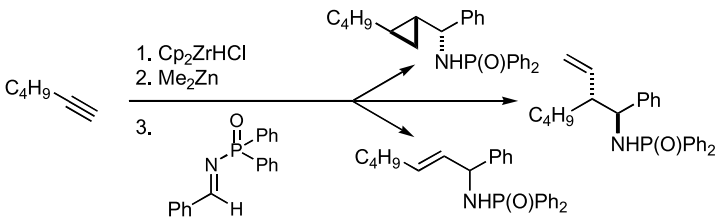
Recent advances in the chemistry of zirconocenes

Guest editors: Keisuke Suzuki[a] and Peter Wipf[b]

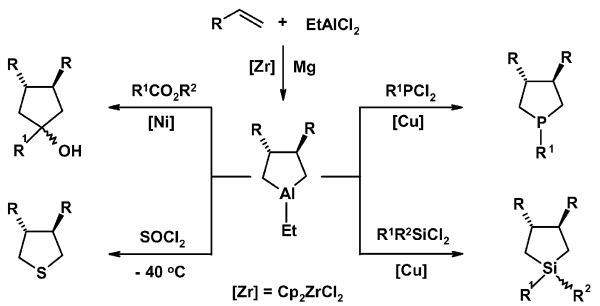
[a]*Department of Chemistry, Tokyo Institute of Technology, 2-12-1, O-okayama, Meguro-ku, Tokyo 152-8551, Japan*

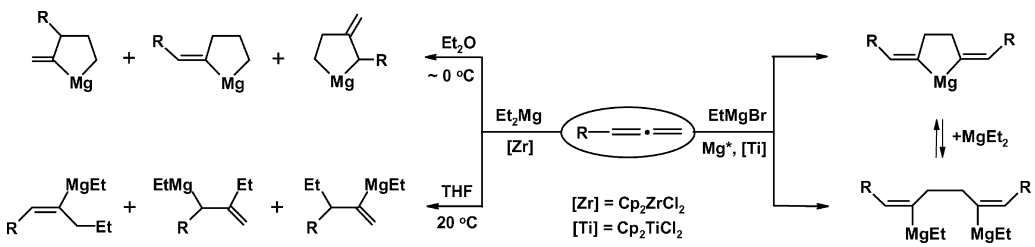
[b]*Department of Chemistry, University of Pittsburgh, Parkman Avenue and University Drive, Pittsburgh, PA 15260, USA*

Contents

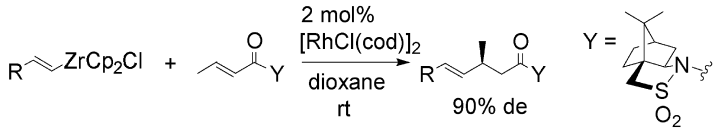


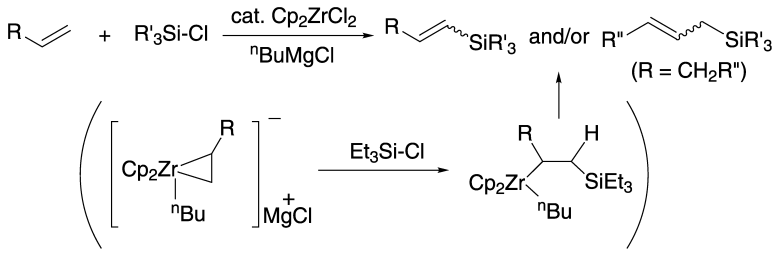
Recent progress in the preparation of alkenylzirconocenes, the transmetalation of zirconium to zinc, palladium, and rhodium, and lithium carbenoid insertions via the 1,2-metalate rearrangement are reviewed. In addition, the regioselective alkylzirconation of alkynes and Zr-promoted cyclizations of diynes are discussed.

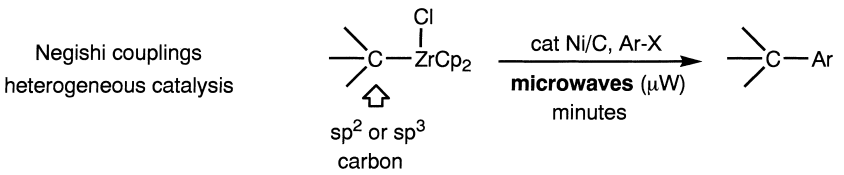


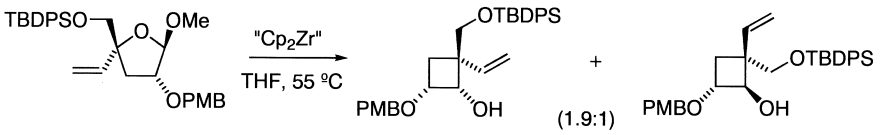


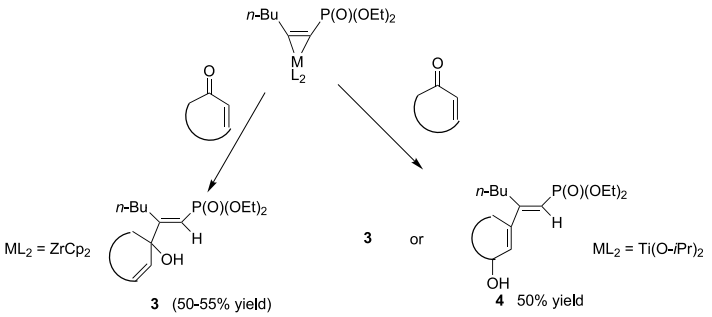
The reaction of $EtMgR'$ (R'=Et, Br) with 1,2-dienes in ethereal solutions catalyzed by Zr and Ti complexes was found to afford the products of cyclo- and (or) carbomagnesiation.

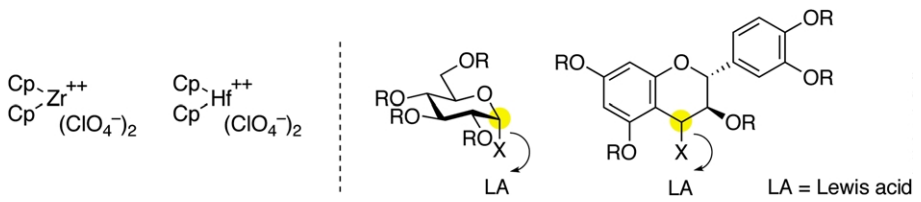


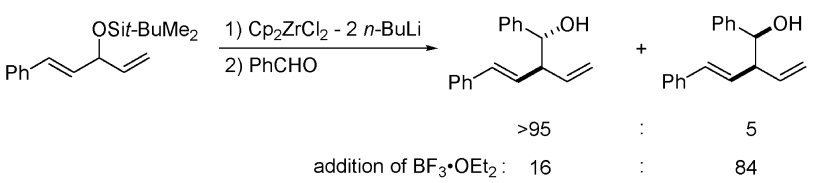


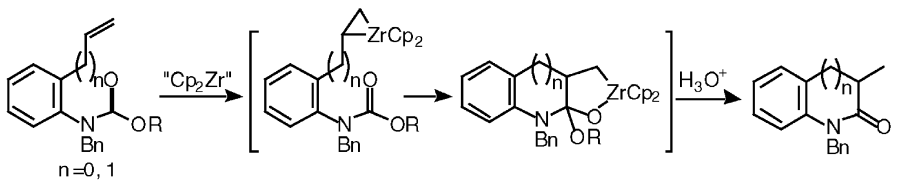


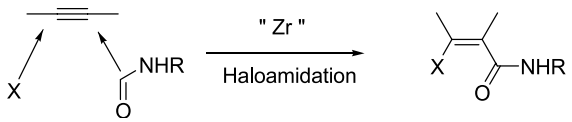


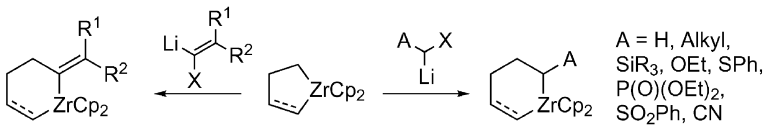


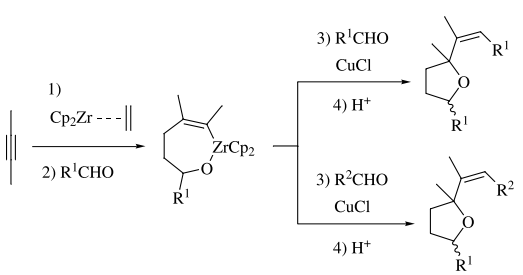












OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

A multifaceted zirconium collage provides a timely overview of the creativity and power of modern synthetic methodologies.

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

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.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 1267

Preface

Recent advances in the chemistry of zirconocenes

Over the past decade, interest in organozirconium chemistry has been rapidly increasing. In April 1995, *Tetrahedron* reported on recent advances in the use of zirconocenes and related compounds in a special Symposium-in-print, edited by Professor Ei-ichi Negishi. In view of the time passed since this volume, the exciting developments in this field as well as the upcoming 50 year anniversary of the synthesis of the first organozirconocene by G. Wilkinson, we felt that it was timely to update the readership on recent advances in the chemistry of zirconocene in celebration of the far-reaching impact and diversity of this field of organo-transition metal research.

The contributed papers in this Symposium-in-print highlight many of the varied aspects of the chemistry of zirconocene complexes, such as transmetalation reactions and catalyzed conjugate additions, carboaluminations in the presence of zirconocenes, cyclometalations, allylic eliminations and backbone rearrangements, aldehyde, imine and carbamate additions, cationic zirconocenes and glycosylations, microwave accelerated and late-transition metal catalyzed cross-coupling reactions, carbenoid insertions, haloamidation and isomerization reactions as well as multicomponent condensations. As components of a multifaceted zirconium collage, they provide an exciting overview of the creativity and power of modern synthetic methodologies.

We wish to express our sincere and deep appreciation to all authors and co-authors who contributed insightful papers on their most recent research findings. Reading their work was not only a pleasure for us, it will undoubtedly stimulate future developments and research collaborations. We also would like to thank the reviewers for their critical comments and Professor Harry Wasserman for the invitation to edit this special issue and for his helpful suggestions. We hope that all readers, newcomers to this field as well as the experts, will find this special issue of *Tetrahedron* rewarding and stimulating for their own research and development projects.

Keisuke Suzuki
Department of Chemistry, Tokyo Institute of Technology, 2-12-1, O-okayama, Meguro-ku, Tokyo 152-8551, Japan
Tel.: +3-5734-2228
Fax: +3-5734-2788
E-mail address: ksuzuki@chem.titech.ac.jp

Peter Wipf
Department of Chemistry, University of Pittsburgh, Parkman Avenue and University Drive, Pittsburgh, PA 15260, USA
Tel.: +1-412-624-8606
Fax: +1-412-624-0787
E-mail address: pwipf@pitt.edu

doi:10.1016/j.tet.2003.12.017

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 1269–1279

Tetrahedron report number 668

Selective carbon–carbon bond formations with alkenylzirconocenes

Peter Wipf[a,*] and Ruth L. Nunes[b]

[a]*Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA*
[b]*Departamento de Química Fundamental, Universidade Federal de Pernambuco, 50.740-540 Recife PE, Brazil*

Received 10 November 2003

Contents

1. Introduction

The efficient assembly of complex molecules requires methods that link functionalized segments by selective carbon–carbon bond formations. In this context, the chemistry of organozirconocenes has made great advances since the preparation of the first zirconocene, Cp_2ZrBr_2 in 1953.[1–3] This Report summarizes recent developments of the use of alkenylzirconocene complexes in organic synthesis in an attempt to highlight the continued potential for new reaction discovery that transmetalation reactions hold.

2. Preparation of alkenylzirconocenes

The major, but not sole, access to alkenylzirconocene intermediates is through the hydrozirconation of alkynes with the Schwartz reagent, $Cp_2Zr(H)Cl$.[4a] Kinetically and thermodynamically favored *syn*-addition of this complex onto a terminal or internal alkyne followed by in situ treatment with electrophilic reagents affords di- or trisubstituted *trans*-alkenes in high stereochemical purity.[4b] For unsymmetrical internal alkynes, the process can lead to mixtures with preference of the isomer derived from a geminal juxtaposition of Zr-species and the sterically less demanding substituent.[4c] Excess of $Cp_2Zr(H)Cl$ and moderate heating are known to isomerize the intermediate adducts and improve the regioselectivity in most cases.[4d] In general, the functional group compatibility of the process is limited by the oxophilic, hard Lewis acid character of the Schwartz reagent. Epoxides, isonitriles, aldehydes, ketones, nitriles, amides, enones, and reactive esters can be reduced competitively with the alkyne moiety and should be avoided. Among the tolerated functional groups are silyl, *t*-butyl or even benzyl esters and ethers, carbamates, sulfonamides, and most simple ethers as well as alkenes if 1 equiv. or less of $Cp_2Zr(H)Cl$ is utilized.[5]

An alternative, rapidly evolving access to alkenylzirconocene complexes is offered by the formal insertion of $Cp_2Zr(II)$ into sp^2 carbon–halogen as well as carbon–sulfur bonds;[6] the functional group tolerance and synthetic scope in C,C-bond formations of this process remains to be fully elucidated.

3. Zirconium→Zn transmetalations

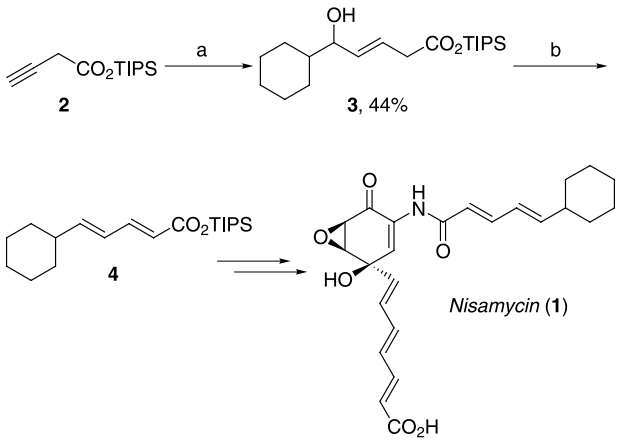
The use of $ZnCl_2$ for acceleration of Pd- and Ni-catalyzed cross-coupling of alkenyl aluminum and zirconium compounds with alkenyl, aryl or alkynyl halides was first

Keywords: Alkenylzirconocenes; Transmetalation; Organic synthesis.
* Corresponding author. Fax: +1-412-6240787;
e-mail address: pwipf@pitt.edu

0040–4020/$ - see front matter
doi:10.1016/j.tet.2003.12.018

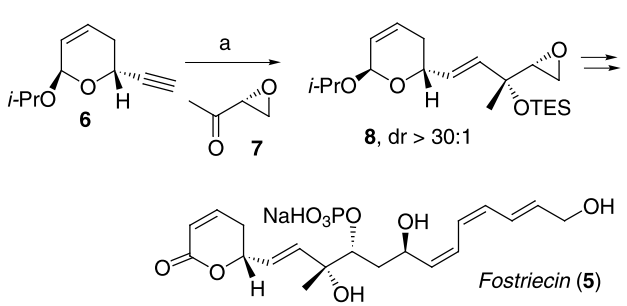
reported by Negishi et al. (vide infra).[7] Wipf and Xu[8] observed that the transmetalation of alkenylzirconocene to the corresponding organozinc compounds occurred rapidly and at low temperatures in the presence of dimethyl- or diethylzinc. Subsequent addition of aldehydes to the reaction mixture afforded allylic alcohols in high yields. In the presence of chiral amino alcohol or amino thiol catalysts, high enantioselectivities were obtained.[8,9]

The high diastereo- and enantioselectivity of the C,C-bond formation contributes greatly to the synthetic versatility of the Zr→Zn transmetalation process.[10] Several natural product total syntheses have used this methodology as a key step in the construction of allylic alcohol moieties, and it has also been applied to the preparation of polyene segments in (+)-curacin A and in the manumycin family.[11,12] Wipf and Coish reported the synthesis of (±)-nisamycin **1**[11c] from alkyne **2**, which was hydrozirconated, transmetalated to the corresponding alkenylzinc intermediate and added to aldehyde, affording **3** in 44% yield (Scheme 1). The newly formed allylic alcohol **3** was subsequently dehydrated to produce the (*E*)-diene **4**.



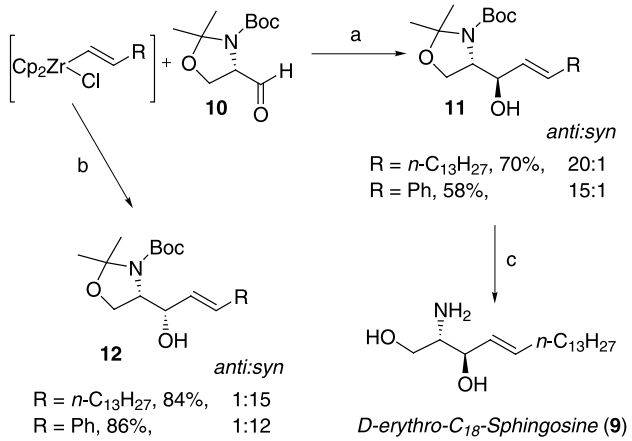
Scheme 1. Dehydration of the allylic alcohol moiety for the construction of the (*E*)-diene side chain of nisamycin: (a) Cp_2ZrHCl, Me_2Zn, *c*-$C_6H_{11}CHO$; (b) (i) CF_3CO-imidazole, THF, pyr., −10 to 10 °C, 1 h; (ii) *i*-Pr_2NEt, rt, 5 h.

An interesting diastereoselective version of the Zr→Zn transmetalation was reported by Jacobsen and Chavez in the synthesis of fostriecin **5** (Scheme 2).[13] After hydrozirconation of alkyne **6**, the alkenylzinc intermediate added diastereoselectively in a 1,2-fashion to the chiral epoxyketone **7**. Protection of the tertiary alcohol provided **8** in 45% yield and >30:1 diastereoselectivity.



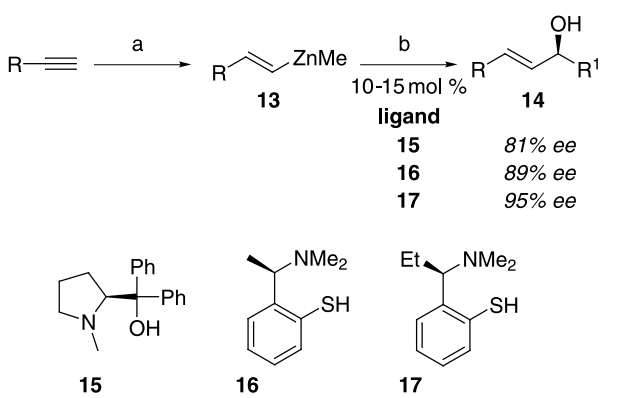
Scheme 2. Diastereoselective 1,2-addition to a chiral epoxyketone: (a) (i) Cp_2ZrHCl, CH_2Cl_2; (ii) Me_2Zn; (iii) **7**; (iv) TES–Cl, imidazole, DMF.

An efficient stereodivergent synthesis of D-*erythro*-C_{18}-sphingosine **9** has been reported by Murakami and Furusawa, who explored the enantioselective addition of alkenylzirconocenes to the L-serine-derived chiral aldehyde **10**.[14] Additives such as Ag[15] and Zn salts were used as catalysts, and the combination of Wipf's[8] and Srebnik's[16] Zr→Zn transmetalation conditions was found to allow a tuning of *anti*/*syn*-selectivity. In fact, the *anti*-selective formation of product **11** in THF at room temperature was due to the presence of catalytic zinc dibromide.[16] Mild acidic hydrolysis afforded the sphingosine **9**. The use of an equimolar amount of Et_2Zn in CH_2Cl_2,[8] at a temperature range from −30 to 0 °C, led to the formation of the *syn*-addition products **12** (Scheme 3).



Scheme 3. Reaction conditions determine the diastereoselectivity in the synthesis of D-*erythro*-C_{18}-sphingosine: (a) $ZnBr_2$, (25–50 mol%), THF, rt; (b) **10**, Et_2Zn, CH_2Cl_2, −30–0 °C; (c) aq. AcOH, 50 °C.

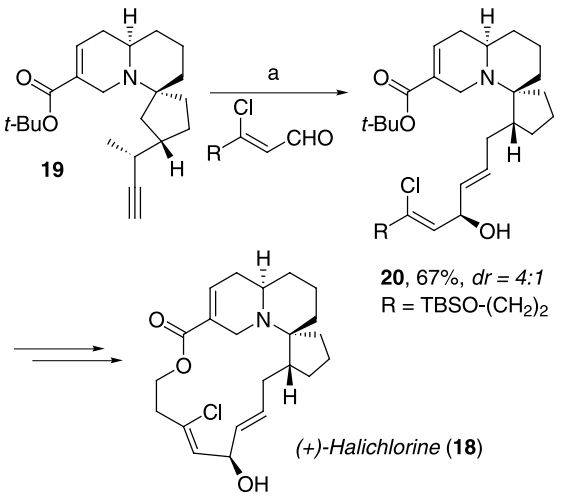
Despite its versatility, the enantioselective protocol for the Zr→Zn transmetalation–aldehyde addition is still being refined. In their first report on this subject, Wipf and Xu did not obtain a satisfactory enantiomeric excess of allylic alcohols when 8 mol% of ligand **15** were used (Scheme 4).[8] The main reason for the low ee of 38% was attributed to the presence of stoichiometric zirconocene complex catalyzing the formation of racemic product. The competitive aldehyde



Scheme 4. Chiral ligand effects in the catalytic asymmetric addition to aldehydes: (a) (i) Cp_2ZrHCl, CH_2Cl_2, 22 °C; (ii) Me_2Zn, −78 °C, toluene; (b) R^1CHO, −30 °C.

addition kinetics are a result of the presence of two Lewis-acidic metals in the Zr→Zn transmetalation mixture. In subsequent work, Wipf and co-workers achieved significant ee improvements by the use of larger amounts of ligand **15** and lower reaction temperatures.[9,17] In addition, amino thiols proved to be superior ligands, most likely due to the higher thiophilicity of zinc versus zirconium (Scheme 4).[9] Treatment of organozinc **13** with 10 mol% of ligand **16** followed by warming from −78 to −30 °C afforded allylic alcohol **14** in 89% ee. Moreover, amino thiol **17** afforded addition product **14** in 95% ee.

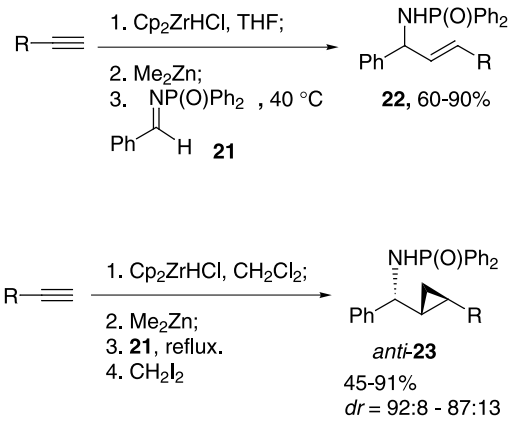
The enantioselective procedure using 10 mol% of ligand **15** was applied by Danishefsky et al. at a late stage of the total synthesis of (+)-halichlorine (**18**, Scheme 5),[18] when the advanced intermediate **19** proved to be too sensitive for classical Horner–Wadsworth–Emmons chain extension conditions.



Scheme 5. Asymmetric Zr→Zn chemistry in a key step of the total synthesis of halichlorine: (a) (i) Cp_2ZrHCl, CH_2Cl_2; (ii) Me_2Zn, heptane; (iii) 10 mol% of ligand **15**, −30 °C.

Aldimines are less reactive towards nucleophiles than carbonyl compounds due to their diminished double bond polarization and softer Lewis basicity at the nitrogen atom. However, with proper activation, organometallic reagents can readily be added in a 1,2-fashion. Stimulated by the results obtained in the use of Zr→Zn transmetalation conditions for allylic alcohol formation,[17] Wipf et al. investigated the corresponding addition to aldimines.[19] After hydrozirconation of 1-hexyne in CH_2Cl_2, (R=C_4H_9, Scheme 6), in situ transmetalation with Me_2Zn and addition to *N*-diphenylphosphinoylimine **21** produced the expected allylic amine **22**, but also revealed an efficient three-component condensation that furnished the *anti*-*C*-cyclopropylalkylamine **23** in 58% yield, after heating for 16 h. A switch of the reaction solvent from CH_2Cl_2 to THF afforded the corresponding allylic amide **22** as the sole product.

Further reaction optimization revealed the scope and provided support for a reaction mechanism in these solvent-dependent conversions.[2k,20] The production of **22** was improved when THF was substituted with toluene at room temperature. Functional group tolerance at the alkyne

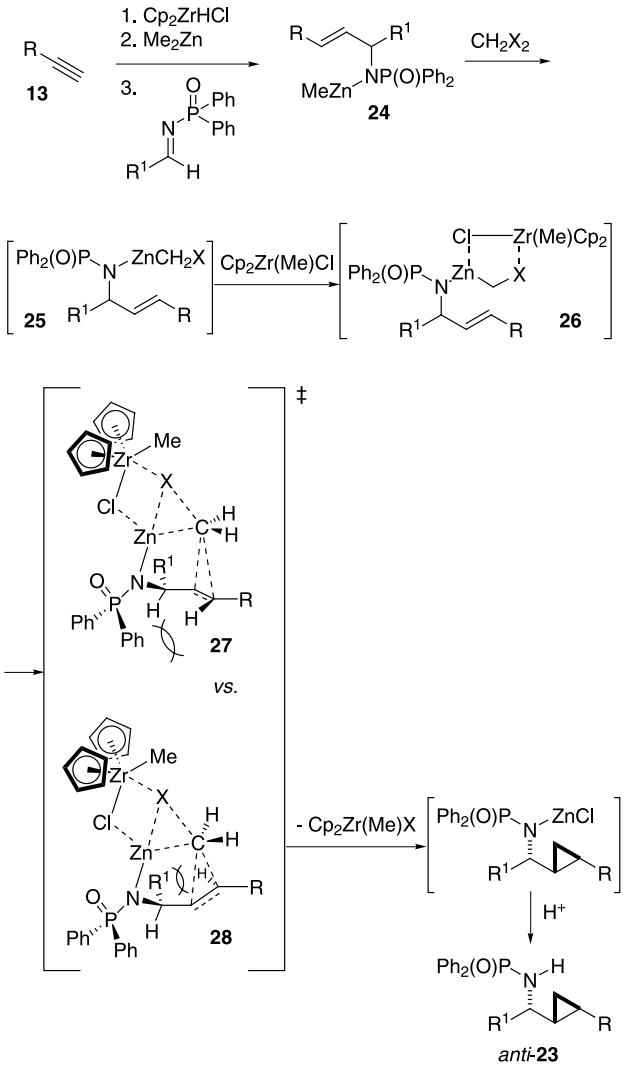


Scheme 6. New solvent-dependent routes for allylic amine and cyclopropylalkylamine preparation.

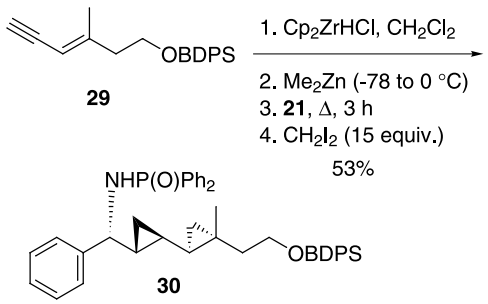
moiety included silyl ethers and silyl esters, sulfonamides and carbamates. Electron-donating aryl substituents on the imine, though, significantly reduced the amount of the isolated amide. Sterically very hindered alkynes proved to be unreactive towards addition, although internal alkynes such as 3-hexyne worked well. It is also noteworthy that *N*-tosylalkylimines and *N*-tosylbenzaldimines were converted to the allylic sulfonamides.

The scope for the cyclopropanation pathway is nearly the same as for the allylic amine formation, except that both electron-donating and electron-deficient substrates worked well and that the presence of bulky substituents on the imine aryl group reduced the diastereoselectivity. The three-component condensation represents the first example of a preparative cyclopropanation reaction in which CH_2Cl_2 serves as the carbene source; the activation of C–Cl bonds poses a considerable kinetic and thermodynamic barrier that is apparently overcome by the concerted action of alkyl zinc and zirconocene species. As expected, addition of CH_2Br_2 and CH_2I_2 further accelerated the cyclopropanation process, and in the general protocol the conversion was completed by adding upto 5 equiv. of CH_2I_2 at room temperature subsequent to the addition of **21** (Scheme 6).

The proposed mechanism for this reaction was based on experimental observations such as the formation of the metalated aldimine addition product as a precursor to the cyclopropane (Scheme 7). In general, *syn*-diastereomers are formed by directed Simmons–Smith-type cyclopropanations of allylic alcohols;[21] in contrast, the *anti*-selectivity confirmed by X-ray structure analysis of *C*-cyclopropylalkylamines **23** was remarkable, and the presence of zirconocene complex proved to be crucial for an efficient cyclopropanation and high *anti*-diastereomeric ratios. It was proposed that the zinc species in the N-metalated allylic amide intermediate **24**, derived from the addition of the Zr→Zn transmetalation intermediate **13** to the aldimine, inserted into a dihalomethane carbon–halogen bond to provide intermediate **25**, a process that is most likely favorably assisted by the nitrogen ligand on the zinc, the zirconocene complex or both.[21b,22a] Subsequently, the $Cp_2Zr(Me)Cl$ complex, originating from the transmetalation step, could act as a Lewis acid activator for zinc

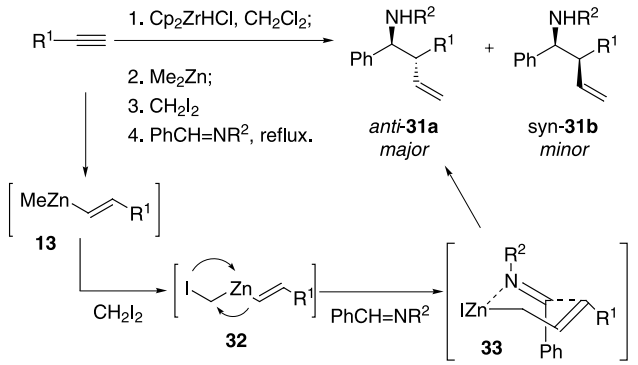


Scheme 7. Mechanistic hypothesis for *C*-cyclopropylalkylamine formation in the Zr→Zn transmetalation–imine addition.



Scheme 8. One-pot conversion of enynes to dicyclopropylalkylamines.

In yet another variant of the three-component coupling of aldimines, diiodomethane and alkenylzirconocenes, Wipf and Kendall observed that the sequence of addition of reactants strongly influences product formation.[23a] When CH_2I_2 was added prior to the imine, the homoallylic amine **31** was obtained in good yield favoring the *anti*-isomer **31a** (Scheme 9).



Scheme 9. Homoallylic amines **31** formed via a 1,2-shift of the organozinc intermediate.

carbenoid formation through complexation of the halomethyl zinc halogen, as represented in complex **26**. *syn*- and *anti*-Product formation can be derived from the two possible transition states **27** and **28**, respectively. The former minimizes 1,3-allylic strain, but suffers from a large steric interaction between the bulky *N*-diphenylphosphinoyl group and the alkene moiety. In contrast, the favored transition state **28** mimimizes diphenylphosphinoyl–alkene interactions, while at the same time suffering from 1,3-allylic strain. The relative configuration of the major product, *anti*-**23**, is in agreement with the trends observed for the cyclopropanation of allylic ethers.

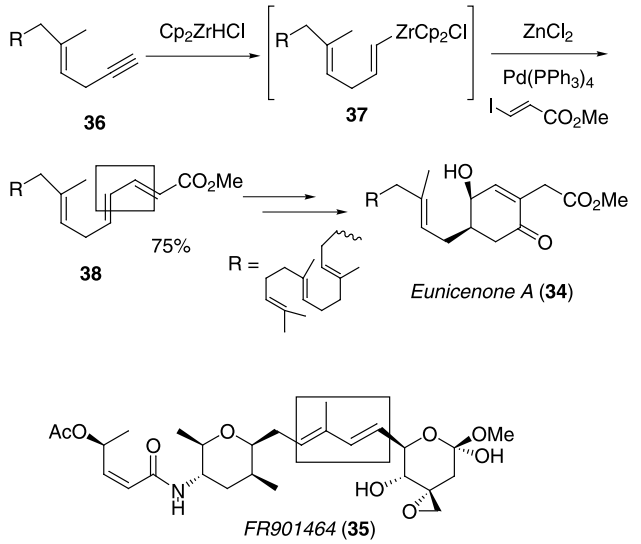
An important extension of this new methodology was accomplished by the conversion of enyne **29** to dicyclopropane **30** (Scheme 8).[20] A single diastereomer was observed and five new C,C-bonds were formed in this cascade reaction. Multistep pathways are traditionally required to accomplish the formation of products of this type. The structure assignment was again based on an X-ray analysis of a desilylated derivative of **30**.

The proposed mechanism was rationalized in terms of a [1,2]-shift in **32**, which is derived from the reaction of **13** with CH_2I_2. 'Homologation' of a metal carbenoid into an alkenyl–metal bond is a known but still mostly unexplored process.[24] The resulting allylic zinc species adds to the aldimine in the chair-like transition state **33** which explains the *anti*-configuration preference. This mechanism is in agreement with the experimental observation that internal alkynes or bulky imine substituents erode the *anti*-selectivity, probably due to steric interactions between the pseudoaxial substituents.

Although many synthetic and mechanistic aspects of the Zr→Zn transmetalation chemistry still need to be further elucidated, the formation of multiple reaction products with different carbon connectivities and cyclopropane rings depending on rather subtle aspects of solvent composition and order of addition is intriguing. As a recent communication on the formation of bicyclo[1.1.0]butanes and *C*,*C*-dicyclopropylmethylamines demonstrates,[23b] the potential of this methodology to serve as a novel, direct route to structurally diverse compounds is far from being exhausted.

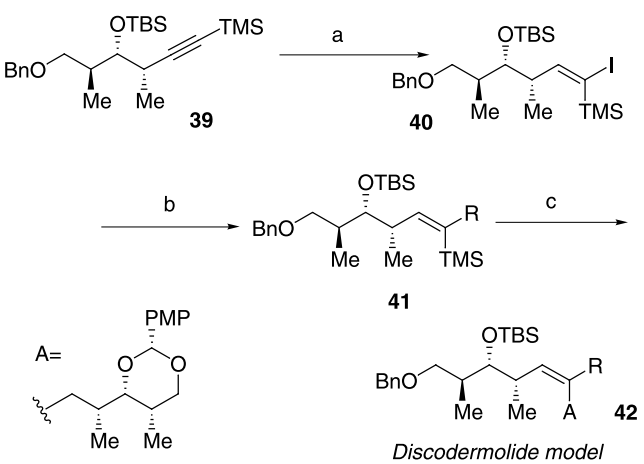
4. The zirconium→Zn→Pd transmetalation sequence

The use of $ZnCl_2$ as a 'shuttle' to facilitate the palladium-catalyzed cross-couplings of organozirconocenes for C,C-bond formations has been further explored lately and has now become a versatile tool in synthesis.[7,25] The versatility of this process was demonstrated by the syntheses of complex molecules such as eunicenone A **34**,[26] pitiamide A[27] and 'FR901464' **35**[28] (Scheme 10).



Scheme 10. Use of $ZnCl_2$ to facilitate cross-couplings of organozirconcenes.

As an example of this sequence, hydrozirconation of alkyne **36** provided the alkenylzirconocene **37** which, however, was unreactive toward direct Zr→Pd exchange reactions. Transmetalation to the less sterically demanding zinc species solved this problem and accelerated the palladium heterocoupling with organohalides. Coupling product **38** was obtained in 75% yield after treatment of **37** with stoichiometric amounts of $ZnCl_2$ in the presence of the vinyl iodide and catalytic $Pd(PPh_3)_4$.



Scheme 11. Synthesis of a discodermolide model: (a) (i) Cp_2ZrHCl, THF, 55 °C; (ii) I_2, THF; (b) RZnCl, $Pd(PPh_3)_4$, THF; (c) (i) I_2, CH_2Cl_2; (ii) *t*-BuLi, $ZnCl_2$, $Pd(PPh_3)_4$, A–I.

Panek et al. preferred to use a Zr→Zn→Pd transmetalation sequence via an intermediate vinyl iodide[2f,3f] in the development of a flexible route to discodermolide and callystatin A (Scheme 11).[29a] Hydrozirconation of the silyl acetylene **39**,[30] followed by iodination, produced **40** in 88% yield. Subsequent palladium cross-coupling with Grignard-derived zinc chlorides produced **41**. Iododesilylation and a second cross-coupling afforded trisubstituted olefin **42**. The same strategy was also applied to the synthesis of the side chain amino acid in microcystin[25] and (−)-motuporin.[29b]

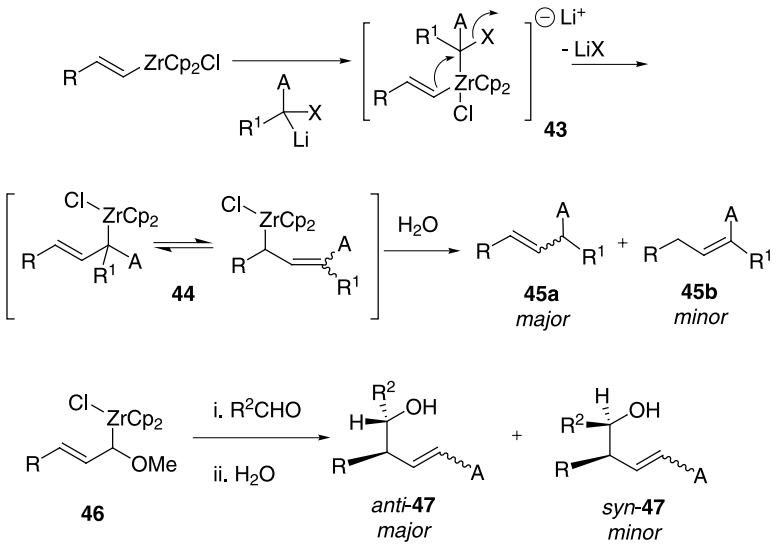
5. Lithium carbenoid insertions via the 1,2-metalate rearrangement

The insertion of lithium carbenoids into metal–carbon bonds via a 1,2-metalate rearrangement is still a rarely applied process.[31] However, this is an interesting and potentially powerful strategy since the product retains the organometallic functionality of the starting material. Whitby and Kasatkin described the use of this reaction for the convergent formation of allylzirconium compounds,[32] whose synthetic importance is based on their high reactivity toward electrophiles. The lithium carbenoid, RC(A)LiX, adds to the alkenylzirconocene, forming the complex **43**; subsequent 1,2-rearrangement leads to the allylic- and homoallylic zirconocenes as major and minor intermediates, respectively, with ratios of quenched **45a/45b** >80:20 (Scheme 12). Generally, deprotonation of the lithium carbenoid precursor is performed in situ with the addition of LiTMP (lithium 2,2,6,6-tetramethylpiperidide) in THF at −100 °C to a solution of an alkenylzirconocene and RC(A)HX and affords, after hydrolysis, product **45a** almost exclusively. The scope of these reactions includes A=ether, cyano, sulfonyl, MOM, TMS or phosphonate groups, and the leaving group X can be Cl or $PhSO_2$. Aldehydes were also used as electrophiles to trap the allylic zirconocene intermediate **46**, followed by hydrolysis to give the *anti*-homoallylic alcohol **47** in good yields and excellent diastereoselectivity.

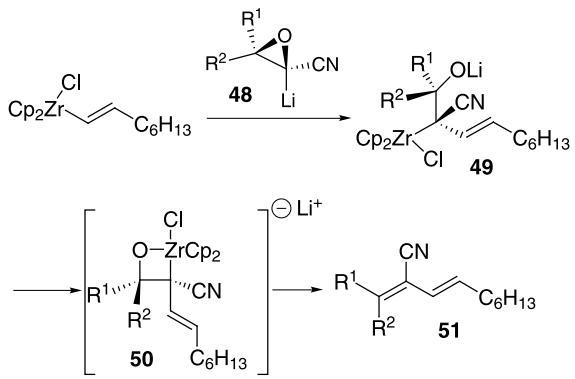
Another variant of this method is the formation of lithium carbenoids from α,β-epoxynitriles **48**, affording (*E*)-2-cyano-1,3-dienes **51** in moderate to good yields (Scheme 13).[33] A reasonable mechanism for this transformation includes epoxide opening by 1,2-migration of the alkenyl fragment, producing **49**. *syn*-β-Elimination of the zirconium alkoxide in complex **50** leads to the observed products.

The process of carbenoid insertion represents an interesting alternative to the usual methods of allyl organometallic formation, such as oxidative addition or transmetalation of species formed from allyl halides. Allyl alcohol derivatives can be used as precursors if low-valent metal complexes such as Cp_2Zr(1-butene) and $(i\text{-PrO})_2Ti$(propene) are employed.[34] Allenes can similarly be hydrozirconated to afford allylzirconocene reagents for organic synthesis.[35]

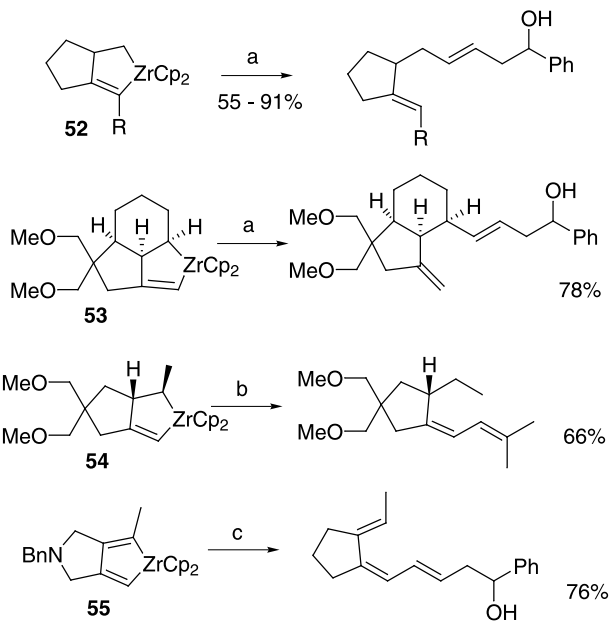
Whitby et al. studied the regiochemistry of carbenoid insertion into unsymmetrical alkenylzirconacycles (Scheme 14).[36] Alkenylzirconocenes **52**, **53**, **54** and **55** were obtained by cyclometalations of terminal alkynes with



Scheme 12. Lithium carbenoid insertion into an alkenylzirconocene intermediate.



Scheme 13. 1,2-Metalate rearrangement in the synthesis of dienyl nitriles.



Scheme 14. (a) (i) CH_2=CH–C(H)LiCl, (ii) PhCHO, $BF_3{\cdot}Et_2O$, (iii) $NaHCO_3$; (b) (i) CH_2=C(Me)–C(H)LiCl, (ii) AcOH; (c) (i) 5 equiv. of CH_2=CH–C(H)LiCl, (ii) PhCHO, $BF_3{\cdot}Et_2O$, (iii) $NaHCO_3$.

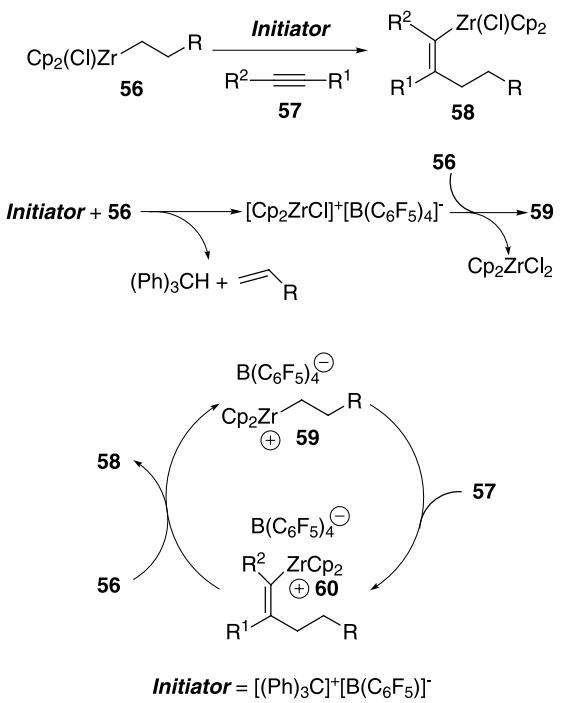
Negishi's reagent.[37] In all cases represented by **52**, the process was completely regioselective, with the insertion occurring into the alkyl–zirconocene bond, which is less sterically hindered than the alkenyl–Zr bond that bears an R substituent. Explanations for exceptions to this rule were much more complicated, as in the case of **53**, in which the insertion occurred at the more congested site, the alkyl–Zr bond. Only in one case, for the cyclic **54**, insertion into the alkenylzirconocene bond was observed. In the cyclopentadienezirconocene **55**, the less substituted site underwent preferential insertion.

HOMO–LUMO calculations were used to explain exceptions to the rule as in **53** and **54**. In **54**, these calculations indicated that the methyl group at the alkyl site was in the same plane of the LUMO, complicating the approach of the carbenoid species. In **52** and **53**, it was shown that the alkyl site groups were pointing well away from the plane of the LUMO, thereby favoring lateral attack on this site. However, steric hindrance in **53** was too high to be ignored and an electrophilic attack mechanism, with a substantial positive charge on the carbenoid species, might be responsible for the unexpected regioselectivity result.

6. Regioselective alkylzirconation of internal alkynes

Suzuki et al. reported the alkylation of unsymmetrical internal alkynes **57** in the presence of $[(Ph)_3C]^+[(C_6F_5)_4B]^-$ as initiator, with the in situ generated alkylzirconocene **56** to produce the tetrasubstituted alkenylzirconocene intermediate **58** (Scheme 15).[38] The regiocontrolled formation of tri- or tetrasubstituted alkenes can be achieved by hydrometalation, followed by proper coupling, or by carbometalation of internal alkynes.[39] The latter procedure has limitations because of reactivity, regioselectivity and side reaction problems deriving from β-hydride transfer when alkyl metals are employed.[40]

The alkyl transfer occurred selectively at the more sterically hindered carbon of the triple bond in excellent yield. The

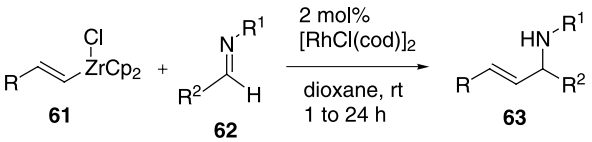


Scheme 15. Alkylzirconation of internal alkynes initiated by $[(Ph)_3C]^+$-$[(C_6F_5)_4B]^-$.

same trend was observed whether the alkynes were diphenyl or dialkyl-substituted, provided the sterics of the two alkyl groups were sufficiently different. The reaction is initiated by the action of a catalytic amount of $[(Ph)_3C]^+[(C_6F_5)_4B]^-$ on **56** to generate a $[Cp_2ZrCl]^+$ species, which reacts with **56** to form **59**. This mechanism was supported by the detection of $(Ph)_3CH$ derived from β-H abstraction of the trityl portion of the initiator. The cationic **59** activated the alkyne **57**, enabling the alkyl transfer to afford the alkenylzirconocene **60**, followed by chloride transfer with **56** to result in **58**.

7. Rh(I)-Catalyzed additions to aldimines

The problem of the inherently low reactivity of organozirconocene compounds towards addition to bulky electrophiles such as aldimines can also be addressed by a rhodium-catalyzed process. Hanzawa et al. presented the first example of a catalytic addition of alkenylzirconocenes to aldimine derivatives.[41] Rh-catalyzed additions of other organometallic reagents to aldehydes, imines or α,β-unsaturated carbonyl compounds are well known and developed.[42] The addition of organozirconocene **61** to the aldimine **62**, catalyzed by 2 mol% of $[RhCl(cod)]_2$, afforded allylic amines **63** in good yields (Scheme 16). This addition requires the use of *N*-activating groups such as $-PO(OEt)_2$ and −COOMe or −Ts groups. Alkyl, ether and phenyl

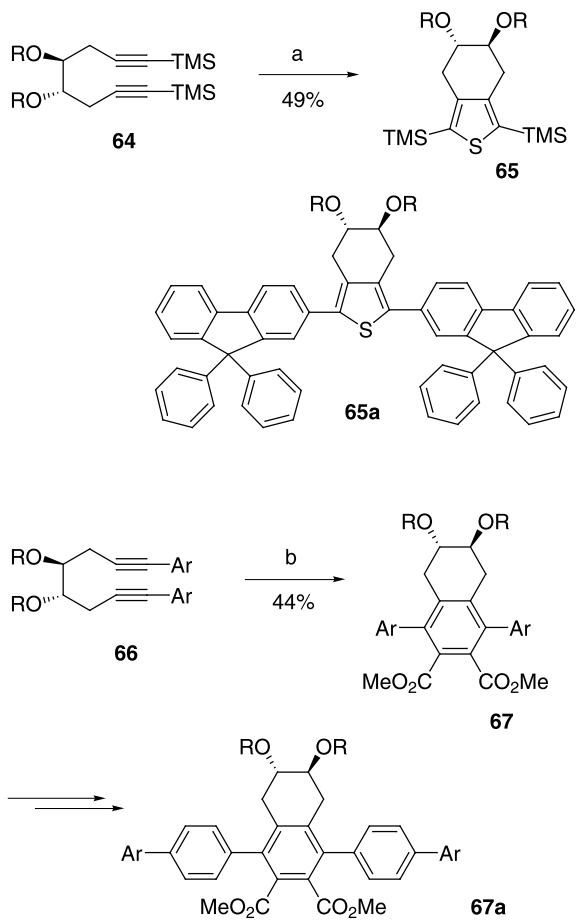


Scheme 16. Rhodium-catalyzed addition of alkenylzirconocenes to aldimines.

substituents at the alkyne were well tolerated, even though internal alkenylziconocenes required longer reaction times. The nature of R^2 had little effect on the reaction rate and product yield. Monodentate or bidentate phosphine ligands only retarded the reaction, and heating had to be applied to accelerate the process. Alkylzirconocene chloride did not react under any conditions tried. The transmetalation of an alkyl ligand from a zirconocene to other metals is more difficult than the corresponding alkenyl transfer, and few examples are known.[2f] The interesting rhodium-catalyzed process is still being further optimized, and the authors are working on its extension to aldehydes and α,β-unsaturated carbonyl compounds. Much of the future practical significance of this process will depend on the development of a catalytic asymmetric variant and the use of a cheaper transition metal catalyst.

8. Zr-Promoted cyclizations of diynes

This process generates synthetic intermediates containing cycloalkenylzirconocene units, which can be transformed into a variety of targets such as thiophenes, phospholes, germoles and highly functionalized benzene derivatives.[43] The utility of these products is most relevant for the material science field.



Scheme 17. (a) (i) Cp_2ZrCl_2, *n*-BuLi, (ii) S_2Cl_2; (b) (i) Cp_2ZrCl_2, *n*-BuLi, (ii) CuCl, DMAD.

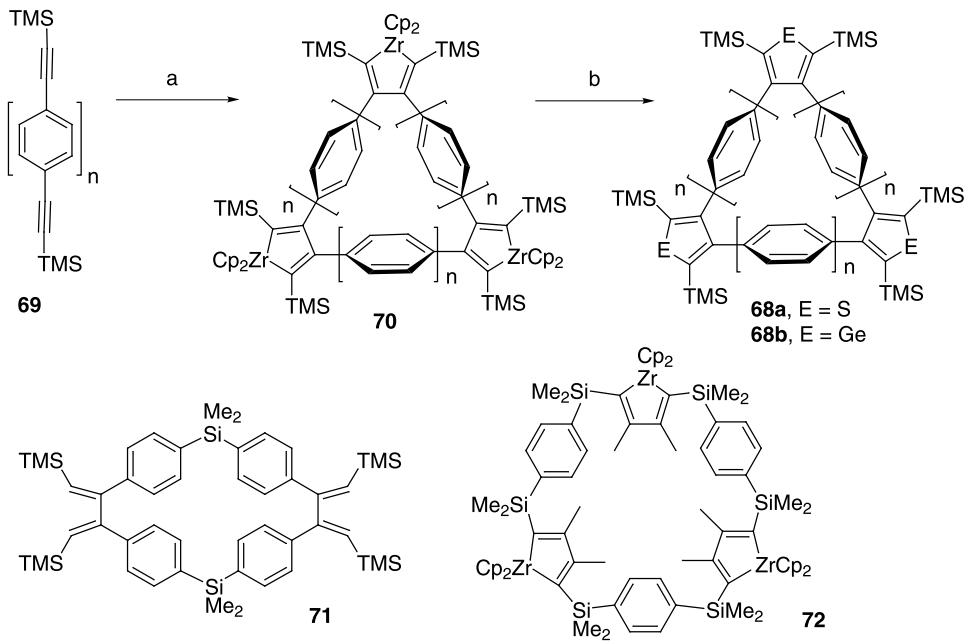
Chemical transformations of this type illustrate new options for efficiently tuning the electronic and optical properties of extended π-systems. Wong and Chen applied the Zr-promoted cyclization of diynes to introduce side chains in C_2-chiral molecules as precursors for new conjugated materials.[44] The tartaric acid derived diyne **64** was treated with in situ prepared Negishi reagent[37] to form a cyclopentadienylzirconocene, which could be quenched with S_2Cl_2 to afford the new C_2-symmetrical, chiral thiophene **65** (Scheme 17). In the same fashion, the zirconacyclopentadiene derived from **66** was converted to the diester **67** in the presence of CuCl and dimethyl acetylenecarboxylate (DMAD). Compounds **65a** and **67a**, obtained after further transformations of **65** and **67**, respectively, showed interesting optical properties.

Tilley et al. have synthesized the unusual triangular germole and thiophene macromolecules **68a** and **68b** by zirconocene-promoted cyclization of diynes (Scheme 18).[45] As a consequence of the exterior functional groups, such structures serve as building blocks (tectons) for designed crystal lattices and discrete supramolecular assemblies. Their synthesis is always a difficult problem because of the high-dilution conditions and exhaustive separations necessary to remove oligomeric products. In this context, the zirconocene coupling reactions served as a promoter of high yielding macrocyclizations. The linear diynes of variable lengths **69** were treated in a 1:1 proportion with in situ prepared Negishi reagent, initially at −78 °C and then heated to 65 °C to generate the corresponding Zr-containing macrocycles **70**. All reactions could be quenched with mild acidic solutions to yield the demetalated version of **70**. Many of the methods of carrying out electrophilic substitutions on zirconacyclopentadienes are not suitable for this target structure because of the presence of TMS groups. The zirconocene promoted coupling of diynes **69**, bearing silyl substituents, allows the control of regiochemistry.[2i,4d,46] In addition, the TMS substituent α to the zirconocene prevents most substitution reactions at zirconium, due to steric hindrance. However, reactions with S_2Cl_2 and $GeCl_4$ have been shown to be feasible and high yielding, affording **68a** and **68b**, respectively.

When the diynes used for the zirconocene coupling were not linear, other interesting classes of macrocycles could be generated, as represented by **71** and **72**, which have the potential for new optical applications.

9. Conclusion

The range of synthetic preparations and applications of alkenylzirconocene species continues to expand rapidly even 50 years after the discovery of the first zirconocene. In particular, new C,C-bond forming methods involving unprecedented organozirconium and -zinc chemistry provide a fertile ground for the development of new efficient cascade reactions and diversity-oriented synthesis. Carbon–heteroatom bond formations are of significant utility for materials chemistry. Important building blocks have been constructed through the simple elaboration of alkenylzirconocenes with proper electrophiles such as sulfonyl chlorides and dialkyl chlorophosphates, which afford (*E*)-disubstituted vinyl sulfones[47] and arylvinylphosphonates, respectively.[48] Kinetic versus thermodynamic control in the hydrozirconation of alkynes and the effect of functional groups on the control of the regioselectivity of hydrozirconation are still areas of investigation. The recent hydrozirconation of alkynyl sulfoxides and sulfones,[49] or the treatment of acetylenic tellurides with Cp_2ZrHCl to afford geminal bimetalloalkenes[50] are noteworthy due to their simplicity and effectiveness. Finally, the zirconocene-mediated activation of a C–F bond in the generation and cross-coupling reaction of 1-fluorovinylzirconocenes[51] is another good example of the seemingly limitless synthetic opportunities in zirconocene chemistry.



Scheme 18. (a) Cp_2ZrCl_2, 2 equiv. *n*BuLi, THF, −78 °C; (b) E_xCl_n=S_2Cl_2 or $GeCl_4$.

Acknowledgements

P.W. thanks the National Science Foundation (CHE-0078944) for support. R.L.N. acknowledges the Brazilian governmental agency Conselho Nacional de Pesquisa e Desenvolvimento Científico (CNPq) for a postdoctoral fellowship.

References and notes

1. Wilkinson, G.; Pauson, P. L.; Birmingham, J. M.; Cotton, F. A. *J. Am. Chem. Soc.* **1953**, *75*, 1011.
2. For representative reviews on zirconocene chemistry, see: (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed.* **1976**, *15*, 333. (b) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1. (c) Wipf, P. *Synthesis* **1993**, 537. (d) Lipshutz, B. H.; Bhandari, A.; Lindsley, C.; Keil, R.; Wood, M. R. *Pure Appl. Chem.* **1994**, *66*, 1493. (e) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed.* **1996**, *35*, 1263. (f) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (g) Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn* **1998**, *71*, 755. (h) Alt, H. G.; Köppl, A. *Chem. Rev.* **2000**, *100*, 1205. (i) Erker, G. *Acc. Chem. Res.* **2001**, *34*, 309. (j) Negishi, E. *Pure Appl. Chem.* **2001**, *73*, 239. (k) Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1778.
3. (a) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494. (b) Wipf, P.; Xu, W. *Synlett* **1992**, 718. (c) Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178. (d) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 825–5880. (e) Wipf, P.; Xu, W.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M. *Tetrahedron* **1994**, *50*, 1935. (f) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558. (g) Wipf, P.; Xu, W. *Tetrahedron* **1995**, *51*, 4551.
4. Cp_2ZrHCl was first prepared by Wailes and Weigold: (a) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405. Subsequently, Schwartz and coworkers pioneered its synthetic applications: (b) Labinger, J. A.; Hart, D. W.; Seibert, W. E.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 3851. (c) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679. (d) Erker, G.; Kropp, K.; Atwood, J. L.; Hunter, W. E. *Organometallics* **1983**, *2*, 1555.
5. For more examples of functional group compatibility, see Ref. 2f.
6. For recent lead references, see: (a) Chinkov, N.; Chechik, H.; Majumdar, S.; Liard, A.; Marek, I. *Synthesis* **2002**, 2473. (b) Farhat, S.; Marek, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 1410. (c) Takahashi, T.; Kotora, M.; Fischer, R.; Nishihara, Y.; Nakajima, K. *J. Am. Chem. Soc.* **1995**, *117*, 11039.
7. Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254.
8. Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197.
9. Wipf, P.; Jayasuriya, N.; Ribe, S. *Chirality* **2003**, *15*, 208.
10. Lipshutz, B. H.; Pfeiffer, S. S.; Tomioka, T.; Noson, K. In *Titanium and zirconium in organic synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 110–148.
11. (a) Wipf, P.; Xu, W.; Takahashi, H.; Jahn, H.; Coish, P. D. G. *Pure Appl. Chem.* **1997**, *69*, 639. (b) Wipf, P.; Coish, P. D. G. *Tetrahedron Lett.* **1997**, *38*, 5073. (c) Wipf, P.; Coish, P. D. G. *J. Org. Chem.* **1999**, *64*, 5053.
12. Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556.
13. Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667.
14. Murakami, T.; Furusawa, K. *Tetrahedron* **2002**, *58*, 9257.
15. Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965.
16. Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995**, *60*, 3278.
17. Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.
18. Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542.
19. Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122.
20. Wipf, P.; Kendall, C.; Stephenson, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 761.
21. (a) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1. (b) Harada, S.; Kowase, N.; Tabuchi, N.; Tagushi, T.; Dobashi, Y.; Dobashi, A.; Hanzawa, Y. *Tetrahedron* **1998**, *54*, 753. (c) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525.
22. (a) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974. (b) Charette, A. B.; Beauchemin, A.; Francoeur, S.; Bélanger-Gariépy, F.; Enright, G. D. *Chem. Commun.* **2002**, 466. (c) Charette, A. B.; Francoeur, S.; Martel, J.; Wilb, N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4539.
23. (a) Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773. (b) Wipf, P.; Stephenson, C. R. J.; Okumura, K. *J. Am. Chem. Soc.* **2003**, *125*, 14694.
24. See, for example: (a) Brown, H. C.; Phadke, A. S.; Bhat, N. G. *Tetrahedron Lett.* **1993**, *34*, 7845. (b) Sidduri, A.; Rozema, M.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 2694.
25. (a) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912. (b) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4914.
26. Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 1872.
27. Ribe, S.; Kondru, R. K.; Beratan, D. N.; Wipf, P. *J. Am. Chem. Soc.* **2000**, *122*, 4608.
28. Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2000**, *122*, 10482.
29. (a) Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett.* **2001**, *3*(21), 3281. (b) Hu, T.; Panek, J. S. *J. Org. Chem.* **1999**, *64*, 3000.
30. Xu, X.; Zheng, W.; Huang, X. *Synth. Commun.* **1998**, *78*, 4165.
31. (a) Negishi, E.; Akiyoshi, K. *J. Am. Chem. Soc.* **1988**, *110*, 646. (b) Negishi, E.; Akiyoshi, K.; O'Connor, B.; Takagi, K.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 3089. (c) Kocienski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933.
32. (a) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 6211. (b) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **1999**, *40*, 9353.
33. Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 6201.
34. (a) Kasatkin, A. N.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. (b) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* **1995**, *51*, 4507.
35. (a) Maeta, H.; Hasegawa, T.; Suzuki, K. *Synlett* **1993**, 341. (b) Chino, M.; Matsumoto, T.; Suzuki, K. *Synlett* **1994**, 359. (c) Chino, M.; Liang, G. H.; Matsumoto, T.; Suzuki, K. *Chem. Lett.* **1996**, 231.
36. (a) Gordon, G. J.; Whitby, R. J. *Synlett* **1995**, 77. (b) Gordon, G. J.; Luker, T.; Tuckett, M. W.; Whitby, R. J. *Tetrahedron* **2000**, *56*, 2113.
37. Negishi, E. I.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
38. (a) Yamanoi, S.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1999**, *40*, 2793. (b) Yamanoi, S.; Seki, K.; Matsumoto, T.; Suzuki, K. *J. Organomet. Chem.* **2001**, 143.

39. For carbometalation of internal alkynes, see: (a) Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753. (b) Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *35*, 93. (c) Suzuki, N.; Kondakov, D. Y.; Kageyama, M.; Kotora, M.; Hara, R.; Takahashi, T. *Tetrahedron* **1995**, *51*, 4519.
40. For β-H transfer reactions in zirconium-catalyzed carboaluminations, see: (a) Negishi, E.; Kondakov, D. Y.; Choueiry, D.; Kasai, K.; Takahashi, T. *J. Am. Chem. Soc.* **1996**, *118*, 9577. For general β-hydride transfer reactions, see: (b) Crandall, J. K.; Collonges, E. *J. Org. Chem.* **1976**, *41*, 4089.
41. Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2003**, *44*, 923.
42. For recent additions of organo-Sn, see: (a) Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, *58*, 91. For organo-Ti, see: (b) Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 12102. For organo-Si, see: (c) Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* **2002**, *4*, 667. For organo-Pb, see: (d) Ding, R.; Chen, Y.; Wang, D.; Li, C. *Synlett* **2001**, 1470. For organo-B, see: (e) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3279.
43. For a recent use of zirconocenes in thiophene synthesis, see: (a) Suh, M. C.; Jiang, B.; Tilley, T. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2870. For phospholes, see: (b) Hay, C.; Hissler, M.; Fischmeister, C.; Rault-Berthelot, J.; Toupet, L.; Nyulaszi, L.; Réau, R. *Chem. Eur. J.* **2001**, *7*, 4222. For germoles: (c) Lucht, B. L.; Buretea, M. A.; Tilley, T. D. *Organometallics* **2000**, *19*, 3469. For highly functionalized benzenes: (d) Takahashi, T.; Tsai, F.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093.
44. Wong, K.; Chen, R. *Tetrahedron Lett.* **2002**, *43*, 3313.
45. (a) Nitschke, J. R.; Tilley, T. D. *J. Organomet. Chem.* **2003**, *666*, 15. (b) Schafer, L. L.; Nitschke, J. R.; Mao, S. S. H.; Liu, F.-Q.; Harder, G.; Haufe, M.; Tilley, T. D. *Chem. Eur. J.* **2002**, *8*, 74.
46. Erker, G.; Zwettler, R. *J. Organomet. Chem.* **1991**, *409*, 179.
47. Duan, D.-H.; Huang, X. *Synlett* **1999**, *3*, 317.
48. Zhong, P.; Huang, X.; Xiong, Z. *Synlett* **1999**, *6*, 721.
49. (a) Zhong, P.; Huang, X.; Ping-Guo, M. *Tetrahedron* **2000**, 8921. (b) Duan, D.-H.; Huang, X. *Chem. Commun.* **1999**, 1741.
50. Sung, J. W.; Jang, W. B.; Oh, D. Y. *Tetrahedron Lett.* **1996**, *37*, 7537.
51. Fujiwara, M.; Ichikawa, J.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 7261.

Biographical sketch

Peter Wipf was born in 1959 in Aarau, Switzerland. He received his Dipl. Chem. in 1984 and his PhD in 1987 from the University of Zürich under the direction of Professor Heinz Heimgartner. After a Swiss NSF postdoctoral fellowship with Professor Robert E. Ireland at the University of Virginia, he started his academic appointment in the fall of 1990 at the University of Pittsburgh where he serves currently as Professor of Chemistry, Professor of Pharmaceutical Sciences, and Director of the Center for Chemical Methodologies and Library Development. His research focuses on the total synthesis of natural products, organometallic and heterocyclic chemistry, combinatorial and computational chemistry. At the center of his program is the study of chemical reactivity and the use of synthesis to augment the chemical toolbox and develop new therapeutic strategies. The discovery of fundamentally new reaction pathways is stimulated by exploratory studies of transition metal complexes, in particular zirconocenes.

Ruth L. Nunes was born in Recife, Brazil, in 1971. She obtained her Chemistry Bachelor degree in 1993 at the Federal University of Pernambuco, Brazil. In 2000, she graduated with a Doctor in Science degree in natural products synthesis from the research group of Dr. Lothar W. Bieber. In 2001, she joined Dr. Peter Wipf's group at the University of Pittsburgh as a postdoctoral fellow, where she was involved in the investigation of the water/zirconium-accelerated carboalumination of alkynes and combinatorial chemistry solid phase synthesis projects. In 2003, she started her position as a development researcher at the Federal University of Pernambuco, working with new sulfoxide, ketoester and oxirane ligands for the synthesis of photo- and electro-luminescence devices.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1281–1286
Tetrahedron

Zirconium-catalyzed preparation of aluminacyclopentanes and synthesis of five-membered carbo- and heterocycles

Usein M. Dzhemilev,* Askhat G. Ibragimov, Ruslan R. Gilyazev and Leila O. Khafizova

Institute of Petrochemistry and Catalysis, Bashkortostan Republic Academy of Sciences, and Ufa Scientific Centre, Russian Academy of Sciences, 141 Prospekt Oktyabrya 141, Ufa 450075, Russian Federation

Received 30 June 2003; revised 29 September 2003; accepted 11 October 2003

Abstract—Novel 'one-pot' catalytic methods for the synthesis of cyclopentanols, tetrahydrothiophenes, silacyclopentanes and phospholanes are based on successive transformations of olefins and organoaluminium compounds (R_2AlR') in the presence of Cp_2ZrCl_2 catalyst. In situ generated aluminacyclopentanes serve as common intermediates in these processes.

1. Introduction

The development of the chemistry of reagents containing active metal–carbon bonds has contributed very significantly to the advancement of organic chemistry. Among the most commonly used reagents, lithium, magnesium, zinc, aluminium and boron organic compounds are also the most useful for carbon–carbon bond formations.

Meanwhile, in the last 10–15 years, new effective methods for construction of carbon–carbon, heteroatom–carbon and metal–carbon bonds based on zirconium organic derivatives have provided interesting carbocyclic and heterocyclic compounds. Negishi E.,[1–6] Takahashi T.,[7–13] Buchwald S.L.,[14–20] Nugent W.A., Fagan P.J.[21–23] and others have contributed to the development of these methods.

Concurrently, the chemistry of cyclic organoaluminium compounds (OAC) and their derivatives, in particular, aluminacyclopentanes and aluminacyclopentenes and their applications toward the synthesis of cyclobutanes,[24,25] cyclopropanes,[26–29] thiophanes and selenophanes[30,31] has been published. Based on these ideas and in order to extend the use of OAC in organic and organometallic synthesis, we focused our attention on 'one-pot' methods for the preparation of substituted cyclopentanols, tetrahydrothiophenes, phospholanes and silacyclopentanes from aluminacyclopentanes,[32–35] which were generated in situ by cycloalumination of olefins in the presence of Zr-containing catalysts.

2. Results and discussion

In accordance with previously reported work,[36] trialkylalanes were found to interact with carboxylic esters at 35–80 °C to give a complicated mixture of alcohols and ketones. We herein report that aluminacyclopentanes **1**, generated in situ from α-olefins and $AlEt_3$ in the presence of Cp_2ZrCl_2 catalyst,[32–35] reacted selectively with carboxylic esters in the presence of 10 mol% CuCl at 20–21 °C for 6–8 h to form cyclopentanols **2a–j** in 60–75% yield (Scheme 1).

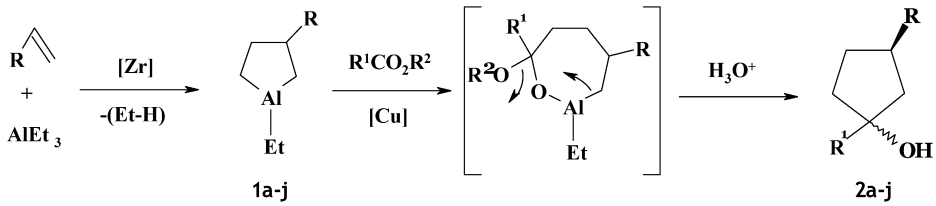
This reaction represents a convenient route for the synthesis of cyclopentanols with substitution patterns determined by the structure of the starting olefins. For example, cycloalumination of styrene, allylbenzene, or 4-vinylcyclohex-1-ene with $AlEt_3$ catalyzed by Cp_2ZrCl_2 was found to generate aluminacyclopentanes **1e–j**. Further transformations of these metallocycles under the action of alkyl formiate and catalytic amounts of CuCl led to the formation of two additional C–C bonds as shown for cyclopentanols **2e–j**.

In an analogous fashion, the interaction between *trans*-3,4-dialkylsubstituted aluminacyclopentanes **3**, generated in situ,[37] and methyl formiate in the presence of CuCl catalyst (10 mol%) led to cyclopentanoles **4** with retention of the relative configuration of the alkyl substituents (Scheme 2).

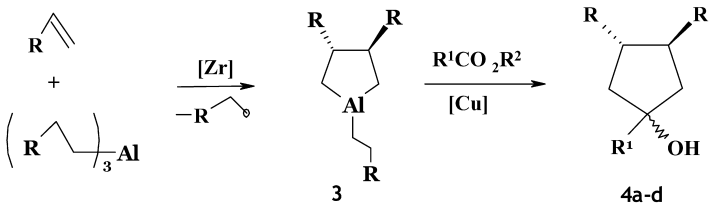
Earlier[30,31] we have demonstrated a method for the selective synthesis of tetrahydrothiophenes from aluminacyclopentanes and S_8 in benzene at 80 °C. In the course of

Keywords: Catalysis; Zr Complexes; Organoaluminium compounds; Olefins; Cycloalumination; Cyclopentanols; Tetrahydrothiophenes; Phospholanes; Silacyclopentanes.
* Corresponding author. Fax: +7-3472-312750;
e-mail address: ink@anrb.ru

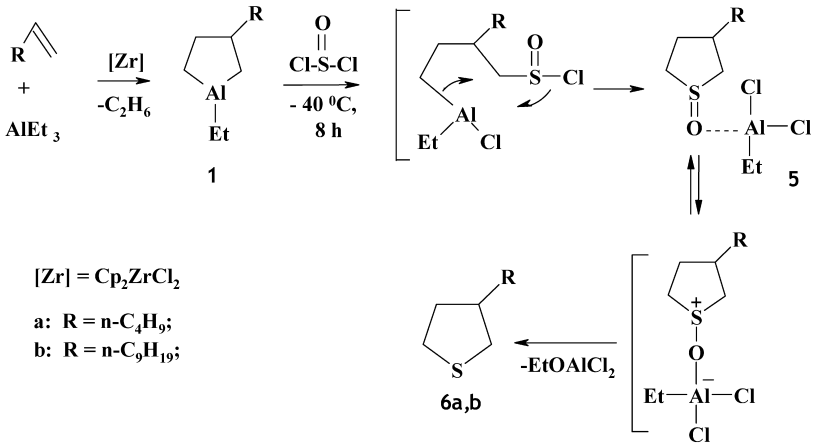
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.10.082



Scheme 1. [Zr]=Cp_2ZrCl_2; [Cu]=CuCl; a: R=*n*-C_4H_9, R^1=H; b: R=*n*-C_6H_{13}, R^1=H; c: R=*n*-C_6H_{13}, R^1=CH_3; d: R=*n*-C_6H_{13}, R^1=C_2H_5; e: R=3-cyclohexenyl, R^1=H; f: R=Ph, R^1=H; j: R=CH_2Ph, R^1=H; R^2=alkyl.



Scheme 2. [Zr]=Cp_2ZrCl_2; a: R=*n*-C_4H_9, R^1=H; b: R=*n*-C_6H_{13}, R^1=H; c: R=*n*-C_4H_9, R^1=CH_3; d: R=*n*-C_4H_9, R^1=C_2H_5, R^2=alkyl.



Scheme 3.

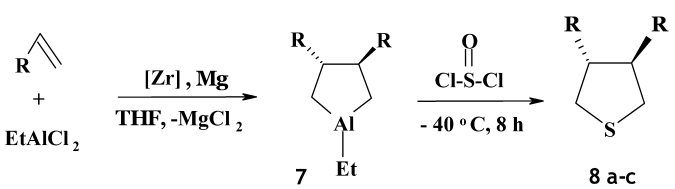
further investigations on transformations of cyclic OAC to give five-membered heterocycles—1-ethyl-3-alkylalumina-cyclopentanes **1**, obtained in situ from α-olefins, $AlEt_3$ and catalytic amounts of Cp_2ZrCl_2,[32–35] were found to interact with thionyl chloride in hexane at −40 °C to give 3-alkyltetrahydrothiophenes **6** in 85% yield. The probable formation of sulfoxide intermediate[38] **5** followed by its further conversion into the isolated product represent the key steps in this reaction (Scheme 3).

In the presence of $EtAlCl_2$, Zr catalyst and Mg-metal, 1-alkyl-*trans*-3,4-dialkylaluminacyclopentanes[39,40] **7** were formed and found to react with thionyl chloride at −40 °C to give *trans*-3,4-dialkyltetrahydrothiophenes **8** in 80% yield (Scheme 4).

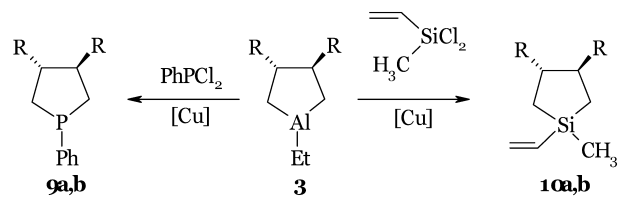
The preparation of phospholes[21,23] or silols[41] from stoichiometric amounts of zirconacyclopentadienes and phosphorus and silicon dihalogenides is well known. To investigate the possibilities of preparing analogous P- or Si-containing heterocycles from aluminacyclopentanes[39,40] in the presence of catalytic amounts of Zr complex, solutions of aluminacyclopentanes **3** in THF were exposed at rt (ca. 20 °C) to copper halides (CuCl, CuBr, CuI, 10–15 mol%) and dichlorophenylphosphine, as well as dichloromethyl-vinylsilane. Gratifyingly, the expected phospholanes **9** or silacyclopentanes 10 were obtained in total yields of 50–65% (Scheme 5).

3. Conclusions

The synthetic strategies presented in this paper allow the straightforward conversion of α-olefins into cyclopentanols, tetrahydrothiophenes, phospholanes or silacyclopentanes



Scheme 4. [Zr]=Cp_2ZrCl_2; a: R=$(CH_3)_2CH(CH_2)_2$; b: R=$PhCH_2$; c: R=3-cyclohexenyl.



Scheme 5. a: R=*n*-C_4H_9; b: R=*n*-C_6H_{13}.

via intermediate in situ prepared aluminacyclopentanes in the presence of Cp_2ZrCl_2 catalyst.

Several carbon–carbon and carbon–heteroatom bonds can be formed in a single reaction setup, and this efficiency combined with catalytic use of the more precious transition metals contributes to the promise of this methodology for the large-scale preparation of organic building blocks. Aluminacyclopentanes were found to react selectively with carboxylic esters, thionyl chloride, dichlorophosphines and dichlorosilanes.

4. Experimental

4.1. General

All solvents were dried (hexane over $LiAlH_4$, Et_2O and THF over Na) and freshly distilled before use. All reactions were carried out under a dry argon atmosphere. The reaction products were analyzed using chromatography on a 'Chrom-5' instrument (1200×3 mm^2 column packed with 5% of SE-30 and 15% PEG-6000 on Chromaton N-AW, carrier gas—He). Infrared spectra (IR) were recorded on a IR-75 instrument (thin film). Mass spectral measurements were performed on a MX-1306 spectrometer at 70 eV and working temperature 200 °C. The ^1H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions on 'Bruker AM-300' spectrometer (75.46 MHz for ^{13}C and 300 MHz for ^1H). The chemical shifts are reported as δ values in ppm relative to internal standard Me_4Si. ^{13}C NMR spectra were edited by *J*-modulation (JMOD) on CH constants.

4.2. Reaction of 1-ethyl-3-alkyl-substituted aluminacyclopentanes with carboxylic esters catalyzed by CuCl

A 50 mL glass reactor was charged with Cp_2ZrCl_2 (0.5 mmol) in dry hexane (3 mL), olefin (10 mmol), and $AlEt_3$ (12 mmol) under a dried argon atmosphere at 0 °C. The resulting solution was raised to ambient temperature and stirred for 12 h, then cooled to −15 °C and after addition of CuCl (1 mmol) the corresponding ester (30 mmol) was added dropwise. The reaction mixture was allowed to warm to ~20 °C and stirred for 8 h. The reaction was quenched with 8–10% (aq.) solution of HCl. The layers were separated and the aqueous phase was extracted with Et_2O or hexane. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$, dried ($CaCl_2$), filtered and concentrated in vacuo. The products were isolated by column chromatography on silica gel (40–100 mesh grade) with hexane/Et_2O=10:1 for elution.

4.2.1. *cis/trans*-3-Butylcyclopentanol ~(2:1) (2a). IR (thin film) 3355, 2985, 2950, 2840, 1730, 1450, 1385, 1230, 1030, 925, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, *J*=6.0 Hz, 3H, CH_3), 1.15–1.52 (m, 6H, CH_2), 1.78–2.35 (m, 7H, CH and CH_2 ring), 4.29 (m, C*H*–OH); ^{13}C NMR ($CDCl_3$) δ 14.50, 22.74, 30.28, 30.78(30.86), 32.08(32.79), 35.97(36.05), 37.98(37.84), 39.95, 76.82(76.47); MS *m/z*: 124 [M^+-H_2O]. Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76; Found: C, 75.82; H, 12.63. Yield 76%.

4.2.2. *cis/trans*-3-Hexylcyclopentanol ~(2:1) (2b). IR (thin film) 3380, 2990, 2950, 2840, 1720, 1460, 1380, 1185, 1030, 950, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, *J*=6.0 Hz, 3H, CH_3), 1.18–1.51 (m, 10H, CH_2), 1.78–2.35 (m, 7H, CH and CH_2 ring), 4.30 (m, C*H*–OH); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.62, 29.46; 28.49, 30.57(30.66), 31.87, 32.20(32.96), 35.77(35.86), 37.90(36.52), 39.62, 76.95(76.55); MS (*m/z*, %): 152 (5, [M^+-H_2O]), 112(1.5), 85(2.5), 71(2.6), 67(100), 57(16), 43(31), 29(27.5). Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02; Found: C, 77.39; H, 12.87. Yield 75%.

4.2.3. *cis/trans*-1-Methyl-3-(*n*-hexyl)cyclopentanol ~(2:1) (2c). IR (thin film) 3350, 2990, 2950, 2840, 1720, 1460, 1380, 1235, 1100, 1030, 1000, 925, 900, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, *J*=6.0 Hz, 3H, CH_3), 1.20–1.58 (m, 10H, CH_2), 1.33 (s, 3H, CH_3), 1.61–2.51 (m, 7H, CH, CH_2 ring); ^{13}C NMR ($CDCl_3$) δ 14.07, 22.67, 28.52(28.78), 29.50, 29.56, 31.19 (31.45), 31.90, 36.52 (36.98), 38.41 (39.06), 40.75 (41.59), 48.62 (48.23), 79.96 (79.74); MS *m/z*: 184 M^+. Anal. Calcd for $C_{12}H_{24}O$: C, 78.19; H, 13.13; Found: C, 78.02; H, 13.01. Yield 68%.

4.2.4. *cis/trans*-1-Ethyl-3-(*n*-hexyl)cyclopentanol ~(2:1) (2d). IR (thin film) 3350, 2990, 2950, 2840, 1720, 1450, 1380, 1230, 1030, 920, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–1.02 (m, 6H, CH_3), 1.20–1.57 (m, 12H, CH_2), 1.61–2.51 (m, 7H, CH and CH_2 ring); ^{13}C NMR ($CDCl_3$) δ 8.72(8.49), 14.00, 22.68, 28.48, 29.49, 30.86(31.38), 31.87, 34.41(34.47), 36.33(36.37), 36.95 (37.14), 38.02(38.57), 46.45 (46.00), 82.80(82.31); MS *m/z*: 198 (M^+). Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21; Found: C, 78.58; H, 13.04. Yield 60%.

4.2.5. *cis/trans*-3-Cyclohexenylcyclopentanol ~(2:1) (2e). ^1H NMR ($CDCl_3$) δ 1.60–2.21 (m, 14H, CH, CH_2), 4.28 (m, H, C*H*–OH), 5.15–5.75 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 25.26, 27.60(27.82), 28.52, 30.73, 35.32(35.68), 37.32(37.68), 39.16(39.39), 43.50(43.07), 76.18(75.81), 126.50, 127.18; MS (*m/z*, %): 166 (0.7, M^+), 148(18), 134(0.6), 122(1), 108(2), 94(8.5), 81(40), 80(100), 58(1), 44(2), 30(1), 29(18). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91; Found: C, 79.28; H, 10.74. Yield 65%.

4.2.6. *cis/trans*-3-Phenylcyclopentanol ~(2:1) (2f). IR (thin film) 3380, 3015, 2990, 2950, 2840, 1710, 1490, 1450, 1395, 1180, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45–2.25 (m, 6H, CH_2), 3.10–3.25 (m, H, C*H*–Ph), 4.40 (m, H, C*H*–OH), 7.00–7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.91(29.20), 32.65(33.49), 35.65(36.01), 44.25(43.95), 73.75(73.51), 126.04, 127.08, 127.53, 128.48, 141.62; MS (*m/z*, %): 162(32, M^+), 145(9),

144(100), 143(53), 118(26), 104(54), 90(2), 77(30), 29(18). Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70; Found: C, 81.23; H, 8.52. Yield 64%.

4.2.7. *cis/trans*-3-Benzylcyclopentanol ~(2:1) (2j). IR (thin film) 3380, 2990, 3015, 2995, 2950, 1715, 1600, 1490, 1450, 1400, 1180, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58–2.25 (m, 7H, CH, CH_2), 2.62 (d, J=5.6 Hz, 2H, CH_2–Ph), 4.28 (m, H, CH–OH), 7.00–7.48 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 30.34(30.54), 32.09(32.39), 38.78(39.36), 39.72(40.33), 42.06(41.60), 76.38(76.57), 126.00, 128.24, 128.42, 141.38; MS (*m*/*z*, %): 176(19, M^+), 158(7), 132(2), 118(7), 104(5), 91(100), 77(7), 29(27). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15; Found: C, 81.59; H, 9.01. Yield 69%.

4.3. Reaction of *trans*-3,4-dialkylaluminacyclopentanes with carboxylic esters catalyzed by CuCl

To the solution of tri(*n*-hexyl)aluminium (10 mmol), prepared in situ according to the literature method[37] at −15 °C under a dried argon atmosphere was added CuCl (1 mmol) and dropwise the corresponding ester (30 mmol). The reaction temperature was raised to rt (ca. 20 °C), and the mixture was stirred for 8 h. The reaction was quenched with 8–10% (aq.) solution of HCl. The layers were separated and the aqueous phase was extracted with Et_2O or hexane. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$, dried ($CaCl_2$), filtered and concentrated in vacuo. The products were isolated by column chromatography on silica gel (40–100 mesh grade) with hexane/Et_2O=10:1 for elution.

4.3.1. *trans*-3,4-Di(*n*-butyl)cyclopentanol (4a). ^1H NMR ($CDCl_3$) δ 0.86–0.90 (m, 6H, CH_3), 1.15–1.30 (m, 12H, CH_2), 1.65–2.35 (m, 6H, CH and CH_2 ring), 5.30 (m, H, CH–OH); ^{13}C NMR ($CDCl_3$) δ 14.12, 22.66, 29.85, 34.35, 39.10, 42.02, 73.25. Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21; Found: C, 76.68; H, 13.01. Yield 75%.

4.3.2. *trans*-3,4-Di(*n*-hexyl)cyclopentanol (4b). ^1H NMR ($CDCl_3$) δ 0.88–0.91 (m, 6H, CH_3), 1.15–1.30 (m, 20H, CH_2), 1.65–2.35 (m, 6H, CH and CH_2 ring), 5.30 (m, H, CH–OH); ^{13}C NMR ($CDCl_3$) δ 14.15, 22.54, 26.15, 29.42, 31.72, 34.31, 39.02, 41.45, 72.18. Anal. Calcd for $C_{17}H_{34}O$: C, 80.24; H, 13.47; Found: C, 80.03; H, 13.29. Yield 74%.

4.3.3. 1-Methyl-*trans*-3,4-di(*n*-butyl)cyclopentanol (4c). ^1H NMR ($CDCl_3$) δ 0.83–0.95 (m, 6H, CH_3), 1.14–1.29 (m, 12H, CH_2), 1.32 (s, 3H, CH_3), 1.65–2.35 (m, 6H, CH and CH_2 ring); ^{13}C NMR ($CDCl_3$) δ 14.12, 22.69, 26.92, 31.93, 34.53, 38.15, 41.94, 72.83. Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29; Found: C, 78.98; H, 13.11. Yield 73%.

4.3.4. 1-Ethyl-*trans*-3,4-di-(*n*-butyl)cyclopentanol (4d). ^1H NMR ($CDCl_3$) δ 0.86–0.92 (m, 9H, CH_3), 1.24–1.62 (m, 14H, CH_2), 1.67–2.54 (m, 6H, CH and CH_2 ring); ^{13}C NMR ($CDCl_3$) δ 8.80, 14.11, 22.69, 29.95, 33.90, 32.42, 37.41, 38.44, 76.65. Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36; Found: C, 79.41; H, 13.20. Yield 69%.

4.4. Reaction of *trans*-3-alkylaluminacyclopentanes with thionyl chloride

A 50 mL glass reactor was charged with Cp_2ZrCl_2 (0.5 mmol) in dry hexane (3 mL), olefin (10 mmol), and $AlEt_3$ (12 mmol) under a dried argon atmosphere at 0 °C. The resulting solution was raised to ambient temperature and stirred for 12 h, then cooled to −40 °C, and thionyl chloride (30 mmol) was added dropwise, stirred for 8 h and treated with 8–10% (aq.) solution of HCl. The crude products were extracted with diethyl ether or hexane and purified by distillation in vacuo.

4.4.1. 3-(*n*-Butyl)tetrahydrothiophene (6a). IR (thin film) 2970, 2940, 2870, 1470, 1385, 1265, 1220, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87–0.95 (m, 3H, CH_3), 1.35 (m, 6H, CH_2), 1.87–2.48 (m, 3H, CH and CH_2 ring), 2.65–3.01 (m, 4H, CH_2–S); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.90, 30.80, 31.00, 33.30, 36.81, 44.80; MS *m*/*z*: 144 M^+. Yield 85%.

4.4.2. 3-(*n*-Nonyl)tetrahydrothiophene (6b). IR (thin film) 2960, 2925, 2855, 1460, 1375, 1260, 1210, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–0.92 (m, 3H, CH_3), 1.21 (m, 16H, CH_2), 1.93–2.47 (m, 3H, CH, CH_2 ring), 2.58–2.83 (m, 4H, CH_2–S); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.70, 28.80, 29.40, 29.70, 29.90, 30.80, 31.90, 33.60, 36.80, 44.80; MS *m*/*z*: 214 M^+. Yield 83%.

4.5. Reaction of *trans*-3,4-dialkylaluminacyclopentanes with thionyl chloride

A 50 mL glass reactor was charged with Cp_2ZrCl_2 (0.5 mmol), Mg (powder) (12 mmol), dry THF (10 mL), olefin (20 mmol), and $EtAlCl_2$ (12 mmol) under a dried argon atmosphere at 0 °C. The resulting solution was allowed to warm to ambient temperature and stirred for 12 h, then cooled up to −40 °C and thionyl chloride (30 mmol) was added dropwise, stirred for 8 h and treated with 8–10% (aq.) solution of HCl. The crude products were extracted with diethyl ether or hexane and purified by distillation in vacuo. Compounds **8a–c** were identified by comparison with the known samples [31].

4.6. Reaction of *trans*-3,4-di(alkyl)aluminacyclopentanes with dichlorophenylphosphine

A 50 mL glass reactor was charged with Cp_2ZrCl_2 (0.5 mmol), Mg (powder) (12 mmol), dry THF (10 mL), olefin (20 mmol), and $EtAlCl_2$ (12 mmol) under a dried argon atmosphere at 0 °C. The solution was raised to ambient temperature and stirred for 12 h, then cooled to −15 °C and dichlorophenylphosphine (12 mmol) was slowly added dropwise. The reaction mixture was allowed to warm to rt (ca. 20 °C), stirred for 8 h and treated with 8–10% (aq.) solution of HCl. The crude products were extracted with diethyl ether or hexane and purified by distillation in vacuo.

4.6.1. 1-Phenyl-*trans*-3,4-di(*n*-butyl)phospholane (9a). ^1H NMR ($CDCl_3$) δ 0.89 (t, J=6.5 Hz, 6H, CH_3), 1.26–1.75 (m, 14H, CH_2 and CH), 3.40–3.51 (m, 4H, CH_2P), 7.17–7.87 (m, 5H, Ph). Anal. Calcd for $C_{18}H_{29}P$: C, 78.22; H, 10.58; Found: C, 77.99; H, 10.42. Yield 60%.

4.6.2. 1-Phenyl-*trans*-3,4-di(*n*-hexyl)phospholane (9b). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J=6.5 Hz, 6H, CH_3), 1.23–1.72 (m, 22H, CH_2 and CH), 3.40–3.51 (m, 4H, CH_2P), 7.10–7.64 (m, 5H, Ph). Anal. Calcd for $C_{22}H_{37}P$: C, 79.47; H, 11.22; Found: C, 79.26; H, 11.07. Yield 60%.

4.7. Reaction of *trans*-3,4-di(alkyl)aluminacyclopentanes with dichlorovinylmethylsilane

A 50 mL glass reactor was charged with Cp_2ZrCl_2 (0.5 mmol), Mg (powder) (12 mmol), dry THF (10 mL), olefin (20 mmol), and $EtAlCl_2$ (12 mmol) under a dried argon atmosphere at 0 °C. The solution was raised to ambient temperature and stirred for 12 h, then cooled to −15 °C and dichlorovinylmethylsilane (12 mmol) was slowly added dropwise. The reaction mixture was allowed to warm to r.t. (ca. 20 °C), stirred for 8 h and treated with an 8–10% (aq.) solution of HCl. The crude products were extracted with Et_2O or hexane and purified by distillation in vacuo.

4.7.1. 1-Vinyl-1-methyl-*trans*-3,4-di(*n*-butyl)silacyclopentane (10a). ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 3H, CH_3), 0.75 (d, J=6.5 Hz, 4H, CH_2–Si), 0.96 (t, J=6.5 Hz, 6H, CH_3), 1.38 (m, 14H, CH and CH_2), 5.80–6.15 (m, 3H, CH_2=CH); ^{13}C NMR ($CDCl_3$) δ −0.74, 14.12, 14.66, 23.06, 29.37, 35.42, 36.81, 35.09, 36.72, 133.16, 136.61. Anal. Calcd for $C_{15}H_{30}Si$: C, 75.4; H, 12.68; Found: C, 75.35; H, 12.51. Yield 56%.

4.7.2. 1-Vinyl-1-methyl-*trans*-3,4-di(n-hexyl)silacyclopentane (10b). ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 3H, CH_3), 0.81 (d, J=6.5 Hz, 4H, CH_2–Si), 0.96 (t, J=6.3 Hz, 6H, CH_3), 1.38 (m, 22H, CH and CH_2), 5.80–6.13 (m, 3H, CH_2=CH); ^{13}C NMR ($CDCl_3$) δ −0.67, 14.12, 14.54, 22.80, 27.81, 29.82, 32.10, 35.09, 36.72, 133.22, 136.67. Anal. Calcd for $C_{19}H_{38}Si$: C, 77.46; H, 13.00; Found: C, 77.25; H, 12.85. Yield 55%.

Acknowledgements

We thank the Russian Foundation of Basic Research (Project Nos. 03-03-33050 and 02-03-97904) for financial support.

References and notes

1. Negishi, E.; Pour, P.; Cederbaum, F. E.; Kotora, M. *Tetrahedron* **1998**, *54*, 7057–7074.
2. Negishi, E.; Montchamp, J.-L.; Anastasia, L.; Elizarov, A.; Choveiry, D. *Tetrahedron Lett.* **1998**, *39*, 2503–2506.
3. Aguel, G.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 7424–7426.
4. Rousset, C. J.; Swanson, F. L.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5105–5108.
5. Negishi, E.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986**, *51*, 4080–4082.
6. Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568–2569.
7. Takahashi, T.; Shen, B.; Nakajima, K.; Xi, Z. *J. Am. Chem. Soc.* **1999**, *121*, 8706–8708.
8. Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Kotora, M. J. A. *J. Am. Chem. Soc.* **1999**, *121*, 11093–11100.
9. Kotora, M.; Xi, C.; Takahashi, T. *Tetrahedron Lett.* **1998**, *39*, 4321–4324.
10. Takahashi, T.; Xi, Z.; Nashihara, Y.; Huo, S.; Kasai, K.; Aoyagi, K.; Denisov, V.; Negishi, E. *Tetrahedron* **1997**, *53*, 9123–9134.
11. Takahashi, T.; Kotora, M.; Xu, Z. J. *Chem. Soc., Chem. Commun.* **1993**, 361–362.
12. Takahashi, T.; Kotora, M.; Kasai, K. *J. Am. Chem. Soc.* **1995**, *117*, 2693–2695.
13. Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N.; Nakajima, K. *Organometallics* **1994**, *13*, 4183–4185.
14. Rege, F. M. G.; Buchwald, S. L. *Tetrahedron* **1995**, *51*, 4291–4296.
15. Tidwell, J. H.; Peat, A. J.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 7164–7168.
16. Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797–11810.
17. Tidwell, J. H.; Senn, D. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 4685–4686.
18. Cuny, G. D.; Gutierrez, F.; Buchwald, S. L. *Organometallics* **1991**, *10*, 537–539.
19. Fisher, R. A.; Nielsen, R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 165–171.
20. Buchwald, S. L.; Fang, Q. *J. Org. Chem.* **1989**, *54*, 2793–2797.
21. Fagan, P. J.; Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 1880–1890.
22. Rajan Babu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128–7135.
23. Fagan, P. J.; Nugent, W. A. *J. Am. Chem. Soc.* **1988**, *110*, 2310–2312.
24. Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Muslukhov, R. R.; Tolstikov, G. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1989**, *38*, 1981.
25. Dzhemilev, U. M.; Ibragimov, A. G.; Azhgaliev, M. N.; Zolotarev, A. P.; Muslukhov, R. R. *Russ. Chem. Bull. Int. Ed.* **1994**, *43*, 252–254.
26. Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Muslukhov, R. R.; Tolstikov, G. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1990**, *39*, 1071–1072.
27. Dzhemilev, U. M.; Ibragimov, A. G.; Ramazanov, I. R.; Luk'yanova, M. P.; Sharipova, A. Z.; Khalilov, L. M. *Russ. Chem. Bull. Int. Ed.* **2000**, *49*, 1086–1089.
28. Dzhemilev, U. M.; Ibragimov, A. G.; Khafizova, L. O.; Parfenova, L. V.; Yalalova, D. F.; Khalilov, L. M. *Russ. Chem. Bull. Int. Ed.* **2001**, *50*, 1465–1468.
29. Dzhemilev, U. M.; Ibragimov, A. G.; Khafizova, L. O.; Ramazanov, I. R.; Yalalova, D. F.; Tolstikov, G. A. *J. Organomet. Chem.* **2001**, *636*, 76–81.
30. Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Tolstikov, G. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1989**, *38*, 1324.
31. Dzhemilev, U. M.; Ibragimov, A. G.; Azhgaliev, M. N.; Muslukhov, R. R. *Russ. Chem. Bull. Int. Ed.* **1994**, *43*, 255–257.
32. Dzhemilev, U. M.; Ibragimov, A. G. *J. Organomet. Chem.* **1994**, *466*, 1–4.
33. Dzhemilev, U. M. *Tetrahedron* **1995**, *51*, 4333–4346.

34. Dzhemilev, U. M.; Ibragimov, A. G. *Russ. Chem. Bull. Int. Ed.* **1998**, *47*, 786–794.
35. Dzhemilev, U. M.; Ibragimov, A. G. *Russ. Chem. Rev.* **2000**, *69*, 121–135.
36. Abenhaim, D.; Namy, J. *Tetrahedron Lett.* **1972**, 3011.
37. Dzhemilev, U. M.; Ibragimov, A. G.; Morozov, A. B.; Khalilov, L. M.; Muslukhov, R. R.; Tolstikov, G. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1991**, *40*, 1022–1025.
38. Brown, H. C.; Ravindran, N. *Synthesis* **1973**, 42–44.
39. Dzhemilev, U. M.; Ibragimov, A. G.; Morozov, A. B.; Muslukhov, R. R.; Tolstikov, G. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1991**, *40*, 1425–1427.
40. Dzhemilev, U. M.; Ibragimov, A. G.; Morozov, A. B. *Mendeleev Commun.* **1992**, 26–28.
41. Kauno, K.-I.; Kira, M. *Chem. Lett.* **1999**, 1127–1128.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1287–1291
Tetrahedron

Cyclo- and carbomagnesiation of 1,2-dienes catalyzed by Zr complexes

Usein M. Dzhemilev,* Vladimir A. D'yakonov, Leila O. Khafizova and Askhat G. Ibragimov

Institute of Petrochemistry and Catalysis, Bashkortostan Republic Academy of Sciences, and Ufa Scientific Centre of Russian Academy of Sciences, 141 Prospekt Oktyabrya, Ufa 450075, Russian Federation

Received 30 June 2003; revised 29 September 2003; accepted 11 October 2003

Abstract—Cyclo- and carbomagnesiation of 1,2-dienes with $EtMgR'$ (R'=Et, Br) in the presence of Cp_2ZrCl_2 catalyst lead to alkylidenemagnesiocyclopentanes. Deuterolysis provides insights into the reaction pathways.

1. Introduction

Introduction of Zr-containing catalysts into the application of organomagnesium reagents stimulated further investigations directed toward the development of novel synthetic methods to produce 'nonGrignard' organomagnesium compounds.

Carbomagnesiation of olefins with $RMgR'$ (R'=alkyl, Hal) in the presence of Cp_2ZrCl_2 complex was first carried out[1] in 1983 and successfully developed since then,[2–4] and is now widely used for the selective construction of C–C and C–M bonds.[5–13] In 1989, these investigations[1–4] resulted in the discovery of the cyclomagnesiation reaction[14] of olefins which allowed the formation of magnesiumcyclopentanes and (or) 1,4-dimagnesium compounds[15–21] in high regio- and stereoselectivity.

In accordance with the reported data,[8,18,20] the cyclo- and carbomagnesiation reactions of olefins catalyzed by Cp_2ZrCl_2 are envisioned to proceed via zirconacyclopentane intermediates responsible for the formation of magnesiumcyclopentanes (and/or acyclic 1,4-dimagnesium compounds). The chemoselectivity of the reactions was found to depend upon the solvent nature, temperature and the ratio of starting compounds.[8,20]

The reactions of organomagnesium compounds (OMC) were studied predominantly with substrates such as α-olefins, norbornenes[1–4] and α,ω-dienes.[7,18] Conjugated 1,3-dienes are essentially inert toward cyclo- and carbomagnesiation.

We now report on the results of our further investigations in the field of cyclo- and carbomagnesiation of 1,2-dienes specifically alkyl-, aryl- and cycloalkenylsubstituted allenes, in the presence of $RMgR'$ and Zr-containing catalysts.[†]

2. Results and discussion

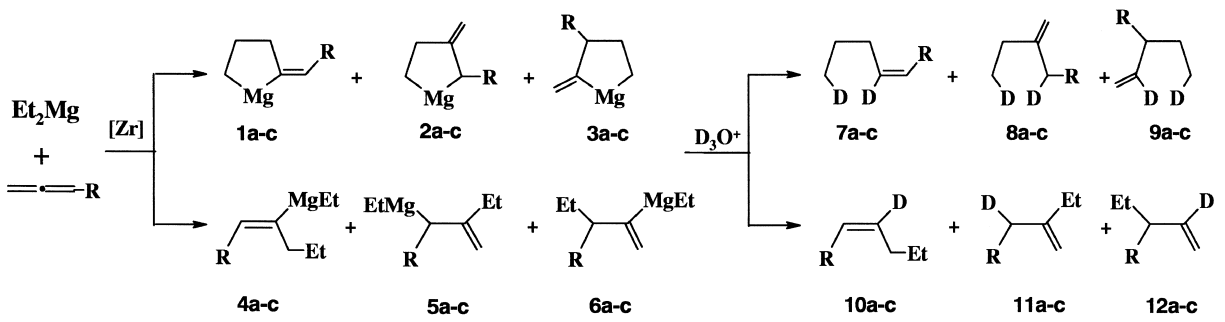
Two different observations are characteristic for the interaction of 1,2-alkadienes and organomagnesium reagents. Thus, the reaction of allenes with Et_2Mg (twofold excess) in diethyl ether (Et_2O) effected by catalytic amounts of Cp_2ZrCl_2 (5 mol%) under the optimized conditions (Et_2O, ~0 °C, 8 h) was found to produce a mixture of regioisomeric magnesiocyclopentanes **1**, **2**, **3** (and/or 1,4-dimagnesium compounds) and the minor products of carbomagnesiation **4**, **5** and **6**, established by deuterolysis (Scheme 1). The reaction mixture upon deuterolysis afforded di- (**7**/**8**/**9**=6:3:1) and monodeuterated olefins (**10**/**11**/**12**=6:3:1) in a ratio of approximately 6:1 (in accord with mass spectral analysis) in a combined yield of 80%. This process did not proceed in the presence of Cp_2TiCl_2.

In contrast to the previous reaction, the interaction between Et_2Mg and allenes in tetrahydrofuran (THF) in the presence of Cp_2ZrCl_2 catalyst at ambient temperature was found to generate predominantly the carbomagnesiation adducts **4**, **5** and **6**, which on deuterolysis afforded a mixture of mono-

Keywords: Catalysis; Zr complexes; Organomagnesium compounds; Cyclomagnesiation; Carbomagnesiation; 1,2-Dienes; Deuterolysis.
* Corresponding author. Fax: +7-3472-312750;
e-mail address: ink@anrb.ru

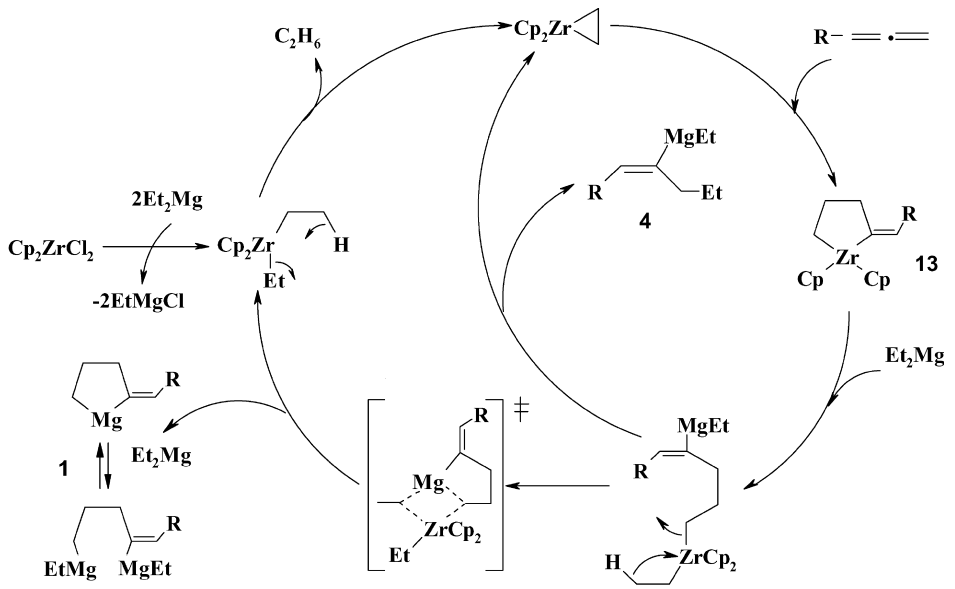
[†] For comparison, in certain experiments Ti complexes were used as catalysts to gain insight into the factors influencing the carbo- and cyclomagnesiation reactions.

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.10.063



a: R = n-C_5H_{11}; b: R = n-C_7H_{15}; c: R = n-CH_2Ph

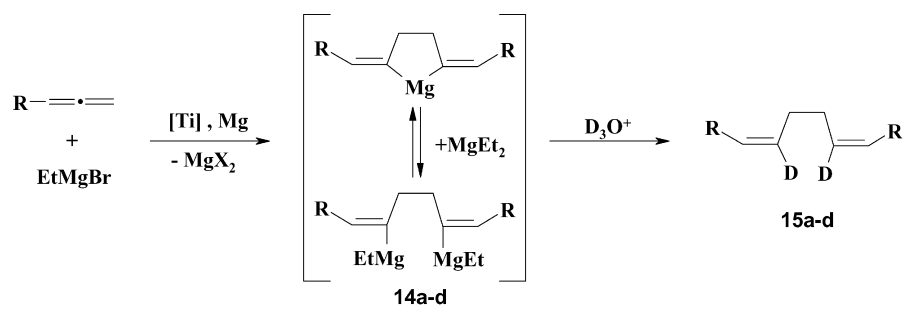
Scheme 1.



Scheme 2.

(**10/11/12**=1:2:2) and dideuterated olefins (**7/8/9**=1:2:2) in a ratio of 8:1 in a combined yield of 76%. In accordance with the reported data,[6,8,18,20] we have represented the formation of cyclic- and acyclic OMC as a sequence of chemical steps combined into a catalytic cycle (Scheme 2), that involves the generation of zirconacyclopentane complexes **13** as the key intermediates. The consecutive transformations of the latter species depending on the reaction conditions affected by Et_2Mg led to adducts of cyclo-(**1**) or carbomagnesiation **4**.

Analogous to the synthesis of aluminacyclopentanes described in literature[22] we have succeeded in the synthesis of magnesiocyclopentanes from RMgHal and Mg (as an acceptor of halogen ions) in the presence of Ti-containing catalysts. Thus, the interaction of 1,2-alkadienes with a twofold excess of EtMgBr in the presence of chemically activated Mg[23] and effected by catalytic amounts of Cp_2TiCl_2 (5 mol%) under the optimum conditions (Et_2O, rt, 8 h) led to 2,5-dialkylidenemagnesiocyclopentanes **14a** and **14b** (and/or 1,4-dimagnesium compounds), which on



[Ti] = Cp_2TiCl_2; X = Cl, Br; a: R = n-C_5H_{11}; b: R = n-C_7H_{15}; c: R = $(CH_2)_2$-C$_6$H$_4$; d: R = CH_2Ph

Scheme 3.

deuterolysis afforded 1,6-dialkyl-2,5-dideuteriohexadienes **15a** and **15b** in a combined yield of more than 90% (Scheme 3).

The replacement of THF by Et_2O did not change product yield and composition of the OMC. However, the use of Cp_2ZrCl_2 as a catalyst instead of Cp_2TiCl_2 decreased the cyclomagnesiation selectivity leading to a regioisomeric mixture of unsaturated OMC. It should be noted that our attempts to effect cyclomagnesiation of allenes using inactivated Mg were unsuccessful.

Similarly, the interaction of ethylmagnesium bromide and 5-(cyclohex-3-enyl)-1,2-pentadiene or 4-phenyl-1,2-butadiene in the presence of Cp_2TiCl_2 catalyst was found to afford **14c** and **14d**.

The selectivity of the cyclomagnesiation of allenes with RMgHal assisted by Cp_2TiCl_2 was established to depend essentially upon the structure of the initial 1,2-diene. Thus, the interaction of phenylallene with ethylmagnesium bromide in the presence of Cp_2TiCl_2 and activated Mg led to unsaturated OMC, which upon deuterolysis afforded a complicated regioisomeric mixture of dideuteriodienes containing di- and trisubstituted double bonds.

3. Conclusion

The interaction between Et_2Mg and 1,2-dienes catalyzed by Cp_2ZrCl_2 was found to afford the products of cyclo- and carbomagnesiation. The reaction of 1,2-dienes with EtMgBr in the presence of activated Mg led to the formation of 2,5-dialkylidenemagnesiumcyclopentanes (and/or unsaturated 1,4-dimagnesium compounds) if Cp_2TiCl_2 was used as a catalyst. These reactions reveal a considerable synthetic potential and are under further investigation in our laboratory.

4. Experimental

4.1. General

All solvents were dried (hexane over $LiAlH_4$, Et_2O and THF over Na) and freshly distilled prior to use. Dialkyl Mg derivatives, prepared from solid Mg alkylate according to a literature method,[24] were used as ethereal solutions. All reactions were carried out under a dry argon atmosphere. The reaction products were analyzed using chromatography on a 'Chrom-5' instrument (2 m×3 mm column packed with 5% of SE-30 and 3 m×3 mm column packed with 5% PEG-6000 on Chromaton N-AW, carrier gas—He). Preparative separation was performed on a 'Carlo Erba Fractovap Mod.GW' instrument (4 m×6 mm column, 5% SE-30 on Chromaton N-AW, helium as a carrier gas, 300 mL min^{-1}). Infrared spectra (IR) were recorded on an IR-75 instrument (thin film). Mass spectral measurements were performed on a MX-1306 spectrometer at 70 eV and working temperature 200 °C. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 'Bruker AM-300' spectrometer (75.46 MHz for ^{13}C and 300 MHz for ^1H). The chemical shifts are reported as δ values in ppm relative to internal standard Me_4Si. NMR ^{13}C spectra were edited by *J*-modulation (JMOD) on CH constants.

4.2. Cyclomagnesiation of 1,2-dienes with Et_2Mg catalyzed by Cp_2ZrCl_2 (method A)

A 50 mL glass reactor was charged with Et_2Mg (1.5 M solution in diethyl ether, 25 mmol), 1,2-diene (10 mmol) and Cp_2ZrCl_2 (0.5 mmol) under a dried argon atmosphere at 0 °C and stirred for 10 h. The reaction mixture was allowed to warm to room temperature and quenched with an 8–10% aqueous solution of HCl (or DCl, 10–12% solution in D_2O). The crude products were extracted with Et_2O or hexane. After the solvent was removed, the residue was distilled in vacuo, and pure adducts were separated by the preparative GLC.

4.3. Carbomagnesiation of 1,2-dienes with Et_2Mg catalyzed by Cp_2ZrCl_2 (method B)

A 50 mL glass reactor was charged with Et_2Mg (1.5 M solution in THF, 25 mmol), 1,2-diene (10 mmol) and Cp_2ZrCl_2 (0.5 mmol) under a dried argon atmosphere at 0 °C. The resulting solution was allowed to warm to rt (ca. 20 °C) and stirred for 10 h. The reaction mixture quenched with an 8–10% aqueous solution of HCl (or DCl, 10–12% solution in D_2O). The crude products were extracted with Et_2O or hexane. After the solvent was removed, the residue was distilled in vacuo, and pure adducts were separated by the preparative GLC.

4.3.1. 1,4-Dideuteriodec-4*Z*-ene (7a). ^1H NMR ($CDCl_3$): δ 0.89 (t, 5H, *J*=6.0 Hz, CH_2D and CH_3); 1.32 (m, 8H, CH_2), 2.00 (m, 4H, CH_2–=–), 5.38 (t, H, *J*=6.0 Hz, C*H*=CD); ^{13}C NMR ($CDCl_3$): δ 13.47 (t, J_{CD}=19.0 Hz), 14.06, 22.66, 22.82, 29.30, 31.00, 31.62, 32.00, 130.21; IR (thin film): 2920, 2910, 2830, 2160, 1620, 1450, 1370, 1100, 880, 720 cm^{-1}; MS, *m/z*: 142 (M^+). Anal. calcd for $C_{10}H_{18}D_2$: C, 84.43; H, 12.76; D, 2.81. Found: C, 84.23; H, 15.34.

4.3.2. 1,4-Dideuteriododec-4*Z*-ene (7b). ^1H NMR ($CDCl_3$): δ 0.89 (t, 5H, *J*=6.0 Hz, CH_2D and CH_3), 1.32 (m, 10H, CH_2), 2.00 (m, 4H, CH_2–=–), 5.38 (t, H, *J*=6.0 Hz, C*H*=CD); ^{13}C NMR ($CDCl_3$): δ 12.75 (t, J_{CD}=19.0 Hz), 14.15, 22.86, 23.06, 28.95, 29.50, 29.66, 31.05, 31.64, 32.08, 130.21, 130.84 (t, J_{CD}=23.5 Hz); MS, *m/z*: 170 (M^+). Anal. calcd for $C_{12}H_{22}D_2$: C, 84.63; H, 13.02; D, 2.35. Found: C, 84.51; H, 15.16.

4.3.3. (3,6-Dideuteriohex-2*Z*-ene-1-yl)benzene (7c). ^1H NMR ($CDCl_3$): δ 0.91 (t, 2H, *J*=6.0 Hz, CH_2D), 1.38 (m, 2H, CH_2), 2.15 (m, H, CH_2–=–), 3.41 (d, 2H, Ph–C*H*$_2$–=), 5.50 (m, 2H, C*H*=C*H*), 7.25 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 13.53 (t, J_{CD}=19.5 Hz), 22.75, 29.17, 39.07, 125.90, 128.18, 128.45, 128.97, 141.37; MS, *m/z*: 162 (M^+). Anal. calcd for $C_{12}H_{14}D_2$: C, 88.83; H, 8.69; D, 2.46. Found: C, 88.62; H, 10.97.

4.3.4. 2-(2-Deuterioethane-1-yl)-3-deuteriooct-1-ene (8a). ^1H NMR ($CDCl_3$): δ 0.89 (t, 5H, *J*=6.0 Hz, CH_2D and CH_3), 1.32 (m, 8H, CH_2), 2.00 (m, 3H, C*H*$_2$–(C=CH_2)–C*H*D), 4.83 (s, 2H, H_2C=); ^{13}C NMR

($CDCl_3$): δ 12.41 (t, J_{CD}=19.5 Hz), 14.06, 22.81, 27.21, 29.75, 31.43, 31.96, 36.02 (t, J_{CD}=19.0 Hz), 107.82, 151.82; MS, *m/z*: 142 (M^+). Anal. calcd for $C_{10}H_{18}D_2$: C, 84.43; H, 12.76; D, 2.81. Found: C, 84.25; H, 15.37.

4.3.5. 2-(2-Deuterioethane-1-yl)-3-deuteriodec-1-ene (8b). ^1H NMR ($CDCl_3$): δ 0.89 (t, 5H, *J*=6.0 Hz, CH_2D and CH_3), 1.32 (m, 12H, CH_2), 2.00 (m, 3H, C*H*$_2$–(C=CH_2)–C*H*D), 4.85 (s, 2H, H_2C=); ^{13}C NMR ($CDCl_3$): δ 12.41 (t, J_{CD}=19.5 Hz), 14.06, 22.84, 27.23, 29.50, 29.75, 28.95, 31.44, 32.03, 36.08 (t, J_{CD}=19.0 Hz), 107.85, 151.84; MS, *m/z*: 170 (M^+). Anal. calcd for $C_{12}H_{22}D_2$: C, 84.63; H, 13.02; D, 2.35. Found: C, 84.44; H, 15.11.

4.3.6. 2-(2-Deuterioethane-1-yl)-3-deuterio-3-benzylprop-1-ene (8c). ^1H NMR ($CDCl_3$): δ 0.91 (t, 2H, *J*=6.0 Hz, CH_2D), 2.20 (m, 3H, C*H*D–C=CH_2–C*H*$_2$), 3.41 (d, 2H, Ph–C*H*$_2$), 4.92 (s, 2H, H_2C=), 7.20 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 11.58 (t, J_{CD}=19.5 Hz), 33.43, 34.41, 38.76 (t, J_{CD}=19.0 Hz), 108.21, 125.90, 128.45, 128.97, 141.37, 148.52; MS, *m/z*: 162 (M^+). Anal. calcd for $C_{12}H_{14}D_2$: C, 88.83; H, 8.69; D, 2.46. Found: C, 88.59; H, 10.94.

4.3.7. 2-Deuterio-3-(2-deuterioethane-1-yl)oct-1-ene (9a). ^1H NMR ($CDCl_3$): δ 0.91 (t, 5H, *J*=6.0 Hz, CH_2D and CH_3), 1.32 (m, 10H, CH_2), 1.95 (m, H, C*H*–C=C), 4.69 (s, 2H, H_2C=CD); ^{13}C NMR ($CDCl_3$): δ 13.89 (t, J_{CD}=20.5 Hz), 14.22, 22.80, 27.29, 27.74, 29.56, 34.77, 45.82, 113.96; MS (*m/z*, %): 142 (4, M^+), 113 (2), 112 (15), 85 (7), 71 (100), 57 (38), 43 (64), 29 (38). Anal. calcd for $C_{10}H_{18}D_2$: C, 84.43; H, 12.76; D, 2.81. Found: C, 84.29; H, 15.42.

4.3.8. 2-Deuterio-3-(2-deuterioethane-1-yl)dec-1-ene (9b). ^1H NMR ($CDCl_3$): δ 0.91 (t, 5H, *J*=6.0 Hz, CH_2D and CH_3), 1.32 (m, 14H, CH_2), 1.95 (m, H, C*H*–C=C), 4.82 (s, 2H, H_2C=CD); ^{13}C NMR ($CDCl_3$): δ 13.78 (t, J_{CD}=20.5 Hz), 14.25, 22.84, 27.74, 27.94, 29.52, 29.80, 32.10, 34.90, 45.96, 115.04; MS, *m/z*: 170 (M^+). Anal. calcd for $C_{12}H_{22}D_2$: C, 84.63; H, 13.02; D, 2.35. Found: C, 84.41; H, 15.13.

4.3.9. 2,5-Dideuterio-3-benzylpent-1-ene (9c). ^1H NMR ($CDCl_3$): δ 0.91 (t, 2H, *J*=6.0 Hz, CH_2D), 1.33 (m, 2H, CH_2), 2.20 (m, H, C*H*–CD=CH_2), 3.44 (d, 2H, Ph–C*H*$_2$), 4.85 (s, 2H, C*H*$_2$=CD), 7.10 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 12.33 (t, J_{CD}=19.5 Hz), 28.91, 41.48, 41.52, 114.57, 125.90, 128.45, 128.97, 141.37; MS, *m/z*: 162 (M^+). Anal. calcd for $C_{12}H_{14}D_2$: C, 88.83; H, 8.69; D, 2.46. Found: C, 88.65; H, 11.01.

4.4. Reaction of 1,2-dienes with EtMgBr catalyzed by Cp_2TiCl_2 in the presence of activated Mg (method C)

A 50 mL glass reactor was charged with chemically activated Mg (12 mmol), EtMgBr (2 M solution in diethyl ether, 22 mmol), Cp_2TiCl_2 (0.5 mmol) and 1,2-diene (10 mmol) under a dried argon atmosphere at 0 °C. The resulting solution was allowed to warm to rt and stirred for 10 h. The reaction mixture was quenched with an 8–10% aqueous solution of HCl (or DCl, 10–12% solution in D_2O). The crude products were extracted with Et_2O or hexane and purified by distillation in vacuo.

4.4.1. 7,10-Dideuteriohexadeca-6*Z*,10*Z*-diene (15a). Bp 114–115 °C (2 Torr). ^1H NMR ($CDCl_3$): δ 0.89 (t, 6H, *J*=6.0 Hz, CH_3), 1.28 (m, 12H, CH_2), 2.06 (m, 8H, C*H*$_2$–=), 5.38 (t, 2H, *J*=5.0 Hz, *H*C=CD); ^{13}C NMR ($CDCl_3$): δ 14.05, 22.61, 27.23, 27.41, 29.45, 31.56, 128.58 (t, J_{CD}=23.5 Hz), 130.02; MS (*m/z*, %): 224 (4, M^+), 167 (0.6), 153 (9), 140 (9), 112 (4.6), 98 (6.6), 84 (13), 71 (7), 70 (100), 57 (14.6), 43 (19), 29 (40). Anal. calcd for $C_{16}H_{28}D_2$: C, 85.64; H, 12.58; D, 1.78. Found: C, 85.89; H, 14.21. Yield 94%.

4.4.2. 9,12-Dideuterioeicosa-8*Z*,12*Z*-diene (15b). Bp 155–156 °C (2 Torr). ^1H NMR ($CDCl_3$): δ 0.89 (t, 6H, *J*=6.0 Hz, CH_3), 1.21 (m, 20H, CH_2), 1.98 (m, 8H, C*H*$_2$–=), 5.30 (t, 2H, *J*=5.0 Hz, *H*C=CD); ^{13}C NMR ($CDCl_3$): δ 14.12, 22.72, 27.34, 27.35, 29.27, 29.29, 29.82, 31.97, 128.96 (t, J_{CD}=23.5 Hz), 130.40. Anal. calcd for $C_{20}H_{36}D_2$: C, 85.63; H, 12.94; D, 1.43. Found: C, 85.88; H, 14.19. Yield 92%.

4.4.3. 4,7-Dideuterio-1,10-(dicyclohex-3-ene-1-yl)deca-3*Z*,7*Z*-diene (15c). Bp 190–192 °C (1 Torr). ^1H NMR ($CDCl_3$): δ 1.10–2.45 (m, 26H, CH and CH_2), 5.30–5.91 (m, 6H, *H*C=CD and *H*C=C*H* cyclic); ^{13}C NMR ($CDCl_3$): δ 25.23, 27.38, 28.81, 31.81, 31.90, 33.04, 36.62, 126.63, 127.08, 129.17 (t, J_{CD}=22.5 Hz), 130.14. Anal. calcd for $C_{22}H_{32}D_2$: C, 87.93; H, 10.73; D, 1.33. Found: C, 88.19; H, 11.85. Yield 90%.

4.4.4. 3,6-Dideuterio-1,8-diphenylocta-2*Z*,6*Z*-diene (15d). Bp 178–179 °C (1 Torr). ^1H NMR ($CDCl_3$): δ 2.37 (M, 4H, –C*H*$_2$–=), 3.36 (d, 4H, *J*=7.0 Hz, Ph–C*H*$_2$–), 5.52 (t, 2H, *J*=5.0 Hz, C*H*=), 7.15 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$): δ 27.18, 33.47, 125.94, 128.44, 128.64, 128.91, 129.65 (t, J_{CD}=22.5 Hz), 141.18. Anal. calcd for $C_{20}H_{20}D_2$: C, 90.86; H, 7.62; D, 1.51. Found: C, 91.13; H, 8.98. Yield 75%.

Acknowledgements

We thank the Russian Foundation of Basic Research (Project Nos. 03-03-33050 and 02-03-97904) for financial support.

References and notes

1. Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1983**, 218–220.
2. Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M.; Kukovinets, A. G.; Khalilov, L. M. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1984**, 2053–2060.
3. Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1985**, 1430–1433.
4. Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285*, 43–45.
5. Hoveyda, A. H.; Xu, Z. M. *J. Am. Chem. Soc.* **1991**, *113*, 5079–5080.

6. Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266–6268.
7. Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268–6270.
8. Lewis, D. P.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *32*, 6797–6800.
9. Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950–8952.
10. Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z. *J. Am. Chem. Soc.* **1992**, *114*, 6692–6697.
11. Rousset, C. J.; Negishi, E.; Suzuki, N.; Takahashi, T. *Tetrahedron Lett.* **1992**, *33*, 1965–1968.
12. Houri, A. F.; Didiuk, M. T.; Xu, Z. M.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614–6624.
13. Hoveyda, A. H.; Morken, J. P. *J. Org. Chem.* **1993**, *58*, 4237–4244.
14. Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G.; Muslukhov, R. R. Tezisy of Vsesouyznoi konferentsii 'Primenenie metallokompleksnogo kataliza v organicheskom sinteze'; 1989; Ufa; p 40.
15. Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G.; Tolstikov, G. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1991**, *40*, 1229–1234.
16. Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G.; Muslukhov, R. R.; Lomakina, S. I.; Tolstikov, G. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1992**, *41*, 770–788.
17. Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G. *Russ.Chem. Bull. Int. Ed.* **1993**, *42*, 149–153.
18. Knight, K. S.; Wang, D.; Waymouth, R. M.; Ziller, *J. Am. Chem. Soc.* **1994**, *116*, 1845–1854.
19. Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G. *J. Organomet. Chem.* **1995**, *491*, 1–10.
20. Lewis, D. P.; Whitby, R. J. *Tetrahedron* **1995**, *51*, 4541–4550.
21. Negishi, E.; Rousset, C. I.; Choveiry, D.; Maye, I. P.; Suzuki, N.; Takahashi, T. *Inorg. Chim. Acta* **1998**, *280*, 8–20.
22. Dzhemilev, U. M.; Ibragimov, A. G.; Morozov, A. B.; Muslukhov, R. R.; Tolstikov, G. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1991**, *40*, 1425–1427.
23. Lai, Y.-H. *Synthesis* **1981**, 585–604.
24. Strohmeier, W.; Seibert, F. *Chem. Ber.* **1961**, *94*, 2356–2357.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1293–1299
Tetrahedron

Rhodium-catalyzed 1,4-addition of alkenylzirconocene chlorides to electron deficient alkenes

Akito Kakuuchi, Takeo Taguchi and Yuji Hanzawa*

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 27 June 2003; accepted 6 August 2003

Abstract—The 1,4-conjugated addition of alkenylzirconocene chloride complexes to α,β-enones, α,β-enoic acid esters, and α,β-enoic acid amides can be efficiently achieved by the use of $[RhCl(cod)]_2$ catalyst. A high diastereoselectivity (95% yield, 90% de) was obtained through the reaction of α,β-enoic acid amide derived from Oppolzer's sultam and 2-butenoyl chloride, while the use of Evans' chiral oxazolidinone as a chiral auxiliary in place of Oppolzer's sultam gave a poor diastereoselectivity (98% yield, 26% de).

1. Introduction

The 1,4-addition of organometallic reagents is an important procedure in organic synthesis, and various organometallic reagents or catalysts which lead to an excellent selectivity for the 1,4-addition have been devised.[1] In the past decade, we have witnessed a progress in rhodium (Rh)-catalyzed 1,4-additions of organometallic reagents to activated alkenes, and various kinds of organometallic reagents in Rh(I)-catalyzed reactions have been employed.[2] Particularly, the 1,4-addition of organoboronic acid derivatives to α,β-enone compounds highlights the efficiency of the Rh(I)-catalyst not only for high chemical yields but also for an applicability to enantioselective reaction.[3] Recently, we reported that the $[RhCl(cod)]_2$-catalyzed (2 mol%) nucleophilic addition of alkenylzirconocene chlorides to *N*-*p*-toluenesulfonyl aldimines afforded allylic amine derivatives in excellent yields under mild reaction conditions.[4] The reaction was the first use of the organozirconocene chloride complex as an organometallic reagent in the Rh(I)-catalyzed reactions and also the first catalytic addition of the organozirconocene chloride complex to imine derivatives.[5] Organozirconocene chloride complexes are readily available by the hydrozirconation of alkenes or alkynes with Schwartz reagent (Cp_2ZrHCl)[6] or by the oxidative insertion of a zirconocene equivalent (Cp_2Zr–1-butene complex) to vinyl halide derivatives.[7] Thus, the exploitation of new reactions of the organozirconocene chloride complexes would increase their significance as an organometallic reagent in organic syntheses. The catalytic 1,4-conjugate addition of alkyl- or alkenylzirconocene chlorides to α,β-unsaturated compounds has been reported by the use of a Cu(I) catalyst[8] or by the use of a low valent Ni catalyst generated in situ.[9] In our study of Rh(I)-catalyzed reactions of the organozirconocene chloride complexes, we are tempted to examine the 1,4-conjugate addition to α,β-enone compounds. Herein, we report on an efficient Rh(I)-catalyzed 1,4-conjugate addition of alkenylzirconocene chlorides **1** to electron deficient olefins such as, α,β-enones **2**, α,β-enoic acid esters **3**, and α,β-enoic acid amides **4**, and the diastereoselective 1,4-addition to chiral acid amide derivatives (Scheme 1).

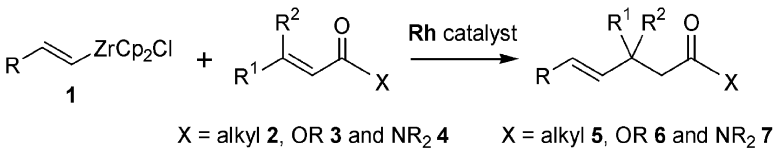
2. Results and discussion

Based on our reported reaction conditions for the Rh(I)-catalyzed additions of alkenylzirconocene chlorides **1** to imines,[5] we examined the 1,4-addition reactions of **1** (2–3 equiv.) to α,β-unsaturated compounds, **2**, **3**, and **4** in the presence of 2 mol% $[RhCl(cod)]_2$ catalyst.

Thus, the 2 mol% $[RhCl(cod)]_2$-catalyzed addition reaction of (*E*)-3,3-dimethyl-1-butenyl zirconocene chloride (**1a**)[10] to **2** in dioxane proceeded smoothly (2 h) at an ambient temperature to give 1,4-addition product **5** in good yields (entries 1–10, Table 1). Although the other Rh(I)-catalysts ($[Rh(cod)_2]BF_3$ or $[Rh(OH)(cod)]_{2)}$ or solvents (toluene or THF) are also efficient in bringing about the reaction, the neutral $[RhCl(cod)_2]$ catalyst, both in terms of the reaction rate and product yield, would be sufficient for the present purpose. The Rh(I)-catalyst did not restrict the 1,4-addition of **1a** to α,β-enones **2**, and thus, α,β-enoic acid esters **3** (entries 11–14) or α,β-enoic acid amides **4** (entries 15–18) are also efficient reactants for the 1,4-addition. In the reactions of **3**, there is not a significant difference in the reactivity of the bulky and small esters **3a-c** (entries 11–13).

* Corresponding author. Tel.: +81-426-76-3274; fax: +81-426-76-3257; e-mail address: hanzaway@ps.toyaku.ac.jp

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.08.073



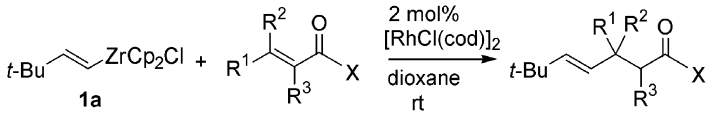
Scheme 1.

In regards to the reactions of **4**, the absence of amide hydrogen is preferable (entry 15), and thus, 1-piperidinyl **4b**[11] or 1-oxazolidin-2-one amide **4c**[12] gave 1,4-adduct **7** in excellent yields (entries 16–18). It has been reported that no reactivity of *N*,*N*-dialkyl derivative such as **4b** in the Rh-catalyzed addition of arylboronic acid.[13] Thus, the present addition of **1a** to **4b** (entry 16) could indicate a high efficiency of organozirconocene chloride complexes under the Rh-catalyzed conditions. In the reactions of β-unsubstituted **2c** and **2e**, a drop in the reaction rate (5 h) and product yield (~30%) was noted, and the improved yields were obtained by the use of 3 equiv of **1a** (entries 3 and 5). The similar β-substituent effect has also been reported in the Rh(I)-catalyzed conjugate addition of organotin compounds to α,β-enones.[14] In the reaction of **3a**, D_2O treatment of the reaction mixture yielded α-deuterated **6a** (>90 %D).[15] It should be mentioned that an alkylzirconocene chloride was an inefficient reagent under the present reaction conditions, and the same inefficiency has been noted in the Rh(I)-catalyzed reaction with imines.[5] Since the transfer of alkyl group from Zr to Rh is slower than the alkenyl group,[16] the present 1,4-addition reaction of **1** is considered to involve the formation of alkenylrhodium species **8** by the transmetalation at the initial stage. The overall process could be depicted as shown in Figure 1, in which the 1,4-adducts are driven out from a catalytic cycle as a Zr-enolate **9**. The addition of a phosphine ligand to the reaction mixture retarded the present Rh(I)-catalyzed 1,4-additions of the alkenylzirconocene chloride **1** to α,β-unsaturated carbonyl compounds.

The efficient additions of **1** to α,β-enoic acid amides **4** under the present conditions led us to examine the diastereoselective 1,4-addition of **1** to chiral α,β-enoic acid amides **10**. The diastereoselective 1,4-additions of **1** to chiral α,β-enoic acid amides **10** derived form 2-butenoyl chloride and chiral amine derivatives are shown in Table 2.

Poor diastereoselectivity has been observed by the use of Evans' chiral oxazolidinone **10a**, **b**[17] (**11a** 96% yield, 11% de and **11b** 98% yield, 26% de) as a chiral auxiliary. A change in the steric environment of the chiral oxazolidinone showed a slight increase in diastereoselectivity (entries 1 and 2). The use of Oppolzer's sultam **10c**,[18] however, induced a much higher diastereoselectivity (88–90% de) to give adducts **11c** and **11d** in an excellent chemical yield, respectively (entries 3 and 4). The diastereomeric ratio of **11** could be determined by HPLC and ^1H NMR analyses of the reaction mixtures. The diastereomeric mixture (95:5) of **11d** was purified by column chromatography to give a pure major isomer of **11d**, $[\alpha]_D^{25}=-65.4$ (*c* 1.02, $CHCl_3$), in 90% yield. The absolute configuration of the newly created chiral center of the major isomer of **11d** was determined to be *S*-configuration by converting to the known methyl

Table 1. 2 mol% $[RhCl(cod)]_2$-catalyzed 1,4-addition reactions of **1a**[a]



Entry	X	R^1	R^2	R^3	Reactant	Product	Yield (%)[b]
1	Ph	Ph	H	H	**2a**	**5a**	93
2	Ph	CH_3	H	H	**2b**	**5b**	60
3	Ph	H	H	CH_3	**2c**	**5c**	72[c]
4	Ph	CH_3	CH_3	H	**2d**	**5d**	56
5	Ph	H	H	H	**2e**	**5e**	98[c]
6	CH_3	Ph	H	H	**2f**	**5f**	94
7	*n*-C_8H_{17}	CH_3	H	H	**2g**	**5g**	53
8		Cyclopent-2-enone			**2h**	**5h**	74
9		Cyclohex-2-one			**2i**	**5i**	93
10		Cyclopent-2-enone			**2j**	**5j**	91
11	CH_3O	Ph	H	H	**3a**	**6a**	93
12	*i*-PrO	Ph	H	H	**3b**	**6b**	90
13	*t*-BuO	Ph	H	H	**3c**	**6c**	96
14	CH_3O	*n*-C_5H_{11}	H	H	**3d**	**6d**	90
15	$PhCH_2NH$	CH_3	H	H	**4a**	**7a**	68
16	Piperidinyl	CH_3	H	H	**4b**	**7b**	92
17	Oxazolidine-2-one	CH_3	H	H	**4c**	**7c**	95
18	Oxazolidine-2-one	CH_3	H	H	**4c**	**7d**	85[d]

[a] A ratio of the reagents; [**1a**]/[Reactant]/$[RhCl(cod)]_2$=2:1:0.02.
[b] Isolated yields.
[c] 3.0 equiv. of **1a** was used.
[d] (*E*)-1-HexenylZrCp_2Cl was used.

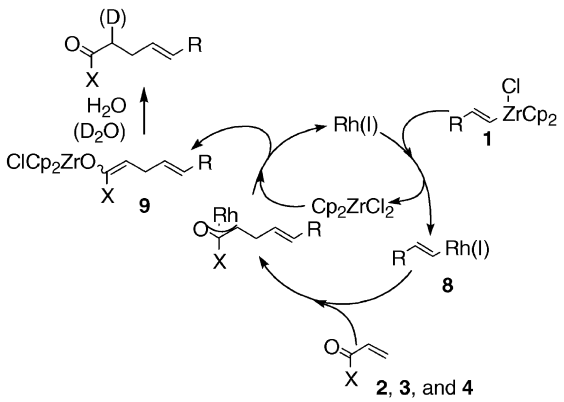
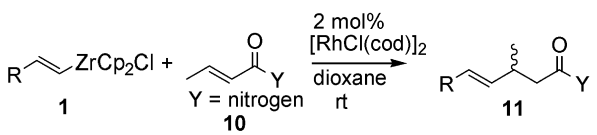
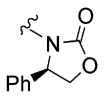
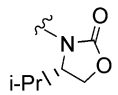
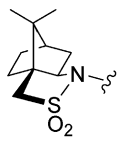


Figure 1. A catalytic cycle for the 1,4-addition reaction of **1**.

Table 2. Diastereoselective 1,4-addition reactions of **1** to **10**

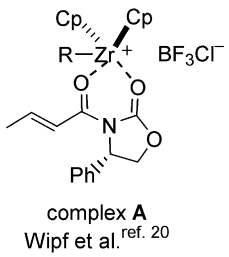


Entry	Y	10	R	11	Yield (%)[a]	de (%)[b]
1		**10a**	*t*-Bu	**11a**	96	11[c]
2		**10b**	*t*-Bu	**11b**	98	26[c]
3		**10c**	*t*-Bu	**11c**	92	88
4		**10c**	*n*-Bu	**11d**	95	90

[a] A mixture of diastereomers.
[b] Determined by HPLC and NMR analyses.
[c] Relative stereochemistry was undetermined.

(3*S*)-3-methyl-4-oxobutanoate (Scheme 2).[19] The relative stereochemistry of the major isomer of **11c** was assigned by analogy with **11d**.

It should be mentioned that in the reported Cu(I)-$BF_3{\cdot}OEt_2$-catalyzed 1,4-additions of alkylzirconocene chloride to **10**,[20] Oppolzer's sultam was a poor auxiliary (19% yield, 9% de), while the Evans' chiral oxazolidinone **10a**, **b** was highly efficient (60–84% yield, 90% de), and the addition of $BF_3{\cdot}OEt_2$ was essential to attain the high diastereoselectivity. It has been proposed that a conformationally rigid cationic zirconocene complex formed by the extrusion of chloride from Cp_2Zr–Cl bond with $BF_3{\cdot}OEt_2$ would have attributed to the high diastereoselectivity (a complex **A** in Fig. 2).[20]



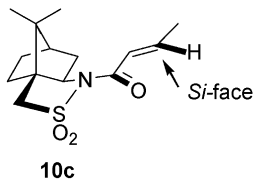
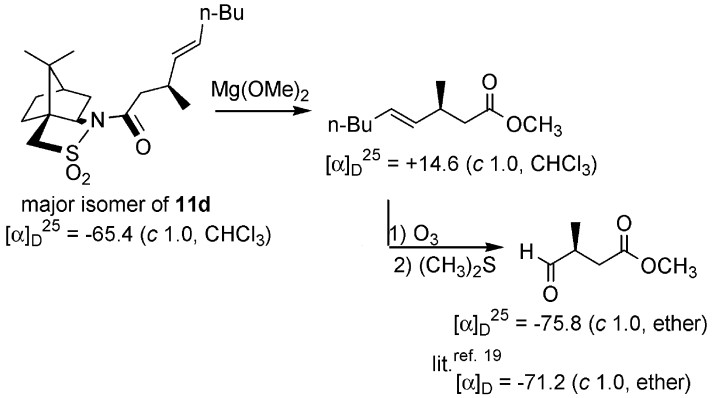


Figure 2. Possible conformation of amide **10c**.

In the present Rh(I)-catalyzed 1,4-addition of **1**, however, the formation of such chelated cationic zirconocene complex is impossible because of the absence of $BF_3{\cdot}OEt_2$, and thus, the use of Evans' chiral oxazolidinone auxiliary poorly discriminated the diastereoface of the carbon–carbon double bond of **10a**, **b** (entries 1 and 2, Table 2). The stereochemical outcome of **11c**, **d** can be explained by invoking a preferential SO_2/C=O *syn* disposition with an *s*–*cis* carbonyl/double bond conformation followed by an attack of alkenyl rhodium **8** to the less hindered alkene *Si*-face at β-carbon (Fig. 2).[21]

3. Conclusion

It has been demonstrated that the highly efficient conjugate addition reactions of alkenylzirconocene chlorides to α,β-enones, -enoic acid esters and -enoic acid amides were brought about by the use of Rh(I) catalyst. The application of the reaction to α,β-enoic acid chiral amides indicated that Oppolzer's sultam turned out to be an excellent chiral auxiliary in terms of diastereoselectivity and chemical yield.



Scheme 2. Absolute stereochemistry of **11e**.

4. Experimental

All non-aqueous reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions. Anhydrous solvents were purchased and used directly without further purification. Materials purchased from commercial suppliers were used without further purification unless otherwise noted. Schwartz reagent (Cp_2ZrHCl) was prepared according to the procedure described by Buchwald et al.[22] Purification of the products was carried out by silica gel column chromatography. Purification by medium pressure silica gel column chromatography (MPLC) was carried out using hexane/ethyl acetate as an eluting solvent and a UV detector at 254 nm. NMR spectra were measured at 300 or 400 MHz for ^1H, and 75.5 or 100.6 MHz for ^{13}C. MS analyses were performed on a spectrometer equipped with a positive electrospray ionization mode (ESI).

4.1. General procedure for the hydrozirconation

Alkyne (1.1 mmol) was added to a suspension of Cp_2ZrHCl (1.0 mmol) in dry CH_2Cl_2 (4 mL) at an ambient temperature, and the mixture was allowed to stir for 15 min. After the removal of the solvent in vacuum, the resulting alkenylzirconocene chloride **1** was dissolved in dry dioxane (4 mL), and the solution was directly used as a 1.0 mmol solution of **1** for the next reaction.

4.2. General procedure for the 1,4-conjugate addition

A solution of α,β-enones **2**, α,β-enoic acid esters **3**, or α,β-enoic acid amides **4** (0.5 mmol) in dry dioxane (1 mL) and $[RhCl(cod)]_2$ (0.01 mmol) were successively added to a 1.0 mmol solution of **1**, prepared as described, at ambient temperature. The reaction mixture was stirred for 1 h before being quenched with saturated aqueous $NaHCO_3$. The solution was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried over $MgSO_4$. The filtered solution was concentrated to dryness in vacuo to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate; a ratio of 10:1 for **5** and **6**, a ratio of 4:1 for **7** and **11**) to give a pure product. Preparation of the analytical sample was carried out by MPLC (hexane/ethyl acetate). The structures of **5b**, **5h**, and **5i** were confirmed by comparing with the authentic samples.[9]

4.2.1. (*E*)-6,6-Dimethyl-1,3-diphenyl-4-hepten-1-one (5a). Mp 51–52 °C. IR (KBr) ν 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 9H), 3.18 (dd, J=6.9, 15.8 Hz, 1H), 3.24 (dd, J=7.8, 15.8 Hz, 1H), 3.91 (q, J=7.1 Hz, 1H), 5.33 (d, J=15.7 Hz, 1H), 5.40 (dd, J=6.8, 15.7 Hz, 1H), 7.03–7.39 (m, 8H), 7.77–7.79 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.5, 32.7, 44.1, 44.9, 126.2, 126.7, 127.5, 128.0, 128.4, 128.5, 132.8, 137.4, 141.8, 144.1, 198.7; ESI m/z 315 $[M+Na]^+$; HRMS Calcd for $C_{21}H_{24}ONa$: 315.1725. Found: 315.1749; Anal. Calcd for $C_{21}H_{24}O$: C, 86.26; H, 8.27; O, 5.47. Found: C, 86.27; H, 8.27.

4.2.2. (*E*)-2,6,6-Trimethyl-1-phenyl-4-hepten-1-one (5c). IR (neat) ν 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.07 (d, J=6.9 Hz, 3H), 2.14 (ddd, J=7.0, 7.4, 13.8 Hz 1H), 2.44 (ddd, J=6.4, 7.4, 13.8 Hz, 1H), 3.46 (m, 1H), 5.26 (dd, J=7.0, 15.6 Hz, 1H), 5.45 (d, J=15.6 Hz, 1H), 7.41–7.55 (m, 3H), 7.92–7.94 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.7, 29.5, 32.8, 36.9, 41.0, 121.4, 128.2, 128.5, 132.7, 136.8, 144.0, 204.0; ESI m/z 253 $[M+Na]^+$; Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63; O, 6.95. Found: C, 83.33; H, 9.62.

4.2.3. (*E*)-3,3,6,6-Tetramethyl-1-phenyl-4-hepten-1-one (5d). IR (neat) ν 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 9H), 1.14 (s, 6H), 2.91 (s, 2H), 5.27 (d, J=16.0 Hz, 1H), 5.33 (d, J=16.0 Hz, 1H), 7.42 (t, J=7.6 Hz, 2H), 7.51 (t, J=7.3 Hz, 1H), 7.89 (d, J=7.6 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.0, 29.5, 32.4, 35.8, 50.0, 128.3, 128.4, 132.5, 133.4, 137.3, 138.6, 200.2; ESI m/z 267 $[M+Na]^+$; HRMS Calcd for $C_{17}H_{24}ONa$: 267.1725. Found: 267.1745.

4.2.4. (*E*)-6,6-Dimethyl-1-phenyl-4-hepten-1-one (5e). IR (neat) ν 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 2.42 (q, J=7.2 Hz, 2H), 3.00 (t, J=7.4 Hz, 2H), 5.38 (td, J=6.6, 15.5 Hz, 1H), 5.51 (td, J=1.1, 15.7 Hz, 1H), 7.43–7.56 (m, 3H), 7.94–7.96 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 27.4, 29.6, 32.7, 38.7, 123.0, 128.0, 128.5, 132.8, 137.1, 142.6, 199.8; ESI m/z 217 $[M+1]^+$; Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32; O, 7.40. Found: C, 83.24; H, 9.40.

4.2.5. (*E*)-7,7-Dimethyl-4-phenyl-5-octen-2-one (5f). IR (neat) ν 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 2.06 (s, 3H), 2.84 (d, J=7.4 Hz, 2H), 3.85 (bq, J=6.9 Hz, 1H), 5.45 (dd, J=5.9, 15.6 Hz, 1H), 5.50 (d, J=15.6 Hz, 1H), 7.17–7.31 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.5, 30.6, 32.8, 43.9, 50.0, 126.3, 126.7, 127.4, 128.4, 141.9, 143.8, 207.3; ESI m/z 231 $[M+1]^+$; Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63; O, 6.95. Found: C, 83.20; H, 9.49.

4.2.6. (*E*)-2,2,5-Trimethyl-3-pentadecen-7-one (5g). IR (neat) ν 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J=6.8 Hz, 3H), 0.94 (s, 9H), 0.96 (d, J=6.7 Hz, 3H), 1.24–1.29 (m, 10H), 1.50–1.55 (m, 2H,), 2.25–2.39 (m, 4H), 2.61 (sep, J=6.9 Hz, 1H), 5.19 (dd, 1H, J=7.4, 15.6 Hz), 5.40 (d, 1H, J=15.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 20.7, 22.6, 23.6, 29.1, 29.2, 29.3, 29.6, 31.7, 32.5, 32.9, 43.5, 50.2, 128.9, 140.3, 210.6; ESI m/z 289 $[M+Na]^+$; HRMS Calcd for $C_{18}H_{34}ONa$: 289.2507. Found: 289.2543.

4.2.7. 3-[(*E*)-3,3-Dimethyl-1-butenyl]cycloheptanone (5j). IR (neat) ν 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.36–1.90 (m, 6H), 2.43–2.61 (m, 5H), 5.23 (dd, J=7.2, 15.6 Hz, 1H), 5.42 (dd, J=1.0, 15.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.0, 28.4, 29.6, 32.6, 37.5, 39.0, 44.0, 50.0, 128.8, 140.1, 214.0; ESI m/z 195 $[M+1]^+$; Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41; O, 8.32. Found: C, 80.29; H, 11.40.

4.2.8. Methyl (*E*)-6,6-dimethyl-3-phenyl-4-heptenoate (6a). IR (neat) ν 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 2.60 (d, J=7.8 Hz, 2H), 3.51 (s, 3H), 3.70 (q, J=7.6 Hz, 1H), 5.38 (dd, J=7.1, 15.7 Hz, 1H), 5.46 (d, J=15.7 Hz, 1H), 7.09–7.23 (m, 5H); ^{13}C NMR (75.5 MHz,

$CDCl_3$) δ 29.6, 32.8, 41.2, 44.9, 51.3, 126.3, 126.4, 126.7, 127.3, 128.5, 142.2, 143.5, 172.3; ESI *m/z* 269 $[M+Na]^+$; HRMS Calcd for $C_{16}H_{22}O_2Na$: 269.1517. Found: 269.1518; Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.09; O, 12.99. Found: C, 77.99; H, 9.02.

4.2.9. *iso*-Propyl (*E*)-6,6-dimethyl-3-phenyl-4-heptenoate (6b). IR (neat) ν 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.14 (d, *J*=6.3 Hz, 3H), 1.18 (d, *J*=6.3 Hz, 3H), 2.65 (d, *J*=7.8 Hz, 2H), 3.79 (q, *J*=7.6 Hz, 1H), 4.93 (sep, *J*=6.3 Hz, 1H), 5.45–5.51 (dd, *J*=7.0, 15.7 Hz, 1H), 5.56 (d, *J*=15.7 Hz, 1H), 7.18–7.32 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 21.8, 29.6, 32.8, 41.6, 44.9, 67.5, 126.3, 126.5, 127.4, 128.4, 141.9, 143.6, 171.5; ESI *m/z* 297 $[M+Na]^+$; HRMS Calcd for $C_{18}H_{26}O_2Na$: 297.1831. Found: 297.1815; Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.77; H, 9.56; O, 11.66. Found: C, 78.77; H, 9.56.

4.2.10. *tert*-Butyl (*E*)-6,6-dimethyl-3-phenyl-4-heptenoate (6c). IR (neat) ν 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.37 (s, 9H), 2.60 (d, *J*=7.8 Hz, 2H), 3.77 (q, *J*=7.6 Hz, 1H), 5.45–5.51 (dd, *J*=6.9, 15.7 Hz, 1H), 5.57 (d, *J*=15.7 Hz, 1H), 7.18–7.31 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.0, 29.6, 32.8, 42.3, 44.9, 80.1, 126.2, 126.7, 127.4, 128.3, 141.7, 143.8, 171.2; ESI *m/z* 311 $[M+Na]^+$; HRMS Calcd for $C_{19}H_{28}O_2Na$: 311.1987. Found: 311.1988; Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78; O, 11.09. Found: C, 79.08; H, 9.75.

4.2.11. Methyl 3-[(*E*)-3,3-dimethyl-1-butene-1-yl]octanoate (6d). IR (neat) ν 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J*=6.7 Hz, 3H), 0.96 (s, 9H), 1.21–1.34 (m, 8H), 2.21 (dd, *J*=8.6, 14.0 Hz, 1H), 2.33 (dd, *J*=6.0, 14.0 Hz, 1H), 2.38–2.42 (m, 1H), 3.62 (s, 3H), 5.06 (dd, *J*=8.6, 15.6 Hz, 1H), 5.44 (d, *J*=15.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.5, 26.6, 29.7, 31.6, 32.7, 34.9, 39.7, 40.9, 51.2, 126.9, 142.4, 173.2; ESI *m/z* 263 $[M+Na]^+$; HRMS Calcd for $C_{15}H_{28}O_2Na$: 263.1987. Found: 263.1980.

4.2.12. (*E*)-*N*-Benzyl-3,6,6-trimethyl-4-heptenamide (7a). Crystals, mp 56–58 °C; IR (neat) ν 3270, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 0.98 (d, *J*=6.8 Hz, 3H), 2.14 (dd, *J*=6.9, 14.1 Hz, 1H), 2.20 (dd, *J*=7.5, 14.0 Hz, 1H), 2.62 (sep, *J*=6.9 Hz, 1H), 4.39 (m, 2H), 5.22 (dd, *J*=7.4, 15.7 Hz, 1H), 5.47 (d, *J*=15.6 Hz, 1H), 6.05 (bs, 1H), 7.24–7.32 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7, 29.6, 32.5, 33.9, 43.4, 44.4, 127.3, 127.7, 128.5, 128.8, 138.3, 140.8, 171.8; ESI *m/z* 282 $[M+Na]^+$; HRMS Calcd for $C_{17}H_{25}NONa$: 282.1834; Found: 282.1811.

4.2.13. (*E*)-3,6,6-Trimethyl-1-(1-piperidinyl)-4-hepten-1-one (7b). IR (neat) ν 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.01 (d, *J*=6.7 Hz, 3H), 1.49–1.64 (m, 6H), 2.20 (dd, *J*=7.9, 14.2 Hz, 1H), 2.33 (dd, *J*=6.6, 14.2 Hz, 1H), 2.61 (sep, *J*=6.9 Hz, 1H), 3.37–3.56 (m, 4H), 5.24 (dd, *J*=7.3, 15.6 Hz, 1H), 5.43 (d, *J*=15.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5, 24.5, 25.6, 26.6, 29.7, 32.5, 33.9, 40.6, 42.6, 47.0, 129.1, 140.0, 170.0; ESI *m/z* 260 $[M+Na]^+$; HRMS Calcd for $C_{15}H_{27}ONNa$: 260.1990. Found: 260.2011.

4.2.14. 3-[(*E*)-3,6,6-Trimethyl-4-heptenoyl]-1,3-oxazolidin-2-one (7c). Mp 33–34 °C; IR (neat) ν 1770, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.04 (d, *J*=6.7 Hz, 3H), 2.65 (sep, *J*=7.0 Hz, 1H), 2.82 (dd, *J*=6.9, 15.3 Hz, 1H), 2.98 (dd, *J*=7.5, 15.3 Hz, 1H), 3.96 (t, *J*=8.1 Hz, 2H), 4.35 (t, *J*=8.1 Hz, 2H), 5.24 (dd, *J*=7.7, 15.6 Hz, 1H), 5.43 (d, *J*=15.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.6, 29.6, 32.5, 33.6, 42.0, 42.4, 61.8, 128.5, 140.6, 153.4, 172.4; ESI *m/z* 262 $[M+Na]^+$; HRMS Calcd for $C_{13}H_{21}O_3NNa$: 262.1419. Found: 262.1433.

4.2.15. 3-[(*E*)-3-Methyl-4-nonenoyl]-1,3-oxazolidin-2-one (7d). IR (neat) ν 1781, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J*=7.1 Hz, 3H), 1.02 (d, *J*=6.8 Hz, 3H), 1.22–1.30 (m, 4H), 1.90–1.95 (m, 2H), 2.67 (sep, *J*=6.8 Hz, 1H), 2.80 (dd, *J*=6.8, 15.7 Hz, 1H), 2.96 (dd, *J*=8.1, 15.7 Hz, 1H), 3.96 (t, *J*=8.1 Hz, 2H), 4.07 (t, *J*=8.1 Hz, 2H), 5.30–5.43 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 20.5, 22.0, 31.5, 32.0, 33.1, 41.9, 42.4, 61.8, 129.5, 133.9, 153.3, 172.2; ESI *m/z* 262 $[M+Na]^+$; HRMS Calcd for $C_{13}H_{21}O_3NNa$: 262.1419. Found: 262.1424.

4.2.16. (4*R*)-4-Phenyl-3-[(3,4*E*)-3,6,6-trimethyl-4-heptenoyl]-1,3-oxazolidine-2-one (minor-11a). Less polar isomer, oil; $[\alpha]_D^{25}=-73.8$ (*c* 0.86, $CHCl_3$); IR (neat) ν 1778, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 9H), 0.98 (d, *J*=6.7 Hz, 3H), 2.64 (sep, *J*=6.9 Hz, 1H), 2.88 (dd, *J*=6.4, 15.4 Hz, 1H), 2.96 (dd, *J*=7.8, 15.4 Hz, 1H), 4.25 (dd, *J*=3.7, 8.9 Hz, 1H), 4.65 (t, *J*=8.8 Hz, 1H), 5.20 (dd, *J*=7.6, 15.6 Hz, 1H), 5.37 (dd, *J*=0.7, 15.3 Hz, 1H), 5.41 (dd, *J*=3.7, 8.8 Hz, 1H), 7.28–7.39 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7, 29.6, 32.5, 33.5, 42.5, 57.5, 69.8, 125.9, 128.4, 128.6, 129.1, 139.2, 140.7, 153.7, 171.6; ESI *m/z* 338 $[M+Na]^+$; HRMS Calcd for $C_{19}H_{25}O_3NNa$: 338.1732. Found: 338.1703.

4.2.17. (4*R*)-4-Phenyl-3-[(3,4*E*)-3,6,6-trimethyl-4-heptenoyl]-1,3-oxazolidine-2-one (major-11a). More polar isomer, crystals, mp 46–47 °C; $[\alpha]_D^{25}=-114.33$ (*c* 0.22, $CHCl_3$); IR (neat) ν 1778, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 9H), 0.97 (d, *J*=6.8 Hz, 3H), 2.66 (sep, *J*=6.8 Hz, 1H), 2.85 (dd, *J*=7.5, 16.2 Hz, 1H), 3.0 (dd, *J*=6.6, 16.2 Hz, 1H), 4.27 (dd, *J*=3.7, 8.9 Hz, 1H), 4.67 (t, *J*=8.9 Hz, 1H), 5.21 (dd, *J*=7.2, 15.7 Hz, 1H), 5.40 (dd, *J*=1.0, 15.7 Hz, 1H), 5.42 (dd, *J*=3.7, 8.7 Hz, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.4, 29.6, 32.5, 32.6, 42.6, 57.6, 69.8, 125.9, 128.6, 128.7, 129.1, 139.1, 140,153.7,171.6; ESI *m/z*338 $[M+Na]^+$; HRMS Calcd for $C_{19}H_{25}O_3NNa$: 338.32. Found: 338.1714.

4.2.18. (4*S*)-4-*iso*-Propyl-3-[(3*,4*E*)-3,6,6-trimethyl-4-heptenoyl]-1,3-oxazolidine-2-one (minor-11b). Less polar isomer, oil; $[\alpha]_D^{25}=+73.3$ (*c* 1.12, $CHCl_3$); IR (neat) ν 1783, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, *J*=6.9 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 3H), 0.95 (s, 9H), 1.06 (d, *J*=6.7 Hz, 3H), 2.29–2.36 (m, 1H), 2.68 (sep, *J*=7.0 Hz, 1H), 2.84 (dd, *J*=8.0, 14.8 Hz, 1H), 2.97 (dd, *J*=6.3, 14.9 Hz, 1H), 4.18 (dd, *J*=3.3, 9.1 Hz, 1H), 4.22 (t, *J*=8.6 Hz, 1H), 4.41 (dt, *J*=3.5, 8.2 Hz, 1H), 5.24 (dd, *J*=7.8, 15.6, 1 Hz), 5.44 (dd, 1H, *J*=0.6, 15.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 17.9, 21.0, 28.4, 29.7,

32.6, 34.0, 42.6, 58.3, 63.1, 128.6, 140.7, 154.0, 172.1; ESI *m/z* 304 $[M+Na]^+$; HRMS Calcd for $C_{16}H_{27}O_3NNa$: 304.1889. Found: 304.1901.

4.2.19. (4*S*)-4-*iso*-Propyl-3-[(3*,4*E*)-3,6,6-trimethyl-4-heptenoyl]-1,3-oxazolidine-2-one (major-11b). More polar isomer, oil; $[\alpha]_D^{25}=+28.3$ (*c* 0.72, $CHCl_3$); IR (neat) ν 1783, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, *J*=6.9 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 3H), 0.96 (s, 9H), 1.04 (d, *J*=6.7 Hz, 3H), 2.30–2.37 (m, 1H), 2.72 (sep, *J*=7.0 Hz, 1H), 2.79 (dd, *J*=8.0, 14.8 Hz, 1H), 3.05 (dd, *J*=6.3, 14.9 Hz, 1H), 4.18 (dd, *J*=3.3, 9.1 Hz, 1H), 4.24 (t, *J*=8.6 Hz, 1H), 4.42 (dt, *J*=3.5, 8.2 Hz, 1H), 5.27 (dd, *J*=7.8, 15.6, 1 Hz), 5.47 (dd, *J*=0.6, 15.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 17.9, 20.6, 28.4, 29.7, 32.6, 32.9, 42.5, 58.4, 63.2, 128.6, 140.5, 154.0, 172.1; ESI *m/z* 304$[M+Na]^+$; HRMS Calcd for $C_{16}H_{27}O_3NNa$: 304.1889. Found: 304.1901.

4.2.20. (4*E*,3*R*)-3,6,6-Trimethyl-4-heptenoyl (*S*)-sultam (minor 11c). Less polar isomer, oil; $[\alpha]_D^{25}=-59.8$ (*c* 1.02, $CHCl_3$); IR (neat) ν 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 0.97 (s, 3H), 1.02 (d, *J*=6.4 Hz, 3H), 1.10 (s, 3H), 1.34–1.42 (m, 2H), 1.84–1.90 (m, 3H), 2.07 (d, *J*=6.3 Hz, 2H), 2.57 (dd, *J*=6.9, 17.6 Hz, 1H), 2.72–2.80 (m, 2H), 3.42 (d, *J*=13.8 Hz, 1H), 3.47 (d, *J*=13.8 Hz, 1H), 3.87 (t, *J*=6.3 Hz, 1H), 5.24 (dd, *J*=7.2, 15.7 Hz, 1H), 5.44 (dd, *J*=0.6, 15.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.9, 20.6, 20.8, 26.4, 29.7, 32.6, 32.8, 33.9, 38.6, 43.2, 44.6, 47.7, 48.2, 53.0, 65.2, 128.6, 140.6, 171.0; ESI *m/z* 390 $[M+Na]^+$; HRMS Calcd for $C_{21}H_{33}NO_3SNa$: 390.2079. Found: 390.2062.

4.2.21. (4*E*,3*S*)-3,6,6-Trimethyl-4-heptenoyl (*S*)-sultam (major 11c). More polar isomer, crystals, mp 109–111 °C; $[\alpha]_D^{25}=-77.4$ (*c* 0.32, $CHCl_3$); IR (neat) ν 1681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3H), 0.96 (s, 3H), 1.03 (d, *J*=6.6 Hz, 3H), 1.15 (s, 3H), 1.31–1.42 (m, 2H), 1.84–1.90 (m, 3H), 2.05 (d, *J*=5.6, 14.6 Hz, 2H), 2.53 (dd, *J*=6.9 Hz, 1H), 2.74–2.84 (m, *J*=7.8, 14.6 Hz, 2H), 3.41 (d, *J*=13.8 Hz, 1H), 3.48 (d, *J*=13.8 Hz, 1H), 3.86 (t, *J*=6.3 Hz, 1H), 5.23 (dd, *J*=6.9, 15.4 Hz, 1H), 5.45 (d, *J*=6.3, 15.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.8, 20.7, 21.0, 26.4, 29.6, 32.6, 32.8, 33.3, 38.5, 42.6, 44.7, 47.7, 48.2, 53.0, 65.2, 128.3, 140.6, 170.9; Anal. Calcd for $C_{20}H_{33}NO_3S$: C, 65.36; H, 9.05; N, 3.81. Found: C, 65.39; H, 8.90; N, 3.80.

4.2.22. (4*E*,3*R*)-3-Methyl-4-nonenoyl (*S*)-sultam (minor 11d). Less polar isomer, oil; $[\alpha]_D^{25}=-61.0$ (*c* 1.0, $CHCl_3$); IR (neat) ν 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.1 Hz, 3H), 0.97 (s, 3H), 1.04 (d, *J*=6.5 Hz, 3H), 1.17 (s, 3H), 1.29–1.40 (m, 7H), 1.85–2.08 (m, 7H), 2.59–2.80 (m, 3H), 3.40 (d, *J*=13.8 Hz), 1H, 3.47 (d, *J*=13.8 Hz, 1H), 3.86 (t, *J*=6.3 Hz, 1H), 5.36 (dd, *J*=6.5, 15.4 Hz, 1H), 5.43 (dt, *J*=6.1, 12.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 19.9, 20.4, 20.8, 22.1, 26.5, 31.7, 32.1, 32.9, 33.7, 38.6, 43.0, 44.8, 47.7, 48.3, 53.1, 65.3, 129.7, 133.0, 170.0.

4.2.23. (4*E*,3*S*)-3-Methyl-4-nonenoyl (*S*)-sultam (major 11d). More polar isomer, oil; $[\alpha]_D^{25}=-65.4$ (*c* 1.0, $CHCl_3$); IR (neat) ν 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J*=6.9 Hz, 3H), 0.94 (s, 3H), 1.01 (d, 3H, *J*=6.6 Hz), 1.12 (s, 3H), 1.23–1.37 (m, 6H), 1.67–2.03 (m, 7H), 2.49 (dd, *J*=5.6, 14.6 Hz, 1H), 2.77 (sep, *J*=6.9 Hz, 1H), 2.81 (dd, *J*=7.8, 14.6 Hz, 1H), 3.39 (d, *J*=13.8 Hz, 1H), 3.47 (d, *J*=13.8 Hz, 1H), 3.84 (t, *J*=6.3 Hz, 1H), 5.31 (dd, *J*=6.9, 15.4 Hz, 1H), 5.40 (dt, *J*=6.3, 15.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 19.8, 20.6, 20.7, 22.1, 26.4, 31.4, 32.0, 32.7, 33.7, 38.4, 42.4, 44.6, 47.6, 48.1, 53.0, 65.1, 129.6, 133.6, 170.9; Anal. Calcd for $C_{20}H_{33}NO_3S$: C, 65.36; H, 9.05; N, 3.81. Found: C, 65.38; H, 8.99; N, 3.58.

4.2.24. (3*S*)-3-Methyl-4-oxobutanoate. To a solution of major-**11d**, $[\alpha]_D^{25}=-65.4$ (*c* 1.0, $CHCl_3$), (377 mg, 1.02 mmol) in MeOH (20 mL) was added a 6–10 wt% solution of $Mg(OMe)_2$ in MeOH (2.1 mL, ca. 2.0 mmol) at 0 °C and the mixture was stirred at 60 °C for 2 h. After adding H_2O, the reaction mixture was extracted with ether. The combined organic layer was washed with brine and dried over $MgSO_4$. The filtered solution was concentrated in vacuo to dryness and the residual oil was purified by silica gel column chromatography (pentane/ether=50:1) to give pure methyl ester, $[\alpha]_D^{25}=+14.6$ (*c* 1.0, $CHCl_3$), (110 mg, 0.6 mmol) in 58% yield. The ester (50 mg, 0.27 mmol) was treated with O_3 in CH_2Cl_2 (6 mL) at −78 °C for 15 min. After bubbling through the mixture with N_2 for 30 min, Me_2S was added at-78 °C and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was dissolved into ether and the solution was washed with brine before drying ($MgSO_4$). The filtered solution was concentrated in vacuo to give a crude product which was purified by silica gel flash column chromatography (pentane/ether=10:1) to give (3*S*)-3-methyl-4-oxobutanoate, $[\alpha]_D^{25}=-75.8$ (*c* 1.0, ether). The NMR spectral data and specific rotation value showed a good agreement to the authentic material reported in Ref. 19.

References and notes

1. For reviews, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. (b) Schmalz, H.-G. *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4. Chapter 1.5. (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
2. For review, see: Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169 and the references therein.
3. For review, see: (a) Hayashi, T. *Synlett* **2001**, 879.
4. Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2003**, *44*, 923.
5. (a) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122. (b) Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773. (c) Wipf, P.; Kendall, C.; Stephenson, C. R. *Chem. Eur. J.* **2002**, *8*, 1778. (d) See also: In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002.
6. Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.
7. Takahashi, T.; Kotora, M.; Fischer, R.; Nishihara, Y.; Nakajima, K. *J. Am. Chem. Soc.* **1995**, *117*, 11039.
8. (a) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494. (b) Wipf, P.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M.

Tetrahedron **1994**, *50*, 1935. (c) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11689.
9. (a) Loots, M.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045. (b) Schwartz, J.; Loots, M.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333. (c) Loots, M. J.; Dayrit, F. M.; Schwartz, *J. Bull. Soc. Chim. Belg.* **1980**, *89*, 897. (d) Dayrit, F. M.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4466.
10. For the sake of the spectral simplicity of the 1,4-addition products, we used *tert*-butyl acetylene as a starting alkyne for the hydrozirconation in most of the examined cases.
11. Wakasugi, K.; Nakamura, A.; Tanabe, Y. *Tetrahedron Lett.* **2001**, *42*, 7424.
12. Knol, J.; Feringa, B. L. *Synth. Commun.* **1996**, *26*, 261.
13. Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944.
14. (a) Oi, S.; Moro, M.; Ono, S.; Inoue, Y. *Chem. Lett.* **1998**, 83. (b) Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, *58*, 91.
15. We have also succeeded in trapping the Zr-enolate **9** (Fig. 1) by a carbon electrophile through an intramolecular aldol reaction, and the results will be published in due course.
16. Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853.
17. (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Nicolas, E.; Russell, K. C.; Hruby, *J. Org. Chem.* **1993**, *58*, 766.
18. Oppolzer, W.; Kingma, A. J.; Poli, G. *Tetrahedron* **2002**, *58*, 91.
19. Bernardi, A.; Cardani, S.; Poli, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 5041.
20. Wipf, P.; Takahashi, H. *Chem. Commun.* **1996**, 2675.
21. Reiser, O. *Organic Synthesis Highlights IV*; Schmalz, H.-G., Ed.; Wiley-VCH: Weinheim, 2000; p 11.
22. Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1301–1308
Tetrahedron

Reaction pathways of zirconocene-catalyzed silylation of alkenes with chlorosilanes

Jun Terao, Yingshi Jin, Kazushi Torii and Nobuaki Kambe*

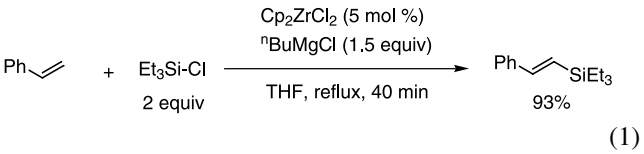
Department of Molecular Chemistry and Science and Technology Center for Atoms, Molecules and Ions Control, Osaka University, Suita, Osaka 565-0871, Japan

Received 4 August 2003; accepted 26 August 2003

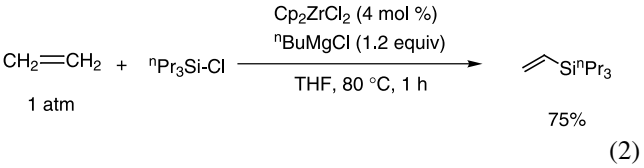
Abstract—Reaction pathways as well as stereochemistries and stoichiometries of zirconocene-catalyzed silylation of olefins with chlorosilanes in the presence of ^{n}BuMgCl were studied and discussed in detail. Rate determining steps were examined by kinetic studies and labeling experiments.

1. Introduction

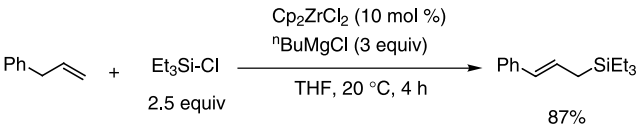
Among a variety of reactions that have been developed for introducing R_3Si moieties into organic molecules, transition metal catalyzed silylation toward carbon–carbon unsaturated bonds have widely been employed as a straightforward and useful method of synthesizing organosilicon compounds.[1] As for the silylating reagents of such reactions, silanes,[2a] disilanes,[2b] silacyclobutanes[2c] or -propanes,[2d] silyl cyanides,[2e] silylgermanes,[2f] silylstannanes,[2g] silylselenides,[2f] and iodosilanes[2h–j] have been employed. Chlorosilanes are the most widely used and easily available silylating reagents in organic synthesis; however, their use in transition metal catalyzed reactions has been limited. This is due to the difficulty of the oxidative addition of the Si–Cl bond to low valent metal complexes.[3] We have reported the first example of transition metal catalyzed silylation of olefins with chlorosilanes by the use of Cp_2ZrCl_2.[4,5] For example, styrene reacted with Et_3SiCl in the presence of ^{n}BuMgCl and a catalytic amount of Cp_2ZrCl_2 in refluxing THF to afford the corresponding alkenylsilane with complete regio- and stereoselectivities as exemplified by Eq. 1. Ethylene gave a vinylsilane at 80 °C in good yield based on the chlorosilane used (Eq. 2). When allylbenzene was employed, only an *E*-allylsilane was obtained as a sole product at room temperature (Eq. 3), whereas alkyl-substituted olefins such as 1-octene affords a mixture of allyl- and vinylsilanes.[4] Herein, we wish to reveal the results obtained in a study performed to shed light on the reaction pathways of this zirconocene-catalyzed silylation of olefins with chlorosilanes.



(1)



(2)



(3)

2. Results and discussion

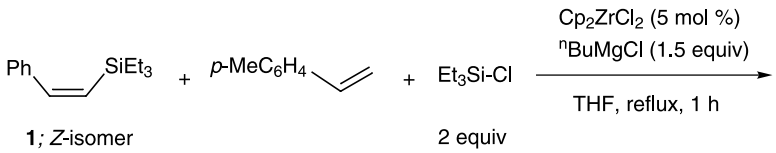
2.1. Stereochemistry

In all reactions using arylalkenes only *E*-isomers of vinylsilanes were formed. In order to determine whether the stereochemistry is controlled kinetically or thermodynamically, we carried out a reaction of *p*-methylstyrene with Et_3SiCl in the presence of *Z*-isomer of β-triethylsilylstyrene **1**. As shown in Eq. 4 only *E*-isomer of β-triethylsilyl-*p*-methylstyrene **2** was obtained in 97% yield and 72% of **1** was recovered as a 20:80 mixture of *E*/*Z* isomers. This result clearly indicates that the stereochemistries of

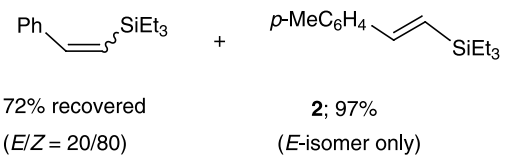
Keywords: Zirconocene; Silylation; Chlorosilanes; Olefins; Grignard reagents.
* Corresponding author. Tel.: +81-6-6879-7388; fax: +81-6-6879-7390; e-mail address: kambe@chem.eng.osaka-u.ac.jp

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.08.077

products are determined kinetically not by the isomerization of products.

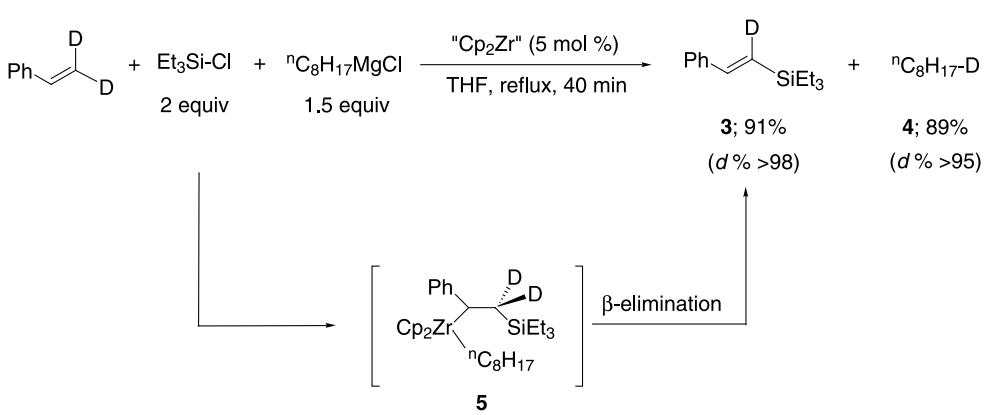


(4)



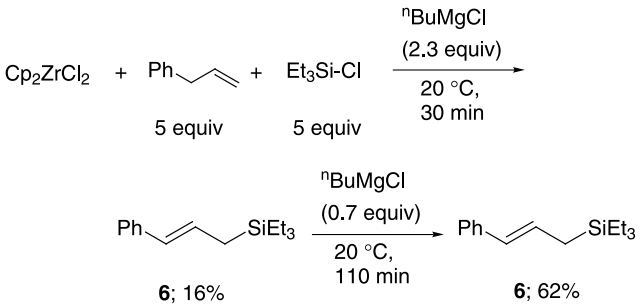
2.2. Stoichiometry of Zr-catalyzed silylation reaction

In this silylation of olefins, vinylic hydrogen is replaced by a silyl group. In order to reveal the exact mass balance of this reaction, we carried out a reaction of styrene-d_2 with Et_3SiCl (2 equiv) and ^{n}OctMgCl (1.5 equiv) in the presence of 5 mol% of 'Cp_2Zr' generated in situ from Cp_2ZrCl_2 and ^{n}BuMgCl.[6] Refluxing the solution for 40 min followed by quenching with 0.1 N HCl_{aq} gave nearly equal amounts of monodeuterated vinylsilane **3** (deuterium content >98%) and octane **4** containing a deuterium at the terminal carbon (deuterium content >95%) (Eq. 5). This result shows that one of the deuterium atoms at the β-carbon of styrene-d_2 was transferred to the α-carbon of the octyl group of the Grignard reagent provably via β-elimination from dialkylzirconocene intermediate **5** (vide infra). The mechanism of β-hydrogen elimination of dialkylzirconocene complexes has been examined and a unique pathway involving direct transfer of a β-hydrogen of one of the alkyl substituents on Zr to an α-carbon of another alkyl group, not via a hydrozirconocene intermediate, has been proposed.[7]



(5)

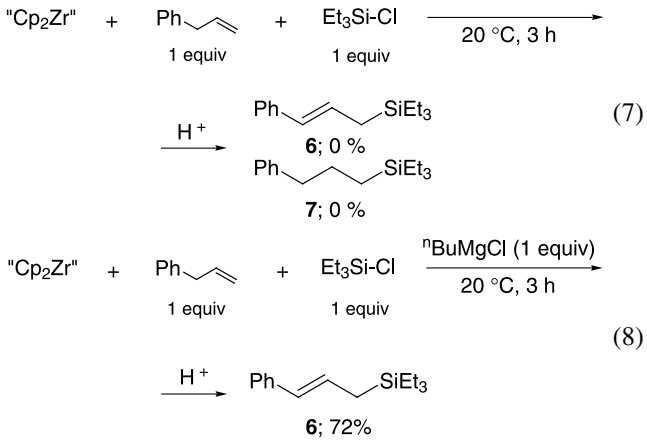
Present silylation reaction provides good yields of products based on the limiting substrates, either on olefins (Eqs. 1 and 3) or on chlorosilanes (Eq. 2); however, we encounter an interesting phenomenon when a limited amount of Grignard reagents was employed. When Cp_2ZrCl_2 was treated with 2.3 equiv. of ^{n}BuMgCl in the presence of 5 equiv. each of allylbenzene and Et_3SiCl, the corresponding allylsilane **6** was obtained only in 16% yield based on Cp_2ZrCl_2 used in 20 min (Eq. 6 and Figure 1). Although the yield of **6** was not improved by elongation of the reaction time, the yield increased up to 62% when 0.7 equiv of ^{n}BuMgCl was introduced additionally to the reaction mixture. It is known that Cp_2ZrCl_2 reacts with 2 equiv. of R-MgX to form Cp_2Zr.[6] This evidence along with the results shown in Eq. 6 and Figure 1 suggests that the products are formed only in the presence of Grignard reagents.



(6)

This phenomenon can more clearly be confirmed by the following control experiments. A reaction of allylbenzene with Et_3SiCl in the presence of a stoichiometric amount of Cp_2Zr, generated in situ by the reaction of Cp_2ZrCl_2 with 2 equiv. of ^{n}BuMgCl, gave no silylated products, such as **6** or **7**, even after quenching the resulting mixture with HCl_{aq} (Eq. 7). On the other hand, a similar reaction in the presence of 1 equiv. of ^{n}BuMgCl (i.e., total amount of ^{n}BuMgCl used is 3 equiv.) afforded **6** in 72% yield (Eq. 8). A reaction of Cp_2Zr with styrene (5 equiv.) and Et_3SiCl under THF reflux condition for 1 h did not afford any silylated products. However, 65% yield of the corresponding vinylsilane was

obtained when a similar reaction was carried out in the presence of 1 equiv. of ^{n}BuMgCl.



2.3. Reaction pathways

Taking into account these results mentioned above and the evidence that zirconocene–ethylene complex reacts with EtMgBr giving rise to zirconate complex,[8] we propose that the present reaction proceeds via zirconate complex **9** that reacts with R'_3SiCl to give dialkylzirconocene **11**, which then undergoes β-elimination to afford **12** (Scheme 1, path A). However, an alternative pathway that involves direct reaction of neutral olefin complexes **8** with chlorosilanes to give **10** may not be ruled out since a neutral zirconocene–ethylene complex $Cp_2Zr(CH_2{=}CH_2)$ reacts with chlorosilanes in the presence of Me_3P to form the corresponding β-silylalkylzirconocene complex.[9] If **10** is formed in only a small amount by an equilibrium process which is biased toward **8**, path B may not be contradicted by the results of Eqs. 6–8.

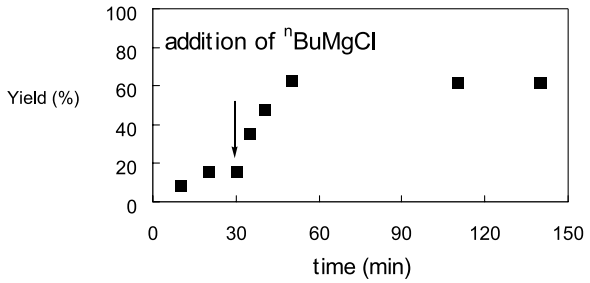
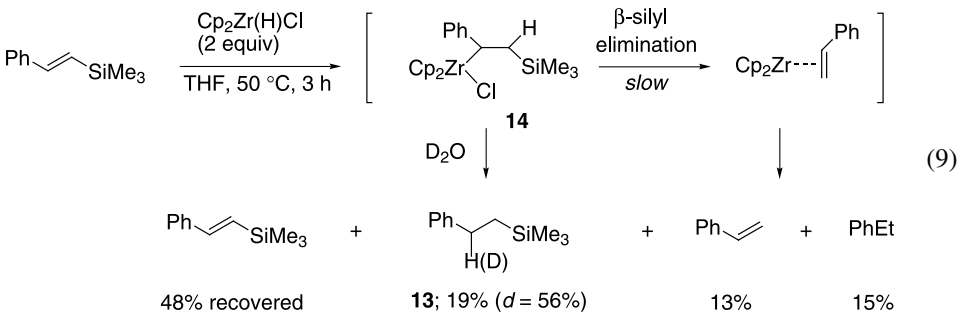
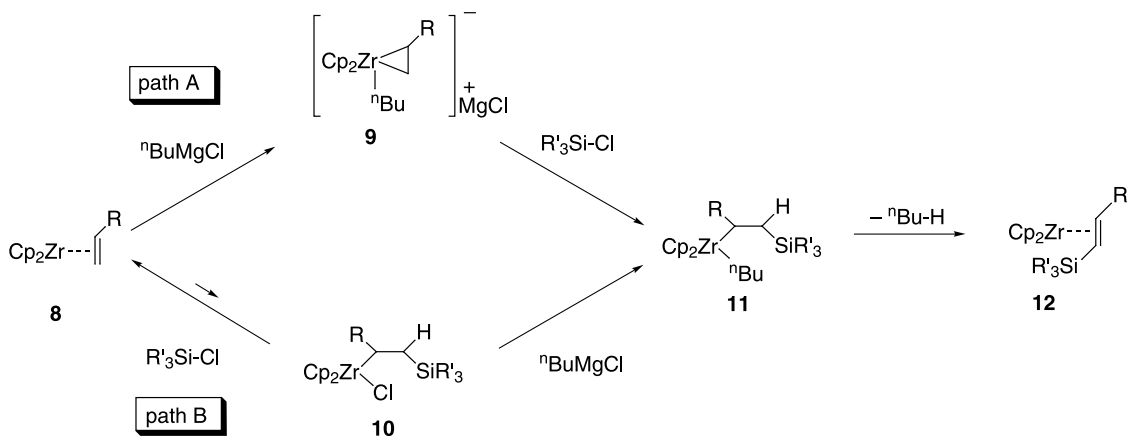


Figure 1.

In order to reveal which path is more likely, we examined whether β-Si elimination process from **10** to **8** can take place rapidly under the present reaction conditions. Since it is known that internal arylalkenes react with Cp_2ZrHCl to give benzylzirconocene complex predominantly,[10] we stirred a THF solution of β-trimethylsilylstyrene and Cp_2ZrHCl at 50 °C for 3 h and quenched the products with D_2O. NMR measurements showed that the resulting mixture contained unreacted β-trimethylsilylstyrene (48% recovered), 19% of saturated silane **13** having a deuterium atom at the benzylic position (56% of deuterium content), 13% of styrene, and 15% of ethylbenzene (Eq. 9). It is likely that incorporation of deuterium in **13** arises from the reaction of **14** with D_2O. Although the formation of styrene and ethylbenzene suggests that β-silyl elimination from **14** proceeds under these conditions, this can not be a rapid process since **14** remained under the conditions of Eq. 9 as suggested by formation of **13**. These results would rule out a possibility of the formation of **10** from **8** in the present reaction.

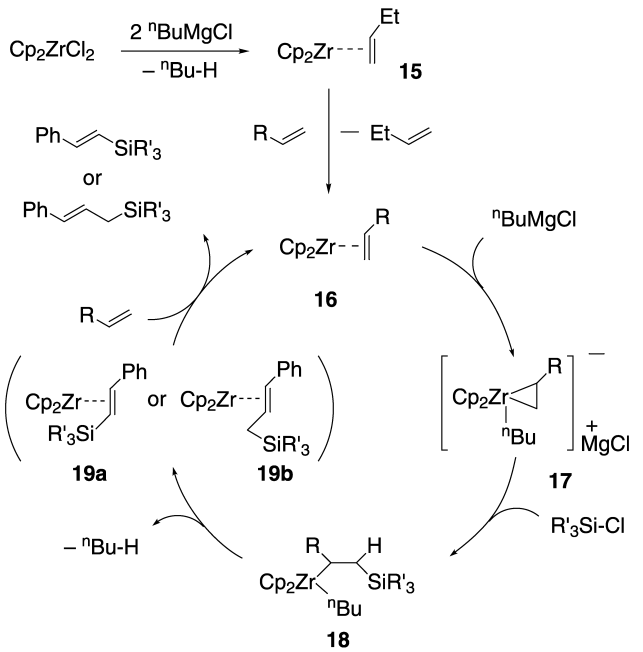




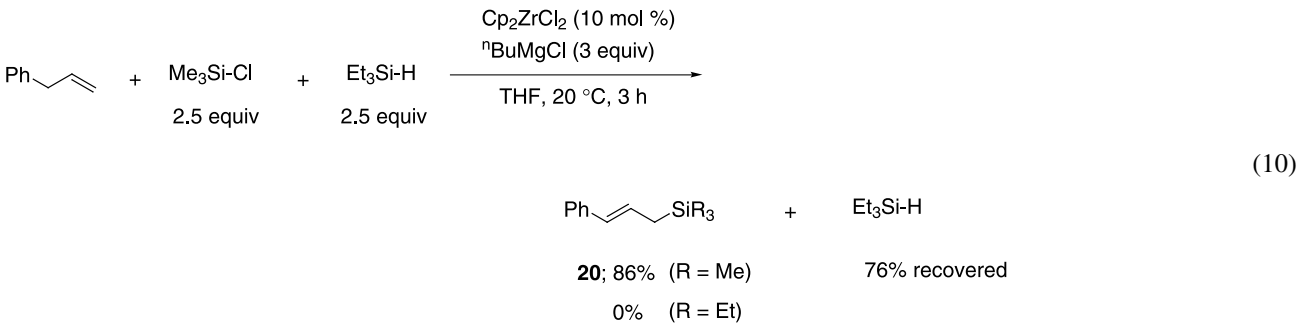
Scheme 1.

A plausible catalytic cycle is shown in Scheme 2. Zirconate complex **17**, formed by the reaction of zirconocene-olefin complex **16** with ^{n}BuMgCl, reacts with chlorosilanes to give dialkylzirconocene complex **18** which undergoes β-hydrogen elimination with removal of one of the β-hydrogen to afford a vinylsilane or allylsilane.

In all of the present silylation reactions examined, a small amount of R_3SiH was formed along with the desired silylation product. Since it is known that Cp_2TiCl_2 catalyzes the reduction of R_3SiCl to R_3SiH[11] in the presence of ^{i}PrMgBr and that $Cp_2Zr^{n}Bu_2$ catalyzes the addition of R_3SiH to olefins,[12] there may still remain a possibility of an alternative pathway involving hydrosilylation process. So we then performed a reaction of allylbenzene with Me_3SiCl in the presence of Et_3SiH. The result that only a trimethylsilylated product **20** was obtained in 86% yield along with 76% recovery of Et_3SiH would suggest that R_3SiH is not involved in this catalytic cycle. When a similar reaction was carried out using styrene, Pr_3SiCl, and Et_3SiH, only tripropylsilylated vinylsilane was obtained in 76% yield and 97% of Et_3SiH was recovered unreacted.



Scheme 2.



2.4. Rate determining steps

To investigate the rate determining step of silylation of styrene with chlorosilanes, we ran the reaction employing different concentrations of substrates in THF at 50 °C for 5 min and quenched with H_2O (Eq. 11 and Fig. 2). Interesting to note, change of the concentration of Et_3SiCl did not affect the product yield indicating that Et_3SiCl is not involved either in the rate determining step or in the preceding equilibrium processes. On the other hand, the yield of the product obeys pseudo first-order kinetics (k=3.9×10^{-5} min^{-1}) on the concentration of styrene. These results suggest that the rate determining step is the ligand exchange process to regenerate zirconocene-styrene complex **21** from **24**. It was also surprising that decreasing the concentration of ^{n}BuMgCl increased the reaction rate. This unexpected phenomenon can be explained by assuming an equilibrium between **24** and **26**. High concentration of ^{n}BuMgCl shifted the equilibrium toward **26** resulting in retardation of the ligand exchange. In fact, when a reaction

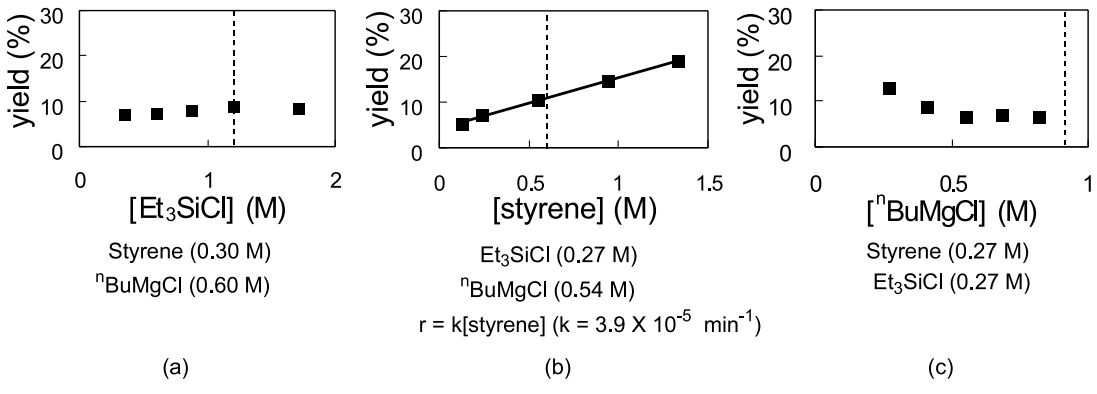
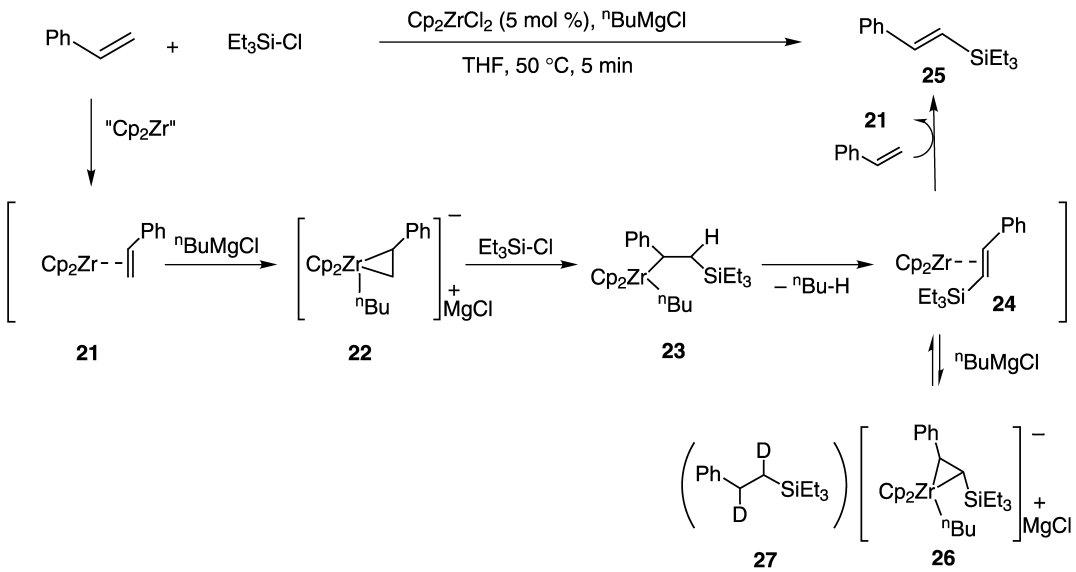


Figure 2. Plots of yields of **25** against concentration of (a) Et_3SiCl, (b) styrene, and (c) ^{n}BuMgCl. The dotted line shows a representative concentration of the standard conditions of this silylation.

mixture was quenched with D_2O after the reaction, a dideuterated silane **27** was obtained, probably by the reaction of **26** with D_2O, in almost the same amount of zirconocene catalyst employed (Fig. 2).

2.5. Mechanisms of C–Si bond forming step

As discussed above carbon–silicon bond forming process is rapid and is not the rate determining step of this silylation reaction. Adopting the intermediary of the ate complex **33**,

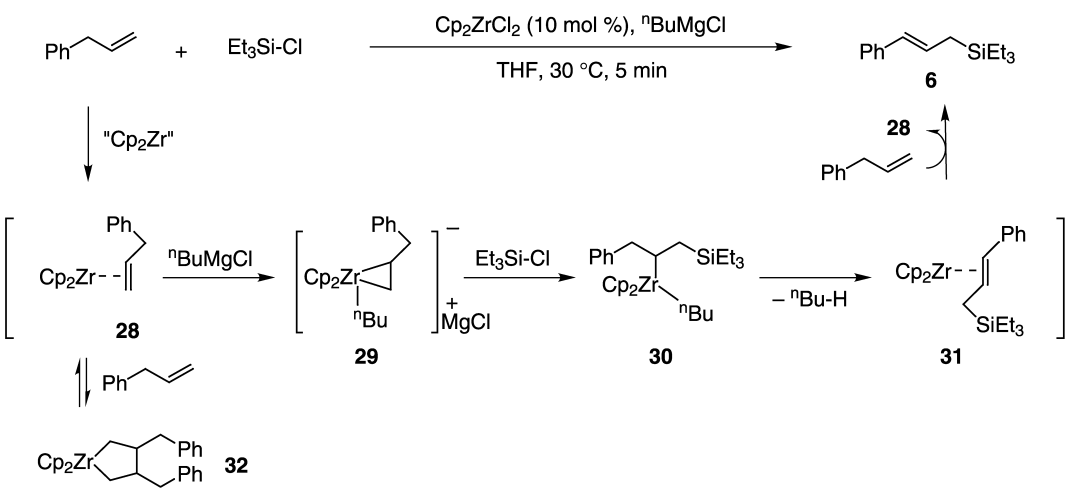


(11)

We next examined the rate determining step of the silylation reaction of allylbenzene by the similar procedures (Eq. 12 and Fig. 3). The rate of allylsilane formation is independent on the concentration of Et_3SiCl as in the case of styrene and also on that of ^{n}BuMgCl. However, the rate surprisingly decreased when the concentration of allylbenzene increased in the region of >0.2 M. With these observations, we would like to propose that the rate determining step is the β-elimination process since the reaction rate was not affected by the concentrations of any substrates in the region of [allylbenzene] <0.2 M. Higher concentration of allylbenzene (>0.2 M) would retard the reaction probably by converting **28** to zirconacyclopentane **32** which is a resting stage of the catalyst. GC and GC-MS analyses of the resulting mixture after quenching with aqueous HCl suggested the formation of a dimerized product of allylbenzene arising by hydrolysis from **32** in ca. 40% based on Cp_2Zr employed (Fig. 3).

we would like to propose three possible mechanisms for this process as shown in Scheme 3. Mechanism A involves electrophilic outside attack of R_3SiCl to the coordinated olefin to give a silylzirconation product **34**. Mechanism B affords **35** via σ-metathesis and mechanism C involves oxidative addition of R_3SiCl to **33** affording a Zr(IV) intermediate and subsequent insertion. In mechanism A, Si and Zr were introduced at vinylic carbons from the opposite sides of olefins and, contrary to this, addition proceeds in *syn* fashion in mechanisms B and C. In order to determine the stereochemistry of this C–Si bond forming process, we prepared *p*-methylstyrenes having one deuterium atom at *trans*- or *cis*-position on the β-carbon (**36** and **37**, respectively) and subjected them to the present silylation reaction.

As mentioned above, only *E*-vinyl silanes were formed from styrenes by kinetic control. If β-elimination of dialkylzirconocene complexes proceeds intramolecularly via direct H shift from the β-carbon of an alkyl group on Zr to the β-carbon



(12)

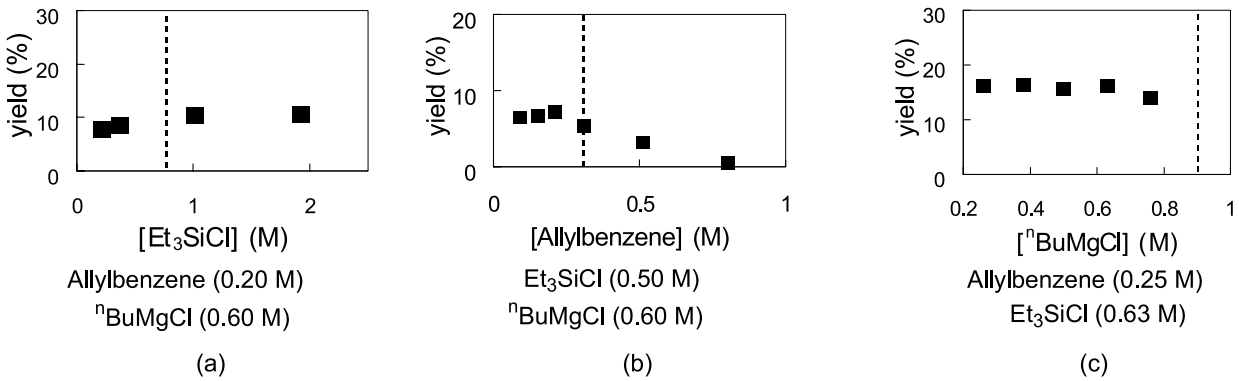


Figure 3. Plots of yields of **6** against concentration of (a) Et_3SiCl, (b) allylbenzene, and (c) ^{n}BuMgCl. The dotted line shows a representative concentration of the standard conditions of this silylation.

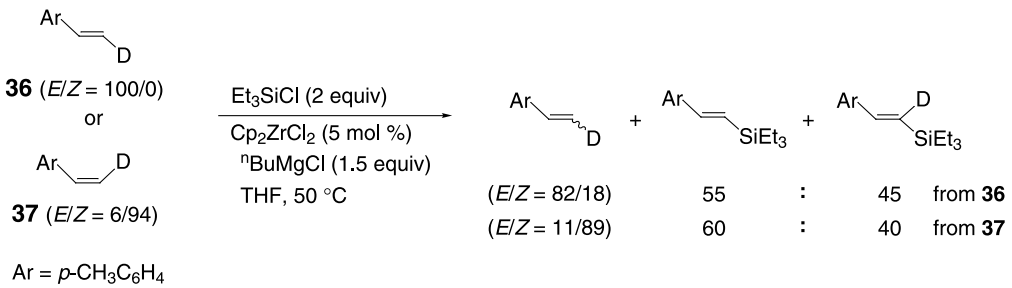
of the other as demonstrated by Negishi et al.,[7] the stereochemistry of this step should be *cis*. So it was expected that D and H contents at the β-carbon of the product reflects the stereochemistry of this process. Unfortunately, both **36** and **37** gave similar mixtures of products with nearly 1:1 ratio of d_0- and d_1-vinylsilanes as shown in Eq. 13 and we could not determine the stereochemistry of this process; however, these experiments provide useful information about relative rates of C–Si bond formation, *cis-trans* isomerization,[13] and ligand exchange process as shown below.

It was confirmed by NMR and GC-Mass analyses that vinylsilanes having more than one deuterium were not formed and the deuterium was attached only to the β-carbon (the carbon bearing a silyl group). The *E*/*Z* ratios of the recovered *p*-methylstyrene-d_1, were 82:18 from **36** and 11:89 from **37** indicating that *cis-trans* isomerization of starting olefin proceeds only to a small extent. These results suggest; (1) *cis-trans* isomerization takes place rapidly on Zr metal, (2) this isomerization reaction is much faster than the competing silylation process leading the products, and (3) this silylation process proceeds faster than olefin exchange reaction on Zr, i.e., most of the coordinated olefin molecules go to the products without dissociation from Zr.

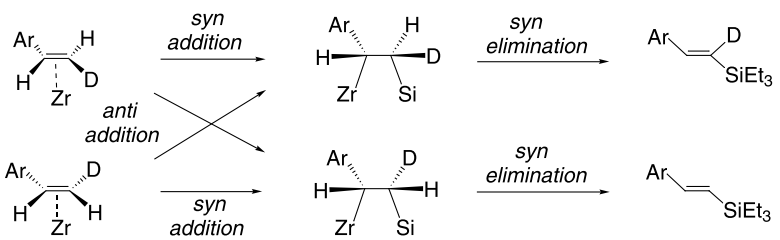
These results also show another important feature of this reaction. It has been reported that the first isotope effect on β-hydrogen elimination of dialkylzirconocene complexes is nearly 6.[14] However, no isotope effect was observed in the reactions of Eq. 13. This evidence indicates that C–Si bond forming process is irreversible under the conditions employed or β-Si elimination, if proceeds, is much slower than the β-hydrogen elimination.

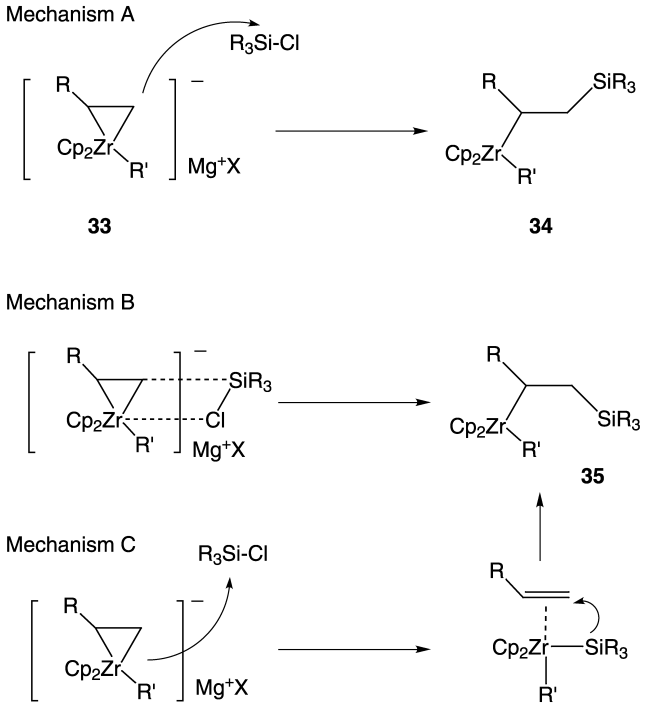
3. Conclusion

Zr-catalyzed silylation of olefins with chlorosilanes have been examined in detail focusing on the reaction pathway and mechanisms of this reaction. Important results obtained are (i) it is likely that this reaction proceeds via zirconocene–olefin ate complexes, (ii) the rate determining step of this catalytic cycle is ligand exchange process in the case of styrene and is β-hydrogen elimination step in the case of allylbenzene, (iii) the C–Si bond forming process is irreversible and faster than olefin exchange reaction on Zr, and (iv) *cis-trans* isomerization of coordinated olefins proceeds rapidly on



(13)





Scheme 3.

Zr and is faster than the C–Si bond forming process. In this reaction the olefinic carbon acts as a nucleophilic center toward chlorosilanes. This unique reactivity may arise from strong back donation from zirconium to olefins and this effect would be enhanced by complexation to form ate complexes.

4. Experimental

4.1. (*E*)-Triethyl(2-phenylethenyl-1-*d*)silane (3)

Ethenyl-2,2-*d2*-benzene was prepared in 87% yield from PhCHO and CD_3I following a reported procedure.[15] A THF solution of Cp_2Zr was prepared by the addition of 2 equiv. of ^{n}BuMgCl (0.9 M in THF, 0.22 ml, 0.20 mmol) to Cp_2ZrCl_2 (29 mg, 0.10 mmol) at −78 °C followed by stirring for 1 h at the temperature. Into this solution were added Ethenyl-2,2-*d2*-benzene (212 mg, 2.0 mmol), Et_3SiCl (603 mg, 4.0 mmol) and ^{n}OctMgCl (1.0 M in THF, 3.0 ml, 3.0 mmol) and the mixture was refluxed for 40 min. The addition of benzaldehyde in order to trap the remaining ^{n}OctMgCl and subsequent quenching with 0.1 N HClaq afforded monodeuterated products **3** (91% NMR yield) and **4** (89% GC yield).

Compound **3**. (Deuterium content >98%), purified by HPLC. IR (NaCl) 2953, 2909, 2874, 1494, 1015, 722, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J=7.1 Hz, 2H), 7.32 (t, J=7.5 Hz, 2H), 7.24 (t, J=5.4 Hz, 1H), 6.88 (s, J=2.4 Hz, 1H), 0.98 (t, J=7.8 Hz, 9H), 0.65 (q, J=7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 138.2, 128.3, 127.6, 126.1, 125.3 (t, J=20.7 Hz,), 7.5, 3.6; MS (EI) *m/z* (relative intensity, %) 219 (M^+, 19), 191 (24), 190 (100), 162 (64), 134 (31), 132 (25). HRMS calcd for $C_{14}H_{21}DSi$ 219.1570, found 219.1547. The deuterium content was determined by a comparison of its mass spectrum with that of the corresponding non-deuterated triethyl(2-phenylethenyl)silane.

4.1.2. Octane-1-*d* (4) (deuterium content >95%). The deuterium content of octane-1-*d* (**4**) was determined similarly by mass spectroscopy. The evidence that only a terminal carbon shows a triplet peak at δ 13.9 (t, J=19 Hz) in the ^{13}C NMR spectrum (100 MHz, $CDCl_3$) indicates that a deuterium is incorporated at the terminal carbon.

4.1.3. (*E*)-1-Phenyl-3-(triethylsilyl)prop-1-ene (6). To a mixture of allylbenzene (382.9 mg, 3.24 mmol), Et_3SiCl (487.9 mg, 3.24 mmol) and a catalytic amount of Cp_2ZrCl_2 (34.0 mg, 0.12 mmol) was added ^{n}BuMgCl (0.90 M in THF, 1.7 mL, 1.49 mmol) at 20 °C under nitrogen. After stirring the solution for 30 min at 20 °C, a small portion of reaction mixture was treated with 1 N HCl_{aq}, followed by the same workup as mentioned above gave **6** in 16% GC yield. To a remaining reaction mixture was added ^{n}BuMgCl (0.90 M in THF, 0.5 mL, 0.45 mmol) at 20 °C under nitrogen. Additional stirring the solution for 90 min at 20 °C, **6** was obtained in 62% GC yield. Purification by silica gel column chromatography with hexane as the eluent afforded 80 mg (53%) of **6**. IR (NaCl) 2952, 2910, 2874, 2360, 960, 728, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 7.30 (m, 4H), 7.11–7.16 (m, 1H), 6.24 (m, 2H), 1.69 (m, 2H), 0.95 (t, J=8.0 Hz, 9H), 0.56 (q, J=8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.3, 128.0, 127.9, 126.0, 125.3, 19.0, 7.6, 3.5; MS (EI) *m/z* (relative intensity, %) 232 (M^+, 32), 115 (100), 87 (91), 59 (28). HRMS calcd for $C_{15}H_{24}Si$ 232.1647, found 232.1634. Anal. calcd: C, 77.51; H, 10.41. Found: C, 77.36; H, 10.61.

4.1.4. (*E*)-1-Phenyl-3-(trimethylsilyl)prop-1-ene (20). To a mixture of allylbenzene (138.8 mg, 1.17 mmol), Me_3SiCl (319 mg, 2.94 mmol), Et_3SiH (341 mg, 2.94 mmol) and a catalytic amount of Cp_2ZrCl_2 (34.2 mg, 0.12 mmol) was added ^{n}BuMgCl (0.90 M in THF, 3.90 mL, 3.51 mmol) at 20 °C under nitrogen. Stirring the solution for 3 h at 20 °C, 1 N HCl_{aq} was added to the solution at 0 °C, and the mixture was again warmed to 20 °C. A saturated aqueous NH_4Cl solution (50 mL) was added, and the product was extracted with ether (50 mL), dried over $MgSO_4$, and evaporated to give **20** (86% NMR yield) along with recovery of Et_3SiH (89% GC yield). Purification by silica gel column chromatography with hexane as the eluent afforded 172 mg (78%) of **20**. IR (NaCl) 3023, 2954, 1248, 1148, 961, 862, 740, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.31 (m, 4H), 7.11–7.17 (m, 1H), 6.21–6.26 (m, 2H), 1.65 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.3, 128.1, 127.7, 126.1, 125.4, 24.1, −1.6. HRMS calcd for $C_{12}H_{18}Si$ 190.1178, found 190.1174. Anal. calcd: C, 75.72; H, 9.53. Found: C, 75.59; H, 9.60.

Acknowledgements

This research was supported financially in part by a grant from the Asahi Glass Foundation, Handai Frontier Research Center and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References and notes

1. (a) In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1989. (b) In *The Chemistry of Organic Silicon Compounds Volume 2*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1998. (c) Hiyama, T.; Kusumoto, T. *Comprehensive Organic Synthesis*; Fleming, I., Ed.; Pergamon: Oxford, 1991; Vol. 8, pp 763–792.
2. (a) Marciniec, B. In *Applied Homogeneous Catalysis with Organometallic Compounds*; 2nd ed. Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 2002; pp 491–512. (b) Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317–1350. (c) Saso, H.; Ando, W. *Chem. Lett.* **1988**, 1567–1570. (d) Sakurai, H.; Imai, T. *Chem. Lett.* **1975**, 891–894. (e) Chatani, N.; Hanafusa, T. *J. Chem. Soc., Chem. Commun.* **1985**, 838–839. (f) Ogawa, A.; Kuniyasu, H.; Takeba, M.; Ikeda, T.; Sonoda, N.; Hirao, T. *J. Organomet. Chem.* **1998**, *564*, 1–4. (g) Hada, M.; Tanaka, Y.; Ito, M.; Murakami, M.; Amii, H.; Ito, Y.; Nakatsuji, H. *J. Am. Chem. Soc.* **1994**, *116*, 8754–8765, and references therein. (h) Yamashita, H.; Kobayashi, T.; Hayashi, T.; Tanaka, M. *Chem. Lett.* **1991**, 761–762. (i) Chatani, N.; Amishiro, N.; Murai, S. *J. Am. Chem. Soc.* **1991**, *113*, 7778–7780. (j) Chatani, N.; Amishiro, N.; Morii, T.; Yamashita, T.; Murai, S. *J. Org. Chem.* **1995**, *60*, 1834–1840.
3. The oxidative addition of chlorosilanes into late transition metals were sluggish due to the strong Si–Cl bond energy, see: Yamashita, H.; Tanaka, M.; Goto, M. *Organometallics* **1997**, *16*, 4696–4704, and references therein.
4. Terao, J.; Torii, K.; Saito, K.; Kambe, N.; Baba, A.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2653–2656.
5. For other transition metal catalyzed silylation using chlorosilanes, see: (a) Terao, J.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1998**, *39*, 9697–9698. (b) Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2000**, *65*, 5291–5297. (c) Watabe, H.; Terao, J.; Kambe, N. *Org. Lett.* **2001**, *3*, 1733–1735. (d) Terao, J.; Oda, A.; Ikumi, A.; Nakamura, A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3412–3414.
6. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829–2832.
7. Negishi, E.; Swanson, D. R.; Takahashi, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1254–1255.
8. Takahashi, T.; Suzuki, N.; Kageyama, M.; Nitto, Y.; Saburi, M.; Negishi, E. *Chem. Lett.* **1991**, 1579–1582.
9. (a) Ura, Y.; Hara, R.; Takahashi, T. *Chem. Lett.* **1998**, 195–196. (b) Ura, Y.; Hara, R.; Takahashi, T. *J. Organomet. Chem.* **2000**, *611*, 299–303.
10. Gibson, T. *Organometallics* **1987**, *6*, 918–922.
11. Corriu, R. J. P.; Meunier, B. *J. Organomet. Chem.* **1974**, *65*, 187–194.
12. (a) Takahashi, T.; Hasegawa, H.; Suzuki, N.; Saburi, M.; Rousset, C. J.; Fanwick, P. E.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 8564–8566. (b) Kesti, M. R.; Abdulrahman, M.; Waymouth, R. M. *J. Organomet. Chem.* **1991**, *417*, C12–C15. (c) Corey, J. Y.; Zhu, X.-H. *Organometallics* **1992**, *11*, 672–683. (d) Kesti, M. R.; Waymouth, R. M. *Organometallics* **1992**, *11*, 1095–1103.
13. Zirconocene-catalyzed *cis-trans* isomerization of olefins has been studied by Negishi et al., and it is revealed that the isomerization obeys the second order kinetics on concentration of zirconocene catalyst and scrambling of vinylic hydrogens does not take place Negishi, E.; Choueiri, D.; Nguyen, T.; Swanson, D. R. *J. Am. Chem. Soc.* **1994**, *116*, 9751–9752.
14. Negishi, E.; Nguyen, T.; Maye, J. P.; Choueiri, D.; Suzuki, N.; Takahashi, T. *Chem. Lett.* **1992**, 2367–2370.
15. Fischetti, W.; Heck, R. F. *J. Organomet. Chem.* **1985**, *293*, 391–405.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1309–1316
Tetrahedron

Microwave accelerated, Ni/C-catalyzed cross-couplings of in situ-derived zirconocenes

Bruce H. Lipshutz* and Bryan Frieman

Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106-9510, USA

Received 4 August 2003; revised 1 October 2003; accepted 11 October 2003

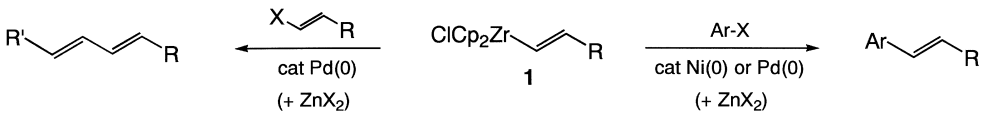
Abstract—Both vinyl and alkyl zirconocenes undergo rapid couplings with aryl halides under heterogeneous conditions in a microwave reactor using Ni/C as catalyst. Ligand variations both in type and stoichiometry play major roles in the extent of conversion.

1. Introduction

As amply documented by the very recent monograph on 'Titanium and Zirconium in Organic Synthesis', edited by Ilan Marek,[1] use of zirconocene intermediates in a wide range of synthetic situations continues to blossom. One of the more fundamental processes associated with organozirconium chemistry is generally regarded as cross-coupling reactions, or the zirconium version of 'Negishi couplings'.[2] As originally disclosed in the mid-to-late 1970's,[3] diene or styrene formation could be achieved via treatment of an in situ generated vinyl zirconocene with a vinyl or aryl halide, respectively (Scheme 1). Nickel(0) was the catalyst employed at first,[3a] although palladium is now regarded in most circles as more broadly applicable.[4] While these seminal studies offered new inroads to valued C–C bond constructions, the relatively low electronegativity (1.2–1.4) of Zr and unreactive nature of the C–Zr bond toward carbon-based electrophiles oftentimes necessitates transmetalations, thereby significantly expanding the scope of zirconocene-based couplings. In the specific case of Negishi couplings, addition of a zinc salt (e.g. $ZnCl_2$) results in a marked rate acceleration leading to extremely valuable technology,[5] especially in light of the many alternatives for preparing (functionalized) organozinc reagents.[6] Notwithstanding these developments, which greatly enhance the utility of zirconocene derivatives (especially those resulting from hydrozirconations,[7] e.g. **1**), we have returned to the basic concept of utilizing sp^2- and sp^3-C–Zr bonds directly. That is, how can vinyl and alkyl zirconocenes be employed more effectively without recourse to zinc salt additives and which rely on a base metal like nickel, rather than palladium? Our focus has also included a shift to a more environmentally benign, inexpensive, and recyclable heterogeneous approach to catalysis, in particular using nickel-on-charcoal (Ni/C).[8] Since the combination of less reactive ziconocenes (e.g. vs the corresponding zinc species) together with catalyst heterogeneity would be expected to depress reaction rates of the desired Negishi couplings, microwave irradiation[9–11] was postulated as a potential means of reaction acceleration. Although such reactions of Ni/C under the influence of microwaves had not been studied previously, there was evidence in the literature that Pd/C could function in a related capacity.[12] Thus, in this report we describe the remarkable effect that microwave irradiation exerts on various types of cross-couplings of organozirconium species catalyzed by heterogeneous Ni/C (Scheme 2).

2. Results and discussion

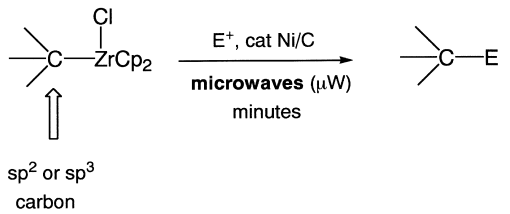
Reactions of vinyl zirconocenes, prepared in the usual fashion from terminal alkynes with $Cp_2Zr(H)Cl$,[7] were



Scheme 1.

Keywords: Microwave; Negishi couplings; Nickel-on-charcoal; Alkyl/vinyl zirconocenes.
* Corresponding author. Tel.: +1-805-893-2521; fax: +1-805-893-8265; e-mail address: lipshutz@chem.ucsb.edu

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.10.029

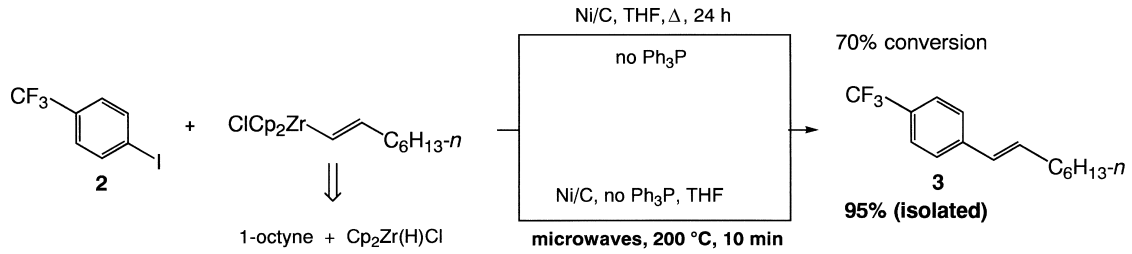


Scheme 2.

initially surveyed in combination with aryl halides in the presence of Ni/C. Unlike the related Suzuki-like couplings mediated by this catalyst,[13] complete consumption of starting material (initially on activated iodide **2**, Scheme 3) could not be accomplished even under reflux conditions (THF) after 24 h. Conversions below 70% were observed when room temperature conditions were applied. Interestingly, while these early trials were mainly unsuccessful, the importance of phosphine concentrations became apparent, as the greatest extent of conversion was noted in the absence of Ph_3P (rt: 4 Ph_3P, <5%; 2 Ph_3P, 20%; no PPh_3, 40% product **3**). Thus, under microwave irradiation and in the absence of phosphines, **2** was converted to **3** within 10 minutes in high yield.

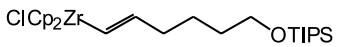
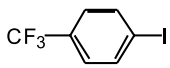
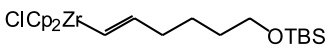
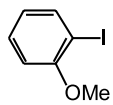
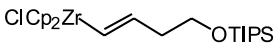
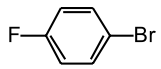
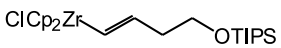
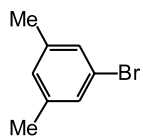
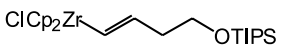
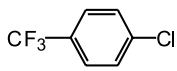
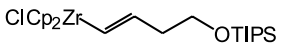
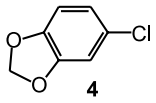
As illustrated in Table 1 (entries 1 and 2), couplings of representative vinyl zirconocenes under these phosphine-free conditions on both an electron-rich and electron-poor substrate proceed with equal facility. In the case of aryl bromides, 2 equiv. of PPh_3 were required (relative to the % Ni/C present) for total conversion (entries 3 and 4). Noteworthy are the cases of aryl chlorides (entries 5 and 6), which are notoriously unreactive toward vinyl zirconocenes even with Ni(0) in solution.[3] Reaction of highly electron-rich chloride **4** was unexceptional under the standard conditions employed, reaching completion within 40 min. However, in going from bromides to chlorides, 4 equiv. of Ph_3P (as opposed to 2 equiv. of PPh_3 with bromides and 0 equiv. of PPh_3 with iodides) were needed to fully consume the aryl halide.

In all of the above cases, Ph_3P was the ligand used. To quickly ascertain the importance of this reaction parameter, four other phosphines were screened: another monodentate



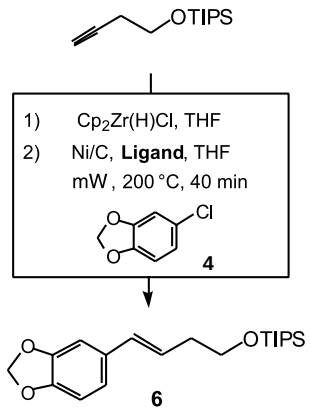
Scheme 3.

Table 1. 'Negishl couplings' of vinyl zirconocenes with aryl halides catalyzed by Ni/C under microwave irradiation at 200 °C in THF

Entry	Vinyl zirconocene	Aryl halide	Time (min)	Yield (%)[a]
1			10	**83**[b]
2			15	**83**[b]
3	 **5**		15	**86**[c]
4			20	**77**[c]
5			30	**76**[d]
6		 **4**	40	**75**[d]

[a] Isolated, chromatographically purified material.
[b] Reaction performed using 5% Ni/C and 0% PPh_3 relative to aryl iodide.
[c] Reaction performed using 5% Ni/C and 10% PPh_3 relative to aryl bromide.
[d] Reaction performed using 5% Ni/C and 20% PPh_3 relative to aryl chloride.

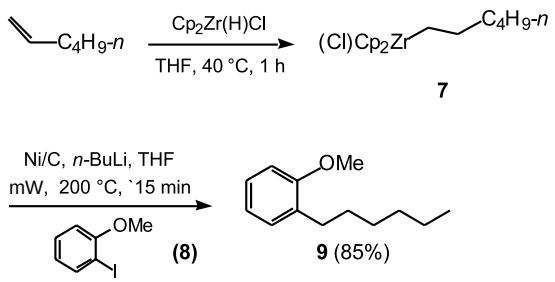
Table 2. Effect of ligands on cross-couplings of vinyl zirconcenes



Phosphine ligand	Ligand (equiv) vs Ni/C	Conversion (%)
Cy_3P	4	5
dppe	2	9
rac BINAP	2	11
dppf	2	18
Ph_3P	**4**	**95**

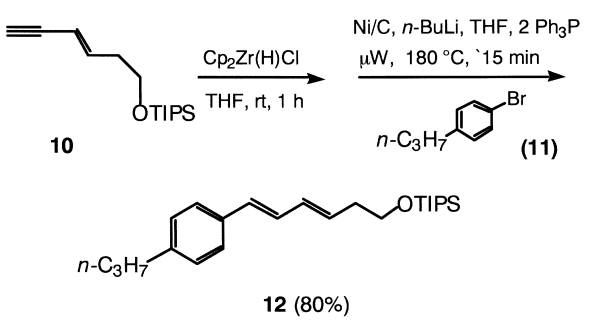
species (Cy_3P), and three of the bidentate variety: dppe, racemic BINAP, and dppf (Table 2). Our findings, based on the coupling of chloride **4** with vinyl zirconocene **5** to afford **6**, clearly indicate that Ph_3P is the only ligand in this group capable of assisting in the oxidative addition step; the recovered mass was the starting chloride.

The corresponding coupling using an sp^3-based C–Zr bond, from hydrozirconation of an alkene, was also tested under microwaves conditions. The combination of alkyl zirconocene **7** and aryl halide **8** led to a smooth conversion to adduct **9** (Eq. (1)).



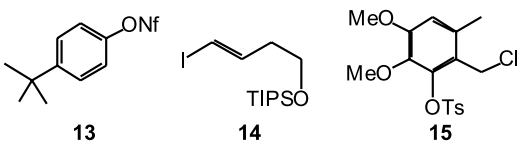
(1)

A more highly conjugated skeleton could be fashioned by hydrozirconation of enyne **10**, followed by Ni/C-catalyzed coupling with aryl bromide **11**. As previously observed for such educts, 2 equiv. of triphenylphosphine (i.e. 8 mol%) led to the desired dienic product **12** in good yield (Eq. (2)).



(2)

Several additional types of substrates were examined under these microwave enhanced, Ni/C-catalyzed conditions without success. Thus, nonaflate **13** and vinyl iodide **14** each led to many unidentified side products in reactions with a vinyl zirconocene. Each was also found to be sluggish, with considerable amounts of starting material remaining. Likewise, benzylic chloride **15**,[14] which couples at room temperature with vinyl alanes under Ni/C catalysis,[15] led to no reaction even at 180 °C for 10 min. It was also disappointing to observe even a simple vinyl zirconocene derived from octyne could not be induced to add in a conjugate fashion[16] to cyclohexenone under microwave irradiation at 200 °C in THF (10 min).



Finally, we have questioned the extent of leaching of nickel from the Ni/C used in these studies, as done in all previous uses of this heterogeneous support.[17] A quantitative ICP AES determination[18] was made based on the reaction mixture associated with entry 1 in Table 1. The data indicated that 2.86% of the 5% Ni/C present (or 2.86% of the 2.18 mg nickel for the amount of catalyst used) in the reaction mixture could be detected. This figure corresponds to 62.36 μg of nickel in solution, or the presence of 1.25 ppm.

3. Summary and conclusions

This study suggests that Ni/C is a viable catalyst for mediating cross-coupling reactions between organozirconium intermediates and aryl halides under microwave irradiation. Aromatic iodides, bromides, and in some cases even chlorides are amenable to these conditions. Microwave accelerated couplings related to these zirconium-based Negishi couplings, for example, involving aryl halides and boronic acids or amines, are also underway and will be reported in due course, as will our study on the use of CuCl as a trivial means of sequestering mono- and bidentate phosphines as used in some of the workups herein.[19]

4. Experimental

4.1. General

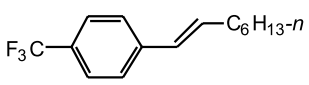
Reactions were performed in oven-dried glassware under an argon atmosphere containing a Teflon coated stir bar and dry septum. THF was freshly distilled from Na/benzophenone ketyl prior to use. Ni/C was stored and weighed out as a black powder in a glove box. All commercially available reagents were distilled either from CaH_2 or molecular sieves under an inert atmosphere before use. Schwartz's reagent, $Cp_2Zr(H)Cl$, was prepared using the standard procedure[20] and titrated using octyne and then analyzed by GC in triplicate and found to be >99% pure. 1-Octyne, 5-hexyn-1-ol, 3-butyn-1-ol, 2-iodoanisole,

5-chloro-1,3-benzodioxole, CuCl, and NaOMe were purchased from Aldrich. 1-Bromo-3,5-dimethylbenzene and 4-chlorobenzotrifluoride were purchased from Lancaster. 1-Hexene, 4-iodobenzotrifluoride, and 4-bromofluorobenzene were purchased from Acros. 3,4-Dimethoxy-6-methyl-2-toluene-sulfonyloxybenzyl chloride was obtained from Optima. All microwave experiments were performed using an Emrys Optimizer in 2–5 mL pyrex reaction vessels which were flame dried under an argon atmosphere. Each contained a Teflon stir bar and Teflon coated reaction vessel cap. ICP-AES analyses was performed on a Thermo Jarrell Ash IRIS plasma spectrometer. GC analyses were carried out using an HP-5 capillary column (0.25 μm×30 m; cross-linked 5% PH ME siloxane) and a time program beginning with 5 min at 50 °C followed by 20 °C/min ramp to 280 °C, then 20 min at this temp. Column chromatography was performed using Davisil Grade 633 Type 60A silica gel. TLC analyses were performed on commercial Kieselgel 60 F_{254} silica gel plates. NMR spectra were obtained on Varian Inova systems using $CDCl_3$ as solvent, with proton and carbon resonances at 400 and 100 MHz, respectively. FTIR spectra were obtained on an ATI Mattson Infinity series spectrometer neat on NaCl plates and are reported in cm^{-1}. Mass spectral data were acquired on a VF Autospec or an analytical VG-70-250 HF instrument.

4.2. Preparation of Ni(II)/C

Darco® KB (5.00 g, 100 mesh) activated carbon (25% H_2O content) was added to a 100 mL round bottom flask containing a stir bar. A solution of 727 mg (Aldrich, 24,407-4, Ni content by ICP determination: 92%; 2.30 mmol) $Ni(NO_3)_2{\cdot}6H_2O$ in 35 mL deionized H_2O was added to the activated carbon and 40 mL of deionized H_2O was added to wash down the sides of the flask. The flask was purged under argon and stirred vigorously for 1 min. The flask was submerged in an ultrasonic bath under a positive argon flow for 30 min. The flask was attached to an argon purged distillation setup and placed in a pre-heated 175–180 °C sand bath with stir plate. As the distillation ended, the flask temperature rises automatically but should be held below 210 °C for an additional 15 min. Upon cooling to rt, the black solid was washed with H_2O (2×50 mL) under argon into a pre-dried in vacuo 150 mL course fritted funnel. The 100 mL of H_2O used to wash the Ni/C was rotavaped and analyzed for any remaining nickel. The fritted funnel was turned upside down under vacuum for 3 h until the Ni/C falls from the frit into the collection flask. The collection flask is then dried in vacuo at 100 °C for 18 h. Using these specific amounts, all of the nickel is mounted on the support, which corresponds to 0.552 mmol Ni(II)/g catalyst, or 3.2% Ni/catalyst by weight.

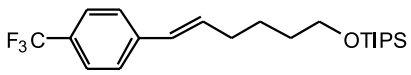
4.3. General procedure for Ni/C-catalyzed cross-couplings of vinyl zirconocenes with aryl halides



4.3.1. E-1-Octenyl-4-trifluoromethylbenzene (3). *Hydrozirconation*. To a 10 mL round-bottom flask wrapped in aluminum foil and under argon was added $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol). THF (2.0 mL) was added followed by 1-octyne (149 μL, 1.00 mmol) via syringe. After 30 min, the hydrozirconation was complete by GC.

Nickel-on-charcoal catalyzed coupling. To an Emrys Optimizer 2–5 mL pyrex reaction vessel was added Ni/C (67.3 mg, 0.04 mmol) under argon at rt. THF (1 mL) was added followed by BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol). The solution was allowed to stir at rt for 5 min after which 4-iodobenzotrifluoride (117 μL, 0.80 mmol) was added dropwise at rt and the mixture allowed to stir for 5 min. The vinyl zirconocene was then transferred via cannula to the Ni/C mixture at rt. The reaction vessel was placed in the Emrys Optimizer and exposed to microwave irradiation according to the following specifications: temperature: 200 °C, time: 600 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After cooling to room temperature, the crude reaction mixture was filtered through a glass frit containing Fullers Earth to remove the Ni/C and the zirconium salts, and the filter cake was further washed with ether and hexanes. The filtrate was collected, solvents were removed on a rotary evaporator, and the crude mixture was purified by flash chromatography on silica gel with pet ether. The title compound was obtained (244 mg; 95%) as a clear, viscous oil; R_f 0.80 (pet ether).

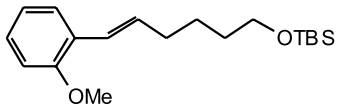
IR (neat): 2929, 2858, 2254, 1916, 1616, 1466, 1413, 1324, 1127, 1068, 1017, 909, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.53 (m, 2H), 7.47–7.42 (m, 2H), 6.43 (d, J=16.1 Hz, 1H), 6.36 (dt, J=6.1, 16.1 Hz, 1H), 2.26 (apparent quartet, J=7.4 Hz, 2H), 1.56–1.46 (m, 2H), 1.44–1.27 (m, 8H), (0.93, t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.66, 138.25, 134.34, 128.77, 126.22, 125.69, 125.65, 125.61, 125.57, 33.33, 31.96, 29.36, 29.15, 22.86, 14.31. MS (EI): m/z (relative %) 256 (16), 185 (29), 172 (100), 165 (12), 115 (19), 55 (10), 43 (13). HREIMS: m/z calcd for $C_{15}H_{19}F_3$ 256.1433; found 256.1438.



4.3.2. Table 1, entry 1. E-Triisopropyl-[6-(4-trifluoromethylphenyl)-hex-5-enyloxy]-silane. TIPS protected 5-hexynol (254 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and THF (2.0 mL) were added to a 10 mL flasked protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. A mixture containing Ni/C (67.3 mg, 0.04 mmol), THF (1 mL), n-BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 4-iodobenzotrifluoride (117 μL, 0.80 mmol) was prepared using the typical procedure above, followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 900 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After a standard workup, chromatography of the residue on silica gel with pet ether afforded 333 mg (83%) of the title compound as a clear oil; R_f 0.38 (pet ether).

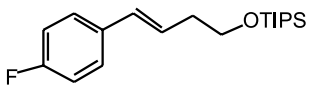
IR (neat): 2941, 2865, 1616, 1462, 1325, 1165, 1126, 1068, 1015, 967, 882, 680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.52 (m, 2H), 7.46–7.41 (m, 2H), 6.44 (d, J=16.0 Hz,

1H), 6.28 (dt, J=7.1, 16.0 Hz, 1H), 3.75 (t, J=6.8 Hz, 2H), 2.29 (apparent q, 2H), 1.69–1.54 (m, 4H), 1.16–1.08 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.59, 134.09, 128.96, 128.68, 126.24, 125.90, 125.67, 125.63, 125.60, 125.56, 123.20, 63.39, 33.10, 32.74, 25.69, 18.25, 18.17, 12.23. MS (EI): *m/z* (relative %) 357 (100), 207 (18), 185 (10), 179 (24), 159 (11), 153 (10), 127 (13), 83 (17), 75 (20), 61 (14), 43 (10). HREIMS: *m/z* calcd for $C_{22}H_{35}F_3OSi$ ($M^+-C_3H_7$) 357.1853; found 357.1861.



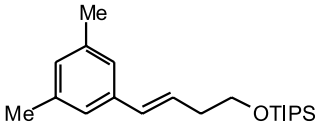
4.3.3. Table 1, entry 2. E*t*-Butyl-[6-(2-methoxyphenyl)-hex-5-enyloxy]-dimethylsilane. TBDMS protected 5-hexyn-1-ol (212 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and 2.0 mL of THF were added to a 10 mL flask and protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. A mixture containing Ni/C (67.3 mg, 0.04 mmol), THF (1 mL), BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 2-iodoanisole (104 μL, 0.80 mmol) was prepared using the typical procedure above followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 900 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After a standard workup, chromatography of the residue on silica gel with pet ether–methylene chloride (95:5) afforded 212 mg (83%) of the title compound as a clear oil; R_f 0.08 (pet ether–methylene chloride).

IR (neat): 2959, 2252, 1701, 1459, 1367, 1148, 1013, 911, 733, 647 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.42 (m, 1H), 7.23–7.17 (m, 1H), 6.96–6.85 (m, 2H), 6.73 (d, J=16.0 Hz, 1H), 6.23 (dt, J=7.0, 16.0 Hz, 1H), 3.86 (s, 3H), 3.66 (t, J=6.5 Hz, 2H), 2.27 (ddt, J=1.2, 7.0, 7.0 Hz, 2H), 1.65–1.50 (m, 4H), 0.92 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.43, 131.82, 128.00, 127.13, 126.56, 124.62, 120.82, 110.94, 63.35, 55.62, 33.46, 32.64, 26.20, 25.96, 18.59, −5.05. MS (EI): *m/z* (relative %) 263 (100), 147 (10), 121 (38), 91 (12), 75 (31), 73 (14). HREIMS: *m/z* calcd for $C_{19}H_{32}O_2Si$ ($M^+-C_4H_9$) 263.1460; found 263.1467.



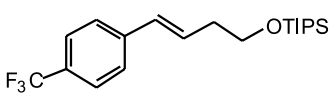
4.3.4. Table 1, entry 3. E-[4-(4-Fluorophenyl)-but-3-enyloxy]-triisopropylsilane. TIPS protected 3-butyn-1-ol (226 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and 2.0 mL of THF were added to a 10 mL flask and protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. A mixture containing Ni/C (67.3 mg, 0.04 mmol), PPh_3 (21 mg, 0.08 mmol), THF (1 mL), *n*-BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 4-bromofluorobenzene (88 μL, 0.8 mmol) was prepared using the typical procedure above, followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 900 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After standard workup, chromatography of the residue on silica gel with pentane afforded 277 mg (86%) of the title compound as a clear oil; R_f 0.36 (pentane).

IR (neat): 2942, 2865, 1602, 1508, 1463, 1382, 1230, 1157, 1104, 1013, 964, 882, 850, 774, 733, 680 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.29 (m, 2H), 7.03–6.97 (m, 2H), 6.43 (d, J=16.0 Hz, 1H), 6.19 (dt, J=7.1, 16.0 Hz, 1H), 3.82 (t, J=6.8 Hz, 2H), 2.47 (ddt, J=1.2, 6.8, 6.8 Hz, 2H), 1.13–1.08 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.38, 160.93, 134.14, 134.10, 130.54, 127.61, 127.53, 127.33, 127.31, 115.63, 115.41, 63.42, 36.98, 18.23, 12.21. MS (EI): *m/z* (relative %) 332 (1), 303 (2), 289 (100), 159 (54), 145 (34), 129 (30), 115 (23), 103 (20), 75 (35), 59 (33), 43 (31). HREIMS: *m/z* calcd for $C_{19}H_{31}FOSi$ ($M^+-C_3H_7$) 279.1575; found 279.1580.



4.3.5. Table 1, entry 4. E-[4-(3,5-Dimethylphenyl)-but-3-enyloxy]-triisopropylsilane. TIPS protected 3-butyn-1-ol (226 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and 2.0 mL of THF were added to a 10 mL flask and protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. Ni/C (67.3 mg, 0.04 mmol), PPh_3 (21 mg, 0.08 mmol), THF (1 mL), *n*-BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 5-bromo-2,3-dimethylbenzene (109 μL, 0.8 mmol) were used according to the typical procedure, followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 1200 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After standard workup, chromatography of the residue on silica gel with petroleum ether afforded 204 mg (77%) of the title compound as a clear oil; R_f 0.22 (pet. ether).

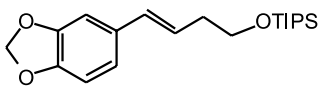
IR (neat): 2865, 2728, 2248, 1602, 1464, 1382, 1248, 1202, 1109, 1013, 996, 965, 909, 883, 851, 793, 734, 681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (apparent s, 2H), 6.89 (apparent s, 1H), 6.43 (d, J=16.0 Hz, 1H), 6.28 (dt, J=7.1, 16.0 Hz, 1H), 3.84 (t, J=6.8 Hz, 2H), 2.51 (ddt, J=1.2, 6.8, 6.8 Hz, 2H), 2.34 (s, 6H), 1.16–1.10 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.05, 137.86, 131.84, 128.87, 127.00, 124.12, 63.57, 37.11, 21.48, 18.24, 12.23. MS (EI): *m/z* (%) 332 (1), 303 (2), 289 (100), 159 (54), 145 (34), 129 (30), 115 (23), 103 (20), 75 (35), 59 (33), 43 (31). HREIMS: *m/z* calcd for $C_{21}H_{36}OSi$ 332.2547; found 332.2535.



4.3.6. Table 1, entry 5. E-Triisopropyl-[4-(4-trifluoromethylphenyl)-but-3-enyloxy]-silane. The TIPS protected 3-butyn-1-ol (226 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and 2.0 mL of THF was added and protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. Ni/C (67.3 mg, 0.04 mmol), PPh_3 (42 mg, 0.16 mmol), THF (1 mL), BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 4-chlorobenzotrifluoride (107 μL, 0.8 mmol) were prepared using

the typical procedure followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 1800 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After standard workup, followed by evaporation of most of the solvent, CuCl (5.3 mg, 0.053 mmol) was added and swirled for 10 min to sequester the triphenylphosphine. Chromatography of the residue on silica gel with petroleum ether afforded 227 mg (76%) of the title compound as a clear oil; R_f 0.35 (pet. ether).

IR (neat): 2943, 2866, 1503, 1465, 1325, 1165, 1125, 1067, 908, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.91–6.90 (m, 1H), 6.79–6.73 (m, 2H), 6.37 (d, J=15.7 Hz, 1H), 6.28 (dt J=7.1, 15.7 Hz, 1H), 3.80 (t, J=6.8 Hz, 2H), 2.51 (ddt, J=1.2, 6.8, 6.8 Hz, 2H), 1.12–1.07 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.45, 130.68, 130.52, 129.10, 126.29, 125.70, 125.66, 125.63, 125.59, 63.15, 37.01, 18.22, 12.21. MS (EI): m/z (%) 329 (100), 198 (11), 128 (14), 120 (45), 92 (15), 74 (11), 58 (10), 42 (28). HREIMS: m/z calcd for $C_{20}H_{31}F_3OSi$ $M^+-(C_3H_7)$ 329.1550; found 329.1549.



4.3.7. Table 1, entry 6. E-(4-Benzo[1,3]dioxol-5-yl-but-3-enyloxy)-triisopropylsilane. TIPS protected 3-butyn-1-ol (226 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and 2.0 mL of THF were added to a 10 mL flask and protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. Ni/C (67.3 mg, 0.04 mmol), PPh_3 (42 mg, 0.16 mmol), THF (1 mL), n-BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 4-chloro-1,3-benzodioxole (93 μL, 0.8 mmol) were used according to the typical procedure, followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 2400 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After standard workup followed by evaporation of most of the solvent, CuCl (5.3 mg, 0.053 mmol) was added and the mixture swirled for 10 min to sequester the triphenylphosphine. Chromatography of the residue on silica gel with petroleum ether afforded 208 mg (75%) of the title compound as a clear oil; R_f 0.10 (pet. ether).

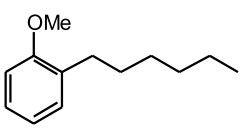
IR (neat): 2943, 2866, 1503, 1490, 1250, 1104, 908, 734, 680, 650, 450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.91–6.90 (m, 1H), 6.79–6.73 (m, 2H), 6.37 (d, J=15.7 Hz, 1H), 6.28 (dt, J=7.1, 15.7 Hz, 1H), 3.80 (t, J=6.8 Hz, 2H), 2.51 (ddt, J=1.3, 6.8, 6.8 Hz, 2H), 1.12–1.07 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.10, 146.85, 132.51, 131.25, 125.73, 120.55, 108.39, 105.58, 101.11, 63.51, 36.93, 18.22, 12.20. MS (EI): m/z (%) 348 (24), 305 (100), 174 (53), 156 (53), 144 (86), 134 (34), 130 (32), 116 (68), 114 (50), 102 (30), 86 (22), 74 (37), 58 (49), 44 (25). HREIMS: m/z calcd for $C_{20}H_{32}O_3Si$ 348.2129; found 348.2121.

4.3.8. Table 2; Cy_3P. TIPS protected 3-butyn-1-ol (226 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and 2.0 mL of THF were added to a 10 mL flask and protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. Ni/C (67.3 mg, 0.04 mmol), Cy_3P (44.9 mg, 0.16 mmol) THF (1 mL), n-BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 4-chloro-1,3-benzodioxole (93 μL, 0.8 mmol) were used according to the typical procedure, followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 2400 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. After standard workup, GC of the title compound indicated 5% conversion.

4.3.9. Table 2; dppe. TIPS protected 3-butyn-1-ol (226 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and 2.0 mL of THF were added to a 10 mL flask and protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. Ni/C (67.3 mg, 0.04 mmol), dppe (31.8 mg, 0.08 mmol), THF (1 mL), n-BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 4-chloro-1,3-benzodioxole (93 μL, 0.8 mmol) were used according to the typical procedure, followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 2400 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. Upon standard workup, GC of the title compound indicated 9% conversion.

4.3.10. Table 2; BINAP. TIPS protected 3-butyn-1-ol (226 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and 2.0 mL of THF were added to a 10 mL flask and protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. Ni/C (67.3 mg, 0.04 mmol), (R)-BINAP (49.8 mg, 0.08 mmol), THF (1 mL), n-BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 4-chloro-1,3-benzodioxole (93 μL, 0.8 mmol) were used according to the typical procedure, followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 2400 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. Upon standard workup, GC of the title compound indicated 11% conversion.

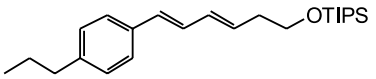
4.3.11. Table 2; dppf. TIPS protected 3-butyn-1-ol (226 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and 2.0 mL of THF were added to a 10 mL flask and protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. Ni/C (67.3 mg, 0.04 mmol), dppf (44.4 mg, 0.08 mmol), THF (1 mL), n-BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 4-chloro-1,3-benzodioxole (93 μL, 0.8 mmol) were used according to the typical procedure, followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 2400 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. Upon standard workup, GC of the title compound indicated 18% conversion.



4.3.12. Eq. 1. 1-*n*-Hexyl-2-methoxybenzene (9). 1-Hexene (124 μL, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and THF (2.0 mL) were added to a 10 mL flask and protected from light using aluminum foil. After 60 min, the hydrozirconation was complete by GC. Ni/C (67.3 mg, 0.04 mmol), THF (1 mL), n-BuLi (31 μL, 2.55 M

in hexanes, 0.08 mmol), and 2-iodoanisole (104 μL, 0.80 mmol) were used according to the typical procedure, followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 900 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. Upon standard workup, chromatography of the residue on silica gel with hexanes afforded 131 mg (85%) of the title compound as a clear oil; R_f 0.41 (hexanes).

IR (neat): 2926, 2856, 1729, 1601, 1493, 1464, 1377, 1289, 1241, 1177, 1128, 1051, 1033, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20–7.12 (m, 2H), 6.91–6.83 (m, 2H), 3.83 (s, 3H), 2.61 (apparent t, *J*=7.7 Hz, 2H), 1.44–1.18 (m, 8H), 0.90 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.63, 131.57, 129.93, 126.93, 120.49, 110.40, 55.46, 31.99, 30.36, 30.04, 29.53, 22.88, 14.35. MS (EI): *m*/*z* (%) 192 (21), 122 (12), 121 (100), 91 (44), 43 (19). HREIMS: *m*/*z* calcd for $C_{13}H_{20}O$ 192.1510; found 192.1514.



4.3.13. Eq. 2. E,E-Triisopropyl-[6-(4-propylphenyl)-hexa-3,5-dienyloxy]-silane (12). Hex-3-en-5-ynyloxytriisopropylsilane[21] (252 mg, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and THF (2.0 mL) were added and protected from light using aluminum foil. After 90 min, the hydrozirconation was complete by TLC. Ni/C (67.3 mg, 0.04 mmol), PPh_3 (21 mg, 0.08 mmol), THF (1 mL), *n*-BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 1-bromo-4-*n*-propylbenzene (124 μL, 0.8 mmol) were prepared using the typical procedure followed by the cross-coupling reaction using the following conditions: temperature: 180 °C, time: 900 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. The filtrate was collected, most of the solvents were removed on a rotary evaporator, and CuCl (2.7 mg, 0.026 mmol) was added and the mixture swirled for 10 min to sequester the triphenylphosphine. Chromatography of the residue on silica gel with hexanes afforded 237 mg (80%) of the title compound as a clear oil; R_f 0.15 (hexanes).

IR (neat): 3019, 2941, 2865, 1509, 1462, 1380, 1246, 1105, 1070, 1013, 985, 931, 882, 779, 739, 681, 658 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (apparent d, 2H), 7.16 (apparent d, 1H), 6.76 (dd, *J*=15.7, 15.7 Hz, 1H) 6.48 (d, *J*=15.7 Hz, 1H), 6.30 (dd, *J*=15.7, 15.7 Hz, 1H), 5.87 (dt, *J*=7.4, 15.7 Hz, 1H), 3.80 (t, *J*=6.8 Hz, 2H), 2.61 (t, *J*=7.4 Hz, 2H), 2.44 (apparent q, 2H), 1.67 (qt, *J*=7.4, 7.4 Hz, 2H), 1.16–1.10 (m, 21H), 0.99 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.05, 135.26, 132.60, 131.38, 130.67, 128.87, 128.60, 126.29, 63.41, 37.99, 36.92, 24.72, 18.23, 14.04, 12.20. MS (EI): *m*/*z* (%) 372 (31), 329 (100), 199 (26), 197 (38), 157 (63), 145 (71), 136 (33), 133 (36), 131 (27), 129 (28), 122 (33), 115 (47), 103 (30), 75 (22), 59 (31), 43 (32). HREIMS: *m*/*z* calcd for $C_{24}H_{40}OSi$ 372.2847; found 372.2848.

4.4. Sample preparation for ICP-AES

Octyne (149 μL, 1 mmol), $Cp_2Zr(H)Cl$ (259 mg, 99% pure, 1.00 mmol) and THF (2.0 mL) were added to a 10 mL flask and protected from light using aluminum foil. After 30 min, the hydrozirconation was complete by GC. Ni/C (67.3 mg, 0.04 mmol), THF (1 mL), *n*-BuLi (31 μL, 2.55 M in hexanes, 0.08 mmol), and 4-iodobenzotrifluoride (117 μL, 0.80 mmol) were used according to the typical procedure, followed by the cross-coupling reaction using the following conditions: temperature: 200 °C, time: 600 s, fixed hold time: on, sample absorption: normal, pre-stirring: 30 s. The reaction mixture was filtered using a 60 mL course filter funnel after cooling to room temperature. The reaction mixture was then washed through the funnel with ether (3×20 mL). The filtrate was refilltered with ether washings (3×10 mL). The solvent was evaporated and the crude material digested with 10 mL of 20% HNO_3 and 5 mL concentrated HCl at reflux for 8 h. Upon cooling and dilution with H_2O (20 mL), the mixture was extracted with hexanes (10 mL) and CH_2Cl_2 (2×10 mL) and the combined organic layers washed with H_2O. The solvents were removed from the combined aqueous phases and the ICP-AES sample was prepared by adding 2% HCl in a way that the final (estimated) nickel concentration was between 1 and 35 ppm. The analytical sample prepared was determined to have 1.25 ppm Ni in solution (2.86% Ni in solution).

Acknowledgements

Financial support provided by the NIH (GM 40287) is warmly acknowledged with thanks. We are indebted to Amgen, Inc., the NSF, and Dean M. Moskovits (UCSB) for the funds needed to purchase the microwave reactor used in this study and to Personal Chemistry for making the Optimizer affordable to us.

References and notes

1. *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002.
2. (a) Negishi, E.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393.
3. (a) Negishi, E.; Van Horn, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 3168. (b) Okukado, N.; Van Horn, D. E.; Klima, W. L.; Negishi, E. *Tetrahedron Lett.* **1978**, 1027.
4. *Handbook of Organopalladium Chemistry*; Negishi, E., Ed.; Wiley/Interscience: New York, 2002.
5. (a) Negishi, E.; Owczarczyk, Z. *Tetrahedron Lett.* **1991**, *32*, 6683. (b) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254.
6. Nakamura, E. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Wiley: Chichester, 2002.
7. Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.
8. Lipshutz, B. H. *Adv. Synth. Catal.* **2001**, *343*, 313.
9. Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578.
10. Stadler, A.; Kappe, C. O. *Org. Lett.* **2002**, *4*, 3541.

11. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
12. Olofsson, K. In *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley: Weinheim, 2003.
13. Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139.
14. Lipshutz, B. H.; Mollard, P. M.; Pfeiffer, S. S.; Chrisman, W. *J. Am. Chem. Soc.* **2002**, *124*, 14282.
15. Lipshutz, B. H.; Kim, S.-K.; Stevens, K. L.; Mollard, P. *Tetrahedron* **1998**, *54*, 1241.
16. Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333.
17. (a) Lipshutz, B. H.; Tasler, S.; Chrisman, W.; Spliethoff, B.; Tesche, B. *J. Org. Chem.* **2003**, *68*, 1177. (b) Tasler, S.; Lipshutz, B. H. *J. Org. Chem.* **2003**, *68*, 1190.
18. *Inductively Coupled Plasma Mass Spectrometry*; Montaser, A., Ed.; Wiley-VCH: New York, 1998.
19. Lipshutz, B. H.; Frieman, B. Manuscript in preparation.
20. Negishi, E. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Wiley: Chichester, 2002.
21. Vivian, R. W. Ph.D. Thesis, UCSB, 2002.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1317–1327
Tetrahedron

Intramolecular coupling of acetylenic groups of bis(alkynyl)phosphanes and silanes mediated by benzynezirconocene: a route to new mono- and tricyclic heterocycles

Nadine Pirio,[a] Stéphane Bredeau,[a] Laurence Dupuis,[a] Peter Schütz,[a] Bruno Donnadieu,[b] Alain Igau,[b] Jean-Pierre Majoral,[b,*] Jean-Claude Guillemin[c] and Philippe Meunier[a,*]

[a]*Laboratoire de Synthèse et d'Electrosynthèse Organométalliques associé au CNRS (UMR 5188), Faculté des sciences Gabriel, Université de Bourgogne, 6 boulevard Gabriel, 21000 Dijon, France*
[b]*Laboratoire de Chimie de Coordination du CNRS (UPR 8241), 205 route de Narbonne, 31077 Toulouse Cedex 4, France*
[c]*Laboratoire de Synthèses et Activation de Biomolécules associé au CNRS (UMR 6052), ENSCR, 35700 Rennes, France*

Received 3 April 2003; revised 30 July 2003; accepted 30 July 2003

Abstract—Benzo-zirconacyclohexadiene-phospha or silacyclobutene fused ring systems are easily prepared via a benzynezirconocene intermediate by means of thermolysis of Cp_2ZrPh_2 in the presence of bis(alkynyl)phosphanes or silanes. These polyunsaturated systems are the source of a variety of new mono- or tricyclic heterocycles incorporating either one or two heteroatoms.

1. Introduction

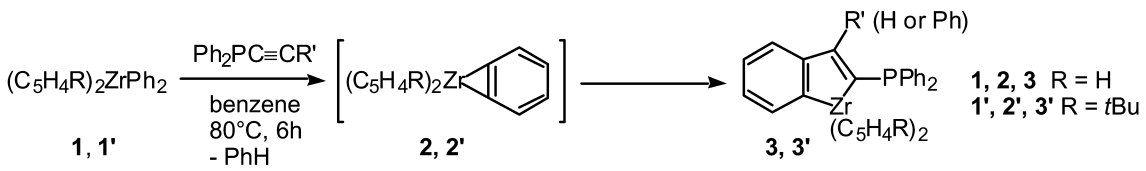
The development of new and practical methods for the formation of carbon–carbon bonds is currently among the main goals of a number of research groups throughout the world. In recent years much attention has been paid to the chemistry of group 4 elements and especially zirconium species to reach this objective.[1] Zirconocene complexes have shown a versatile behavior for such reactions. It was well demonstrated that the zirconocene fragment [Cp_2Zr] promoted the intramolecular coupling of alkynyl groups with formation of cyclic derivatives[2] or coupling of diynes with formation of zirconacyclic cumulenes[3,4] to quote a few examples. Some of the resulting metallacycles were found to be useful starting reagents for the synthesis of a variety of carbo- and heterocycles with carbon–carbon bond formation.[5] As an example, azazirconacyclopentadienes or zirconacyclopentadienes are a source of pyridine or benzene derivatives when reacted with alkynes.[6] Insertion of isocyanide[7,8] or carbon monoxide[8,9] on zirconacyclopentadienes and related species allowed the preparation of the corresponding cyclic imines or ketones. Insertion of acetylenic or olefinic systems into benzynezirconocene has also been described[10–12] leading via carbon–carbon bond formation to new metallafused rings.

A few years ago we reported a novel intramolecular coupling reaction of a bis(alkynyl)phosphane *t*BuP($C{\equiv}CPh)_2$ mediated by benzynezirconocene which provided a quite unexpected tricyclic zircona-1,2-dihydrophosphete which treated with HCl or $PhSbCl_2$ gave access to unprecedented mono- or tricyclic 1,2-dihydrophosphetes.[13] This was the first example, to our knowledge, of a reaction of dialkynes with arynezirconocene complexes. Therefore there was a need to check whether the cleavage of zirconium–carbon bonds with HCl, or transmetallation with various dihalogenated derivatives, of various zircona polyunsaturated heterocycles should allow us to propose a general and convenient procedure for the regioselective synthesis of a variety of new mono- or tricyclic heterocycles incorporating either one or two heteroatoms.

This paper affords a positive answer to these interrogations with the synthesis, using this methodology, of a variety of polyunsaturated systems incorporating one or two of the following elements: zirconium, phosphorus, silicon, germanium, tin, antimony and arsenic. None of these families of polycycles are accessible using known procedures. X-Ray diffraction studies of three of these

Keywords: C–C coupling; Diynes; Main-group element; Phosphorus; Silicon; Zirconium.
* Corresponding authors. Tel.: +33-561-333-123; fax: +33-561-553-003 (J.-P. M.); tel./fax: +33-380396100 (P. M.);
e-mail addresses: majoral@lcc-toulouse.fr; philippe.meunier@u-bourgogne.fr

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.07.013



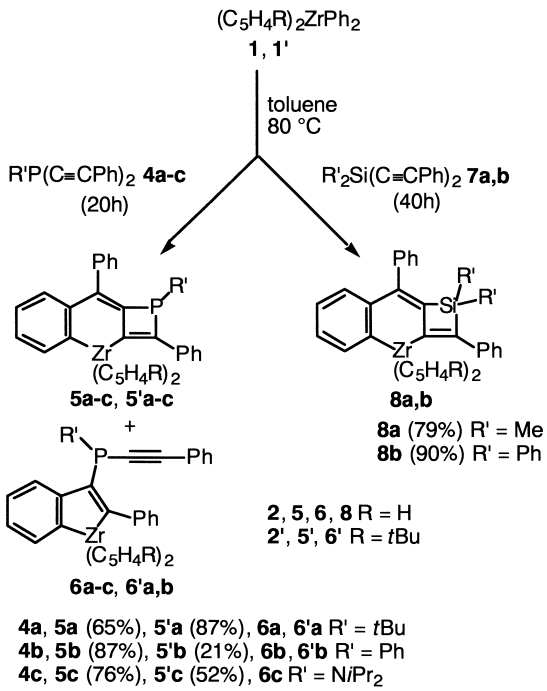
Scheme 1.

derivatives corroborated their structure and brought arguments for the mechanism of formation of these compounds.

2. Results and discussion

Thermolysis of $(\eta^5\text{-}C_5H_4R)_2ZrPh_2$ **1**, **1′** in the presence of mono(alkynyl)phosphanes $Ph_2PC{\equiv}CR'$ has previously been shown to produce 2-phosphino-1-zirconaindenes **3**, **3′** arising from the regiospecific insertion of the carbon–carbon triple bond of the acetylenic group into the zirconium–carbon bond of the in situ-generated benzyne-zirconocenes **2**, **2′** (Scheme 1).[11b]

A similar reaction was undertaken with bis(alkynyl)-phosphanes and diphenylzirconocene. Treatment of $R'P(C{\equiv}CPh)_2$ (**4a**: R′=*t*Bu, **4b**: R′=Ph, **4c**: R′=N*i*Pr$_2$) with $(\eta^5\text{-}C_5H_5)_2ZrPh_2$ **1** in toluene at 80 °C over 20 h did not afford the expected 2-(alkynyl)phosphino-1-zirconaindenes. Surprisingly, trapping of the transient benzyne complex $Cp_2Zr(\eta^2\text{-}C_6H_4)$ **2** by the diacetylenic phosphanes resulted in the formation of fused benzo-zirconacyclohexadiene-phosphacyclobutene rings **5a-c** (Scheme 2). ^{31}P NMR spectra of crude products displayed a largely major signal (>85%) at 59.9 (**5a**), 21.3 (**5b**) and 46.3 (**5c**) ppm beside a minor peak at −11.8, −30.1 and 4.2 ppm, respectively. A simple wash with pentane allowed the isolation of the zirconacycles **5a-c** in 65, 87, and 76% yield, respectively. The $\delta\,^{31}P$ values for **5a-c** are deshielded compared with those of starting phosphanes (**4a**: −38.9 ppm; **4b**: −62.8 ppm; **4c**: −16.6 ppm) indicating that the phosphorus atom is no more bonded to a sp carbon atom. The side complexes were identified as 3-(alkynyl)phosphino-1-zirconaindenes **6a-c** and will be discussed later.



Scheme 2. Synthesis of zirconacycles **5a-c**, **5′a-c** and **8a**,**b**.

Complexes **5a-c** were further characterized by the usual spectroscopic and analytical methods: ^1H NMR (two signals around 6 ppm for the two unequivalent cyclopentadienyl ligands) and ^{13}C NMR (no classical acetylenic carbon resonances in the 70–110 ppm range), IR (no characteristic C≡C absorption band around 2100 cm^{-1}), mass spectrometry and elemental analyses. Nevertheless identification based only on spectroscopic data was uncertain. However, an X-ray structural analysis of **5a** established the molecular structure of these tricyclic zircona-1,2-dihydrophosphetes and demonstrated the intramolecular coupling reaction of dialkynylphosphanes and zirconabenzyne. The solid-state structure of **5a** has already been reported in a preliminary communication.[13]

The same reaction performed with the more hindered bis(*tert*-butylcyclopentadienyl)diphenyl zirconium **1′** and the bis(phenylalkynyl)phosphanes **4a-c** led to the fully characterized *t*BuCp-substituted tricyclic complexes **5′a-c** (Scheme 2). These zirconacycles presented similar spectroscopic data to those of **5a-c** ($\delta\,^{31}P$=61.7 (**5′a**), 22.9 (**5′b**), 46.4 (**5′c**) ppm). In some cases, the side complexes namely 3-(alkynyl)phosphino-1-zirconaindenes **6′a**,**b** were also detected in the ^{31}P NMR spectra of the crude products (**6′a**: −12.6; **6′b**: −30.7 ppm).

Thermolysis of diphenylzirconocene in the presence of bis(alkynyl)silanes was investigated, in order to check if such a quite unusual intramolecular carbon bond formation involving *gem*-alkynyl groups can or cannot be extended to other *gem*-diacetylenic systems.

Addition of $R'_2Si(C{\equiv}CPh)_2$ (**7a**: R′=Me, **7b**: R′=Ph) to the transient benzynezirconocene **2** in toluene at 80 °C over 40 h provided the fused benzo-zirconacyclohexadiene-silacyclobutenes **8a**,**b** isolated as powders in 79 and 90% yield, respectively, after work-up (Scheme 2). Their ^1H NMR spectra showed one cyclopentadienyl signal at δ=5.99 (**8a**) and δ=6.05 (**8b**) ppm. IR and ^{13}C NMR data corroborated the absence of a Si–C≡C–Ph group indicating that the 2-(alkynyl)sila-1-zirconaindenes were not formed. All the other NMR data were in agreement with the tricyclic structure of **8**. Nevertheless, an X-ray structure determination of **8a** was undertaken in order to complete the characterization of these zirconacycles. The molecular view of **8a** is shown in Figure 1, and the most representative bond lengths and angles are summarized. This clearly shows that

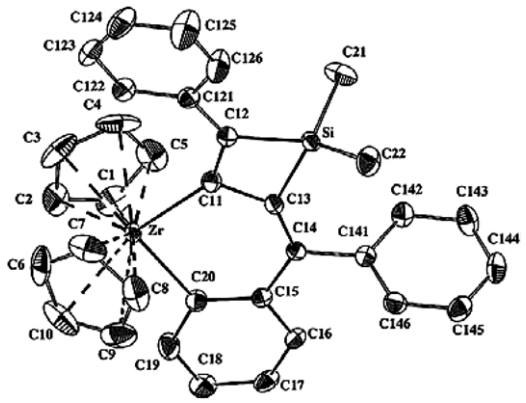
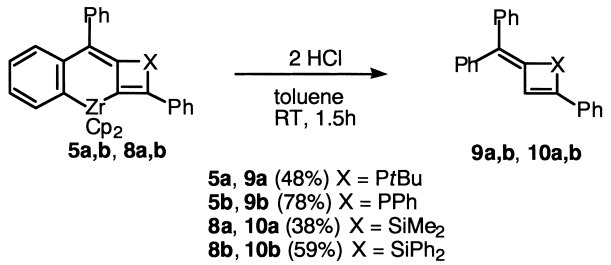


Figure 1. Molecular structure of **8a** (thermal ellipsoids at 50% probability). Selected bond lengths (Å) and angles (°): Zr–C20 2.267(2), C20–C15 1.416(3), C15–C14 1.483(3), C14–C13 1.357(3), C13–C11 1.522(3), Zr–C11 2.241(2), C11–C12 1.374(3), Si–C12 1.860(2), Si–C13 1.869(2); C20–Zr–C11 94.97(8), Zr–C11–C13 111.03(14), Zr–C11–C12 145.92(15), C12–C11–C13 103.05(17), C11–C13–Si 88.33(13), C11–C12–Si 93.32(14), C13–Si–C12 74.92(9).

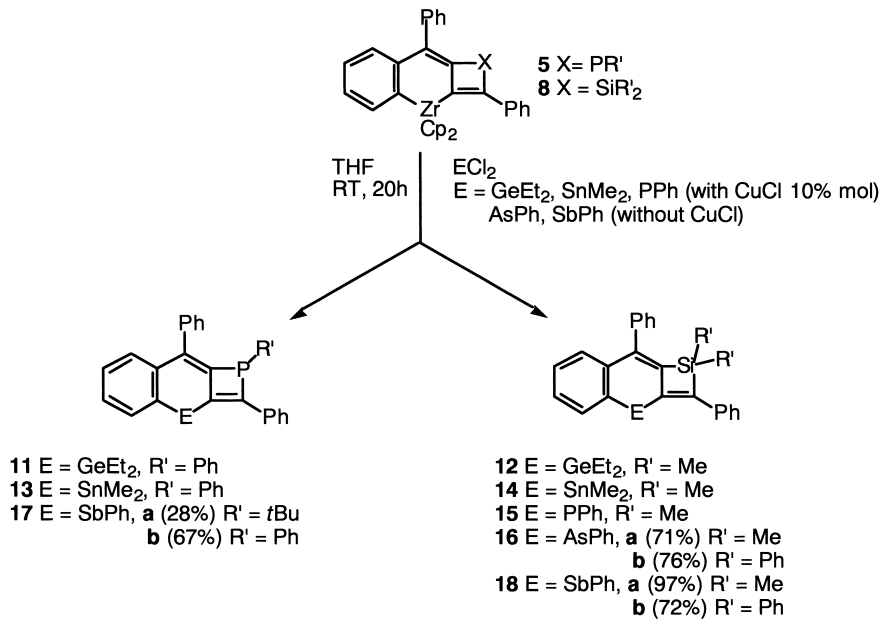
a fused benzo-zirconacyclohexadiene-silacyclobutene ring system is present in the structure. Interestingly only a few examples of metallacyclohexadienes of group 4 are known.[13,14] The molecular structure reveals a characteristic bent metallocene arrangement of the ligands around zirconium. Distances from the metal to the cyclopentadienyl ring centers are both 2.223 Å. The angle between the geometrical centers of both Cp rings and the zirconium is 134.36°. The bond lengths of the two Zr–C(sp^2) are 2.267(2) Å and 2.241(2) Å for Zr–C20 and Zr–C11, respectively. The C20–Zr–C11 angle is 94.97(8)°. These data are in good agreement with those of previously described zirconocenes. Indeed the molecular structures of **8a** and **5a** closely resemble each other, differences coming only from the four-membered ring.



Scheme 3. Reactivity of benzo-zirconacyclohexadiene-phospha or -sila-cyclobutenes towards HCl.

Amazingly, these new zirconacyclic complexes were found to be stable on exposure to air during several weeks in the solid state. Two types of reaction were performed with these zirconacycles: addition of HCl, and exchange reactions with a variety of dihalogenated main group element species. The cleavage of the two covalent zirconium–carbon bonds in **5** or **8** was achieved upon treatment with HCl leading to (*exo*-alkylidene)phospha- or silacyclobutene derivatives (Scheme 3), thus offering a new preparative method of these four-membered rings.[15] After appropriate work-up, the compounds **9** (X=PR′) and **10** (X=SiR'_2) were obtained as coloured oils in good to moderated yields (38–78%). They were characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectral analysis.

Exchange of the Cp_2Zr moiety was also attempted with group 14 and 15 elements by the way of a metallacycle transfer reaction of the carbon fragment from the six-membered zirconacycle to a main group halide (Scheme 4).[16] Complexes **5**, **8** did not react with Et_2GeCl_2 or Me_2SnCl_2 to give the corresponding six-membered germa- or stannacycles, even under prolonged reaction times or as high temperature. However, expected derivatives were obtained when the reaction was conducted in the presence of 10 mol% of CuCl.[17] The compounds **11**–**14** could not be isolated in pure form since a small amount of Cp_2ZrCl_2 always remained even after several column chromatographies, but mass spectrometry (parent ion $[M]^+$ and fragmentation peaks $[M-Et_2Ge]^+$ or $[M-Me_2Sn]^+$) was in



Scheme 4. Exchange reactions from benzo-zirconacyclohexadiene-phospha or -silacyclobutenes.

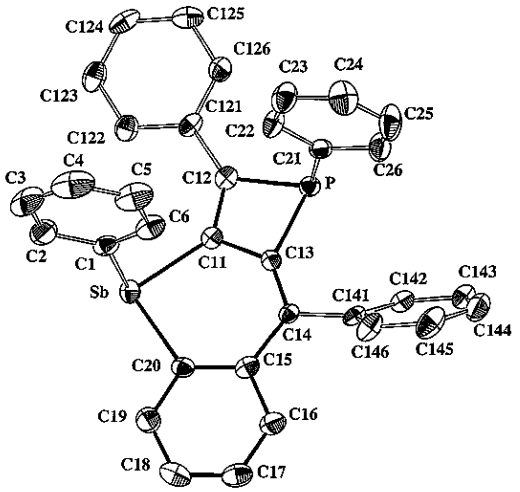
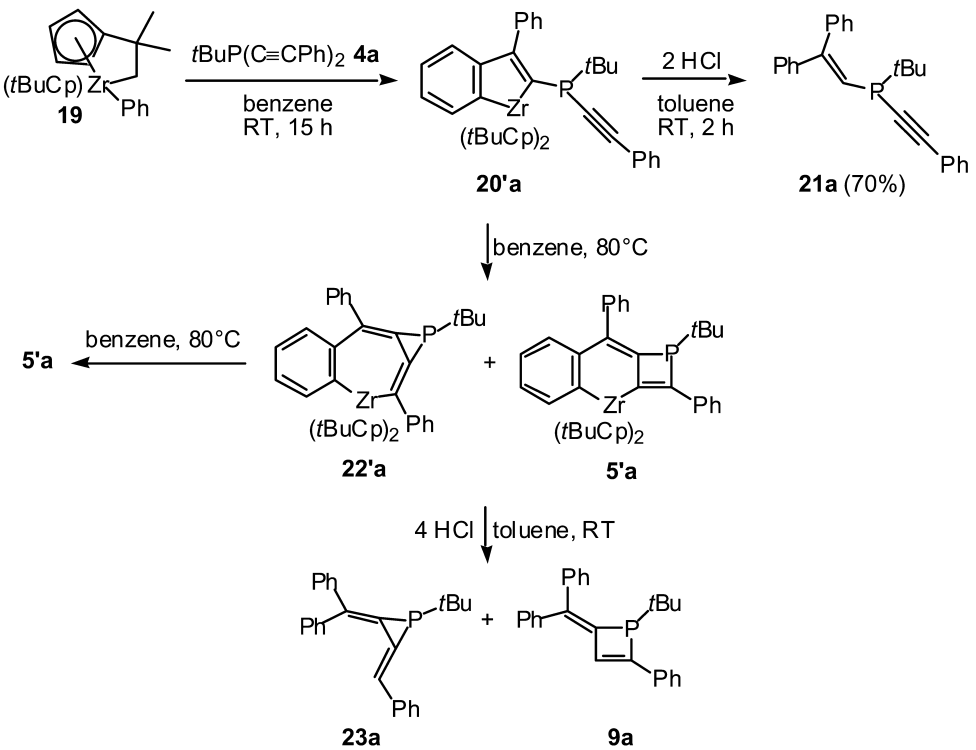


Figure 2. Molecular structure of **17b** (thermal ellipsoids at 50% probability). Selected bond lengths (Å) and angles (°): Sb–C1 2.155(4), Sb–C20 2.159(4), C20–C15 1.416(6), C15–C14 1.483(6), C14–C13 1.358(6), C13–C11 1.450(5), Sb–C11 2.122(4), C11–C12 1.364(6), P–C12 1.851(4), P–C13 1.858(4); C20–Sb–C1 98.14(15), C11–Sb–C1 92.25(16), C20–Sb–C11 90.64(15), Sb–C11–C13 121.3(3), Sb–C11–C12 137.0(3), C12–C11–C13 101.0(4), C11–C13–P 91.9(3), C11–C12–P 95.1(3), C13–P–C12 71.69(18).

agreement with the general formula of **11**–**14** and the other NMR data corroborated the proposed structure. Similarly the phosphorus tricyclic compound **15** contaminated by traces of Cp_2ZrCl_2 was obtained from the reaction of **8** with $PhPCl_2$. In marked contrast the treatment of **5** with $PhPCl_2$ gave rise to several phosphorus species as indicated by ^{31}P NMR. The six-membered arsacycles **16** were prepared from **8** and $PhAsCl_2$ and fully characterized; interestingly, it was not necessary to use CuCl in this case. The best results were obtained when $PhSbCl_2$ was used. The six-membered stibacycles **17**, **18** were isolated in quite good yield after work-up and characterized by usual spectroscopic and analytical methods. For the heterocycles incorporating phosphorus and antimony atoms, the transformation was diastereoselective as indicated by the singlet in the ^{31}P NMR spectrum of the crude product (δ ^{31}P=73.7 **17a**, 42.2 **17b** ppm). Confirmation of the identity of **17b** and as a consequence of the other tricyclic systems was achieved by a single-crystal X-ray study. The representation of the structure of **17b** is shown in Figure 2, and the relevant bond lengths and angles are summarized. The molecular structure shows that the compound **17b** has the expected [6,6,4]-fused ring system and is very similar to that of the previously described zirconacycle **5a**.[13] In the six-membered stibacyclic ring, the three Sb–C(sp^2) distances are identical in length to those found in known tertiary stibines,[18] e.g. Ph_3Sb 2.155 Å; $(C_4H_3S)_3Sb$ 2.129 Å. The phenyl groups linked to antimony and phosphorus atoms are in *trans* position.

Therefore, zirconatricyclic complexes appear to be useful reagents allowing, via reactions involving selective Zr–C bond cleavage or Zr-groups 14–15 exchanges, the formation of a variety of new polyunsaturated mono or tricyclic systems.

In order to gain a deeper understanding of the unusual intramolecular coupling of acetylenic groups of bis(phenylalkynyl)phosphanes or silanes using benzynezirconocene complexes, we investigated the reaction mechanism. When the bis(alkynyl)phosphane **4a** was allowed to react with $(\eta^5\text{-}C_6H_4t\text{Bu})_2ZrPh_2$ **1′** in benzene at 80 °C for only 4 h, the formation of several phosphorus species can be detected. The ^{31}P NMR spectrum of the crude product showed a major peak at δ=−16.5 ppm in addition to four minor peaks at δ=61.6 (**5′a**), δ=−12.6, δ=−38.9 (**4a**) and δ=−181.9 ppm. Further reaction time (16 h) at 80 °C resulted

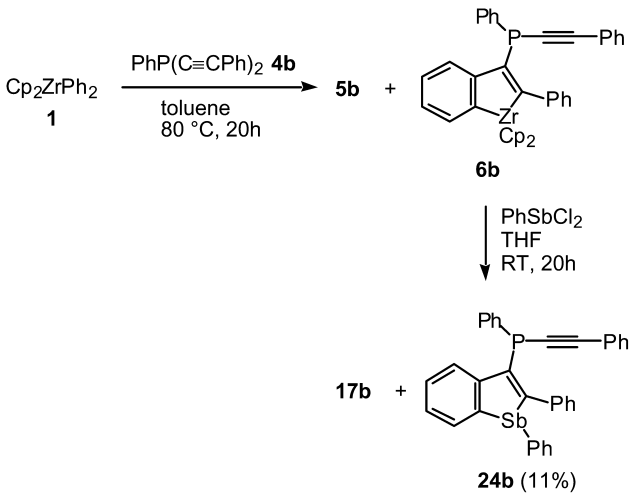


Scheme 5. Chemical evidence for the formation of a 2-(alkynyl)phosphinozirconaindene complex.

in the disappearance of the signals of the two intermediate complexes at −16.5 and −181.9 ppm as well as of the signal of the starting phosphane **4a**. The *t*BuCp-substituted tricyclic complex **5′a** was isolated after removal of the side product responsible of a signal at −12.6 ppm in ^{31}P NMR with pentane. In order to avoid the twofold insertion reaction of the bis(alkynyl)phosphane with the zirconium species, and to characterize the intermediates (δ^{31}P= −16.5, −181.9 ppm), we performed a similar reaction with the cyclometallated complex **19**. This compound, as a consequence of C–H bond activation of the methyl substituent of a *tert*-butyl group, often reacts at lower temperatures than benzynezirconocene.[19] Treatment of a freshly prepared solution of **19** in benzene at room temperature with **4a** afforded only one compound (δ^{31}P=−16.5 ppm) formed in near quantitative yield after stirring for 15 h (Scheme 5). It could not be isolated in pure form since a small amount of (*t*BuCp)$_2$ZrPh$_2$ **1′** always remained even after several treatments. Attempts to get suitable crystals for X-ray structure determination have failed up to now. The ^{31}P chemical shift is in the expected range for a P–C≡C unit. IR data are also instructive, as one characteristic absorption band appeared at 2172 cm^{-1} which can be assigned to the P–C≡C stretching mode of **20′a**. Surprisingly, the regioisomeric complex **6′a** (see Scheme 2) was not observed in the crude product. Thermolysis of **20′a** for 20 h at 80 °C in benzene gave **5′a** (Scheme 5). The reaction was monitored by ^{31}P NMR spectroscopy which showed the disappearance of the signal due to **20′a** which was replaced by the signal of the zirconacycle **5′a** along with a small signal at −181.9 ppm. Such a shielded signal is in favor of a constrained three-membered phosphorus ring, i.e. phosphirane.[20] This assumption is supported by the following experiment: addition of HCl 1N to the mixture of compounds obtained after heating **4a** and **1′** at 80 °C for 4 h, gave rise to the known compounds **9a**, **21a** and to the phospharadialene **23a** (δ^{31}P=−143.5 ppm)[20] (Scheme 5). Therefore, the structure of the intermediate at −181.9 ppm can be reasonably formulated as a zirconacycloheptatriene–phosphacyclopropane **22′a**.

The cleavage of the two covalent zirconium–carbon bonds of **20′a** was achieved upon treatment with HCl leading to the (alkenyl)(alkynyl)phosphane **21a** in 70% isolated yield as a coloured oil (Scheme 5). Mass spectrometry analysis (parent ion at 368 [M]$^+$) was in agreement with the general formula for **21a**. The δ^{31}P (−34.8 ppm) was in the expected range,[20] and the IR spectrum showed an absorption band at 2163 cm^{-1} clearly indicating the presence of a P–C≡C group. The ^{1}H and ^{13}C NMR data agreed with the proposed phosphane structure.

The last uncertainty is related to the structure of the compound responsible of the signal at −12.6 ppm which was postulated to be the regioisomeric complex **6′a**. A similar compound, i.e. **6b** was observed also when **4b** was directly heated in the presence of **1**. In order to have a better indirect knowledge of the structure of these derivatives, an exchange reaction with dichloro phenylstibine was attempted on the mixture **5b**+**6b** (Scheme 6). Addition of $PhSbCl_2$ to a solution of Cp_2ZrPh_2 **1** and $PhP(C{\equiv}CPh)_2$ **4b** in toluene afforded the two stibacyclic compounds **17b** and



Scheme 6. Chemical evidence for the formation of a 3-(alkynyl)phosphinozirconaindene complex.

24b. ^{31}P NMR spectrum exhibited as expected two singlets with very different chemical shifts (δ^{31}P=42.2 (**17b**) and −57.4 (**24b**) ppm). The 3-(alkynyl)phosphinostibaindene **24b** was isolated by fractional recrystallization as orange crystals in a very low yield. Full characterization by usual spectroscopic and analytical methods was completed by successful X-ray diffraction analysis. The molecular structure of the 3-substituted stibole **24b** is represented in Figure 3 and important bond lengths and angles are summarized. Therefore, these results clearly demonstrated that the two (alkynyl)phosphinozirconaindenes **20** or **20′** (major) and **6** or **6′** (minor) are formed when a diacetylenic phosphane is treated with zirconabenzyne: the strong interaction between the phosphorus lone pair and zirconium explains the high regioselectivity observed.

Therefore on the basis of NMR experiments and X-ray diffraction studies, we can propose the mechanism outlined in Scheme 7 for the preparation of **5** (i) formation of an

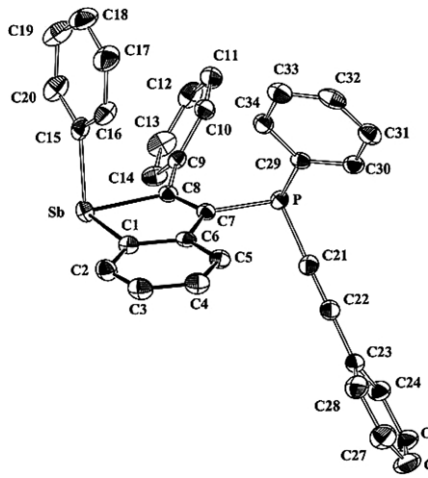
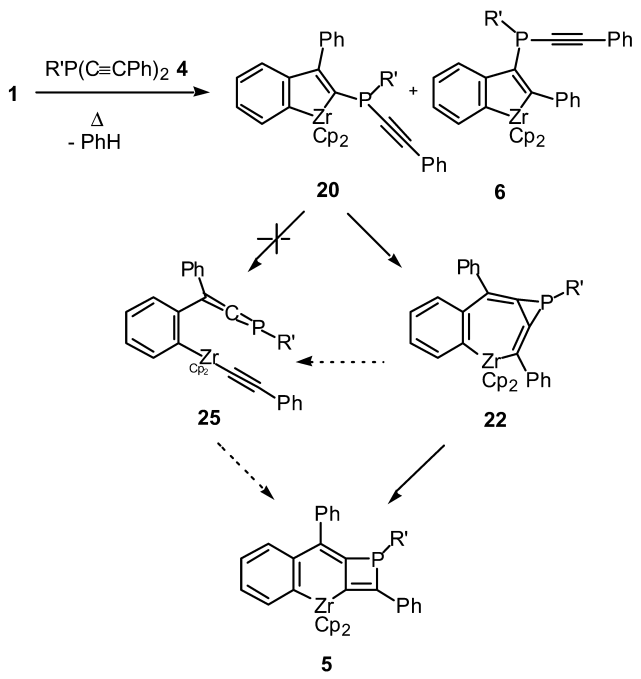


Figure 3. Molecular structure of **24b** (thermal ellipsoids at 50% probability). Selected bond lengths (Å) and angles (°): Sb–C15 2.1593(18), Sb–C1 2.1235(19), Sb–C8 2.1594(16), P–C7 1.8436(16), P–C29 1.8431(17), P–C21 1.7654(19), C21–C22 1.208(3), C22–C23 1.434(3); C15–Sb–C8 88.29(6), C1–Sb–C15 95.48(7), C1–Sb–C8 80.30(7), C29–P–C7 100.96(7), C21–P–C29 100.70(8), C21–P–C7 102.25(8), C22–C21–P 173.69(15), C21–C22–C23 177.78(19).



Scheme 7. Multistep insertion mechanism involved in the formation of fused zirconacycles **5**.

2-(alkynyl)phosphino-1-zirconaindene **20** arising from insertion reaction of one of the C≡C triple bond of **4** into a Zr–C bond of the transient zirconabenzyne **2** (ii) intramolecular insertion reaction of the second alkynyl group into a Zr–C bond of the intermediate **20** providing zirconacycloheptatriene **22** with a phosphacyclopropane side ring (iii) 1,2-migration of the phosphanyl group leading to zirconacycle **5**. In this case it is noteworthy that it is not possible to further transform complex **6** because of its regiochemistry. In addition the transient formation of the intermediate **25** from **22** which might give **5** cannot be completely ruled out even if no evidence of the formation of a phosphaallene species[21] was found in ^{31}P NMR spectra in any experiments (δ ^{31}P in the range 39–93 ppm). A similar mechanism was already proposed by Takahashi in the case of intramolecular coupling of acetylenic groups of bis-(alkynyl)silanes promoted by zirconocene [Cp_2Zr] or $Cp_2Zr(\eta^2\text{-}C_2H_2)$.[14b]

3. Conclusion

Thermolysis of Cp_2ZrPh_2 in the presence of bis(alkynyl)-phosphanes or silanes provides new tricyclic systems, namely benzo-zirconacyclohexadiene-phospha or -silacyclo-butenes. A three step mechanism can explain the unusual regioselective formation of these polycyclic compounds leading to new mono or tricyclic derivatives incorporating one or two group 14–15 elements. Studies on the reactivity and properties of these new families of heterocycles are underway.

4. Experimental

4.1. General data

All manipulations were carried out under an argon atmosphere. Mass spectra were determined by using a Kratos concept IS or a Nermag R10-10H spectrometer while NMR spectra were obtained by using a Bruker AC200 or DRX500 instrument at 300 K (chemical shifts are given in ppm relative to TMS for ^1H, ^{13}C nuclei and to H_3PO_4 for ^{31}P nucleus). IR spectra were recorded on a Bruker IFS66V spectrometer (only significant IR bands are reported). Combustion analyses were performed by the analytical service of LSEO of the Université de Bourgogne.

The diphenylzirconocene **1**[22] and the bis(*tert*butylcyclo-pentadienyl)diphenyl zirconium **1′**[23] were synthesized as described in literature.

4.2. Preparation of zirconacycles 5, 5′ and 8

A solution of $(C_5H_4R)_2ZrPh_2$ **1** (R=H) or **1′** (R=*t*Bu) and bis(phenylalkynyl)phosphane **4** or silane **7** in toluene was heated to 80 °C for 20 h (phosphane) to 40 h (silane). After removal of the solvent in vacuo, the resulting solid was washed with pentane (**5**, **5′**) or ether (**8**) to afford the expected complex.

4.2.1. Complex 5a. ($\eta^5\text{-}C_5H_5)_2ZrPh_2$ (1.195 g, 3.184 mmol) and *t*BuP(C≡CPh)$_2$ (0.923 g, 3.184 mmol) gave **5a** as orange crystals after recrystallization in toluene/pentane. Yield: 65% (1.210 g, 2.058 mmol).

$^{31}P\{^1H\}$ NMR (81 MHz, C_6D_6): δ=59.9 (s); ^1H NMR (200 MHz, C_6D_6): δ=7.39–6.63 (m, CH_{arom}), 6.56 and 6.26 (d, J(H,P)=0.6 Hz, 5H, CH_{Cp}), 0.74 (d, J(H,P)=11.3 Hz, 9H, (CH_3)$_3$CP); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ= 214.4 (d, J(C,P)=4.3 Hz, C_{quat}), 184.5 (s, C_{quat}), 163.9 (d, J(C,P)=2.4 Hz, C_{quat}), 150.1 (d, J(C,P)=6.2 Hz, C_{quat}), 143.1 (d, J(C,P)=6.2 Hz, C_{quat}), 142.2 (d, J(C,P)=10.1 Hz, C_{quat}), 140.9 (d, J(C,P)=6.7 Hz, C_{quat}), 140.0 (d, J(C,P)= 13.9 Hz, C_{quat}), 138.3, 131.7, 131.5, 129.5, 128.7, 128.4, 127.4, 127.0, 125.8, 125.7, 125.0 and 123.2 (s, CH_{arom}), 112.7 and 112.6 (s, CH_{Cp}), 33.2 (d, J(C,P)=29.8 Hz, (CH$_3$)$_3$$C$P), 28.2 (d, J(C,P)=12.0 Hz, (CH$_3$)$_3$CP); MS (DCI/CH_4): m/z (%): 587 (100) $[M+1]^+$. Anal. calcd for $C_{36}H_{33}PZr$ (587.9): C 73.55, H 5.66; found: C 73.76, H 5.86.

4.2.2. Complex 5b. ($\eta^5\text{-}C_5H_5)_2ZrPh_2$ (0.490 g, 1.300 mmol) and PhP(C≡CPh)$_2$ (0.400 g, 1.300 mmol) gave **5b** as an orange powder. Yield: 87% (0.690 g, 1.135 mmol).

$^{31}P\{^1H\}$ NMR (81 MHz, C_6D_6): δ=21.3 (s); ^1H NMR (200 MHz, C_6D_6): δ=7.03–6.85 (m, CH_{arom}), 6.08 and 5.94 (s, 5H, CH_{Cp}); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=235.2 (s, C_{quat}), 184.2 (s, C_{quat}), 162.5 (d, J(C,P)=6.1 Hz, C_{quat}), 150.7 (d, J(C,P)=6.1 Hz, C_{quat}), 142.5 (d, J(C,P)=5.0 Hz, C_{quat}), 139.4 (d, J(C,P)=4.4 Hz, C_{quat}), 138.0 (d, J(C,P)= 14.4 Hz, C_{quat}), 137.5 (s, C_{quat}), 136.7 (d, J(C,P)=6.6 Hz, C_{quat}), 133.0, 132.7, 132.4, 131.8, 131.4, 130.7, 130.1, 129.9, 128.4, 127.9, 127.5, 124.8 and 118.1 (s, CH_{arom}), 112.3 and 111.9 (s, CH_{Cp}); MS (70 eV): m/z (%): 606 (20) $[M]^+$. Anal. calcd for $C_{38}H_{29}PZr$ (607.9): C 75.09, H 4.81; found C 74.88, H 5.03.

4.2.3. Complex 5c. ($\eta^5\text{-}C_5H_5)_2ZrPh_2$ (0.143 g, 0.390 mmol) and (iPr)$_2$NP(C≡CPh)$_2$ (0.130 g, 0.390 mmol) gave **5c** as an orange powder. Yield: 76% (0.186 g, 0.295 mmol).

$^{31}P\{^1H\}$ NMR (81 MHz, C_6D_6): δ=46.3 (s); ^1H NMR (200 MHz, C_6D_6, 343 K): δ=7.49–6.45 (m, CH_{arom}), 6.18 and 5.90 (d, J(H,P)=2.7 Hz, 5H, CH_{Cp}), 3.39 (m, 2H, $(CH_3)_2CHNP$), 1.06 (d, J(H,H)=5.9 Hz, 6H, $(CH_3)_2CHNP$), 0.52 (d, J(H,H)=5.7 Hz, 6H, $(CH_3)_2CHNP$); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=217.4 (d, J(C,P)=10.4 Hz, C_{quat}), 184.2 (s, C_{quat}), 172.0 (s, C_{quat}), 151.5 (d, J(C,P)=5.5 Hz, C_{quat}), 148.3 (s, C_{quat}), 142.0 (d, J(C,P)=6.5 Hz, C_{quat}), 139.8 (d, J(C,P)=10.1 Hz, C_{quat}), 138.8 (d, J(C,P)=15.7 Hz, C_{quat}), 132.0, 131.9, 131.8, 130.5, 128.2, 127.6, 127.0, 126.4, 125.4, 125.3, 123.8 and 122.7 (s, CH_{arom}), 111.9 and 111.5 (s, CH_{Cp}), 25.3 (s, $(CH_3)_2CHNP$), 15.0 (s, $(CH_3)_2CHNP$); MS (70 eV): m/z (%): 629 (87) $[M]^+$. Anal. calcd for $C_{38}H_{38}NPZr$ (630.9): C 72.34, H 6.07, N 2.22; found C 72.58, H 6.01, N 2.11.

4.2.4. Complex 5′a. (η^5-C_5H_4tBu)$_2$ZrPh$_2$ (0.241 g, 0.496 mmol) and tBuP(C≡CPh)$_2$ (0.143 g, 0.493 mmol) gave **5′a** as a yellow powder. Yield: 87% (0.301 g, 0.430 mmol).

$^{31}P\{^1H\}$ NMR (81 MHz, C_6D_6): δ=61.7 (s); ^1H NMR (200 MHz, C_6D_6) δ=7.53–6.79 (m, CH_{arom}), 6.62–6.57 (m, 2H, CH_{arom}+CH_{tBuCp}), 6.41, 6.28, 6.21, 5.95, 5.87, 5.79 and 5.74 (pseudo-q, 1H, CH_{tBuCp}), 1.13 and 1.02 (s, 9H, $(CH_3)_3C_{tBuCp}$), 0.93 (d, J(H,P)=10.8 Hz, 9H, $(CH_3)_3CP$); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=214.2 (d, J(C,P)=4.6 Hz, C_{quat}), 184.8 (s, C_{quat}), 164.1 (s, C_{quat}), 150.5 (s, C_{quat}), 145.7 (s, C_{quat}), 143.5 (d, J(C,P)=5.5 Hz, C_{quat}), 142.7 (d, J(C,P)=10.2 Hz, C_{quat}), 142.0 (d, J(C,P)=4.6 Hz, C_{quat}), 141.2 (s, C_{quat}), 140.9 (d, J(C,P)=13.8 Hz, C_{quat}), 132.1, 131.8, 131.4, 128.3, 127.1, 126.9, 126.0, 125.8, 125.5 and 122.5 (s, CH_{arom}), 118.6, 114.0, 113.2, 111.3, 110.6, 106.1, 105.3 and 103.4 (s, CH_{tBuCp}), 33.9 (s, $(CH_3)_3C_{tBuCp}$), 33.6 (d, J(C,P)=31.4 Hz, $(CH_3)_3CP$), 33.3 (s, $(CH_3)_3C_{tBuCp}$), 31.6 and 30.9 (s, 2$(CH_3)_3C_{tBuCp}$), 28.5 (d, J(C,P)=12.0 Hz, $(CH_3)_3CP$); MS (DCI/CH_4): m/z (%): 699 (100) $[M+1]^+$. Anal. calcd for $C_{44}H_{49}PZr$ (700.1): C 75.49, H 7.05, P 4.42; found C 75.71, H 7.36, P 4.10.

4.2.5. Complex 5′b. (η^5-C_5H_4tBu)$_2$ZrPh$_2$ (0.502 g, 1.070 mmol) and PhP(C≡CPh)$_2$ (0.330 g, 1.070 mmol) gave **5′b** as a yellow powder. Yield: 21% (0.206 g, 0.286 mmol).

$^{31}P\{^1H\}$ NMR (81 MHz, $CDCl_3$): δ=22.9 (s); ^1H NMR (200 MHz, $CDCl_3$) δ=7.32–6.80 (m, CH_{arom}), 6.38 and 6.29 (dd, 4H, CH_{tBuCp}), 1.16 (s, 18H, $(CH_3)_3C_{tBuCp}$); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=216.6 (d, J(C,P)=5.3 Hz, C_{quat}), 184.4 (s, C_{quat}), 161.0 (d, J(C,P)=6.9 Hz, C_{quat}), 150.9 (d, J(C,P)=6.1 Hz, C_{quat}), 144.3 (s, C_{quat}), 142.6 (s, C_{quat}), 142.0 (d, J(C,P)=10.7 Hz, C_{quat}), 141.6 (d, J(C,P)=7.6 Hz, C_{quat}), 138.3 (d, J(C,P)=15.2 Hz, C_{quat}), 137.8 (s, C_{quat}), 137.1 (s, C_{quat}), 133.2, 132.8, 132.6, 131.1, 128.6, 128.5, 127.8, 127.7, 127.4, 126.4, 125.2, 125.1 and 122.6 (s, CH_{arom}), 114.8, 112.8, 111.2, 110.6, 109.8, 107.9, 107.8 and 105.3 (s, CH_{tBuCp}), 33.7 and 33.5 (s, $(CH_3)_3C_{tBuCp}$), 31.5 and 31.1 (s, $(CH_3)_3C_{tBuCp}$); MS (70 eV): m/z (%): 718 (93) $[M]^+$. Anal. calcd for $C_{46}H_{45}PZr$ (720.1): C 76.73, H 6.30; found C 76.85, H 6.49.

4.2.6. Complex 5′c. (η^5-C_5H_4tBu)$_2$ZrPh$_2$ (0.206 g, 0.424 mmol) and (iPr)$_2$NP(C≡CPh)$_2$ (0.141 g, 0.423 mmol) gave **5′c** as orange powder. Yield: 52% (0.163 g, 0.219 mmol).

$^{31}P\{^1H\}$ NMR (81 MHz, C_6D_6): δ=46.4 (s); ^1H NMR (200 MHz, C_6D_6, 345 K): δ=7.47–7.42 (m, 2H, CH_{arom}), 7.34–6.63 (m, CH_{arom}), 6.45 and 6.22 (pseudo-q, 1H, CH_{tBuCp}), 6.18–6.14 (m, 2H, CH_{tBuCp}), 5.95–5.85 (m, 4H, CH_{tBuCp}), 3.42 (m, 2H, $(CH_3)_2CHNP$), 1.16 (s, 9H, $(CH_3)_3C_{tBuCp}$), 1.06 (d, J(H,H)=6.2 Hz, 6H, $(CH_3)_2CHNP$), 1.01 (s, 9H, $(CH_3)_3C_{tBuCp}$), 0.76 (d, J(H,H)=6.6 Hz, 6H, $(CH_3)_2CHNP$); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=217.5 (d, J(C,P)=9.6 Hz, C_{quat}), 184.9 (s, C_{quat}), 171.6 (s, C_{quat}), 151.7 (d, J(C,P)=5.7 Hz, C_{quat}), 149.7 (s, C_{quat}), 144.7 (s, C_{quat}), 142.6 (d, J(C,P)=7.6 Hz, C_{quat}), 142.0 (s, C_{quat}), 140.6 (d, J(C,P)=10.5 Hz, C_{quat}), 139.1 (d, J(C,P)=16.3 Hz, C_{quat}), 132.1, 131.9, 131.1, 128.4, 127.9, 127.3, 126.6, 125.9, 125.7, 125.2 and 122.4 (s, CH_{arom}), 115.3, 114.2, 110.9, 110.8, 110.1, 108.9, 107.8 and 105.4 (s, CH_{tBuCp}), 33.5 and 33.4 (s, $(CH_3)_3C_{tBuCp}$), 31.7 and 31.0 (s, $(CH_3)_3C_{tBuCp}$)—NMR resonances for $(CH_3)_2CHNP$ moiety were not observed; MS (DCI/CH_4): m/z (%): 742 (100) $[M+1]^+$. Anal. calcd for $C_{46}H_{54}NPZr$ (743.1): C 74.34, H 7.42, N 1.88, P 4.16; found C 74.45, H 7.37, N 1.81, P 4.15.

4.2.7. Complex 8a. (η^5-C_5H_5)$_2$ZrPh$_2$ (0.900 g, 0.240 mmol) and Me_2Si(C≡CPh)$_2$ (0.620 g, 0.240 mmol) gave **8a** as a yellow powder. Yield: 79% (1.060 g, 0.190 mmol).

^1H NMR (200 MHz, C_6D_6) δ=7.35–6.85 (m, CH_{arom}), 5.99 (s, 10H, CH_{Cp}), 0.19 (s, 6H, $(CH_3)_2Si$); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=230.4, 185.6, 175.0, 153.1, 152.1, 147.1, 142.9 and 141.4 (s, C_{quat}), 134.0, 131.2, 129.9, 128.3, 128.0, 127.0, 126.7, 125.8, 124.5 and 122.8 (s, CH_{arom}), 111.4 (s, CH_{Cp}), −0.3 (s, $(CH_3)_2Si$); MS (DCI/CH_4): m/z (%): 557 (12) $[M]^+$. Anal. calcd for $C_{34}H_{30}SiZr$ (557.9): C 73.20, H 5.42; found C 73.22, H 5.52.

4.2.8. Complex 8b. (η^5-C_5H_5)$_2$ZrPh$_2$ (1.190 g, 3.170 mmol) and Ph_2Si(C≡CPh)$_2$ (1.220 g, 3.170 mmol) gave **8b** as a yellow powder. Yield: 90% (1.940 g, 2.850 mmol).

^1H NMR (200 MHz, C_6D_6) δ=6.57–8.14 (m, CH_{arom}), 6.05 (s, 10H, CH_{Cp}); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=235.6, 185.9, 172.3, 152.5, 150.2, 146.2, 144.1 and 140.9 (s, C_{quat}), 135.6 and 135.1 (s, CH_{arom}), 134.9 (s, C_{quat}), 133.5 (s, CH_{arom}), 133.2 (s, C_{quat}), 132.5, 131.7, 130.5, 129.6, 128.5, 128.4, 128.3, 127.8, 127.4, 125.8, 124.6 and 123.0 (s, CH_{arom}), 111.9 (s, CH_{Cp}); MS (70 eV): m/z (%): 680 (8) $[M]^+$. Anal. calcd for $C_{44}H_{34}SiZr$ (682.1): C 77.53, H 4.99; found C 77.24, H 5.24.

4.3. Preparation of heterocycles 9 and 10

A solution of toluene (20 mL) saturated with HCl was added dropwise at 0 °C to a solution of zirconacycles **5** or **8** in toluene (20 mL) and stirred for 1.5 h at room temperature. The volatile components were then removed in vacuo and the resulting oil was extracted with pentane (20 mL) and filtered. The crude product was purified by column chromatography (SiO_2, pentane/ether: 99/1) to afford the expected compound as coloured oil.

4.3.1. Compound 9a. From 0.826 g of complex **5a** (1.400 mmol) was isolated 0.250 g (0.680 mmol, 48%) of **9a** as a yellow oil.

$^{31}P\{^1H\}$ NMR (81 MHz, C_6D_6): δ=39.7 (s); ^1H NMR (200 MHz, C_6D_6) δ=7.59–6.90 (m, CH_{arom} and =C*H*), 0.92 (d, *J*(H,P)=11.7 Hz, 9H, (CH_3)$_3$CP); $^{13}C\{^1H\}$ NMR (125 MHz, C_6D_6): δ=154.6 (d, *J*(C,P)=5.5 Hz, C_{quat}), 142.3 (s, C_{quat}), 140.9 (d, *J*(C,P)=5.5 Hz, C_{quat}), 138.1 (d, *J*(C,P)=6.5 Hz, C_{quat}), 136.6 (d, *J*(C,P)=10.2 Hz, =*C*H), 136.3 (d, *J*(C,P)=10.2 Hz, C_{quat}), 135.5 (s, C_{quat}), 131.0, 130.9, 130.7, 128.8, 128.6, 128.4, 128.3, 127.9, 127.7, 126.7 and 126.6 (s, *C*H$_{arom}$), 32.4 (d, *J*(C,P)=27.0 Hz, (CH$_3$)$_3$*C*P), 27.8 (d, *J*(C,P)=12.3 Hz, (*C*H$_3$)$_3$CP); MS (70 eV): *m*/*z* (%): 368 (8) $[M]^+$.

4.3.2. Compound 9b. From 0.600 g of complex **5b** (0.990 mmol) was isolated 0.300 g (0.770 mmol, 78%) of **9b** as a yellow oil.

$^{31}P\{^1H\}$ NMR (81 MHz, C_6D_6): δ=13.2 (s); ^1H NMR (200 MHz, C_6D_6) δ=7.59 (s, 1H, =C*H*), 7.58–6.52 (m, CH_{arom}); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=154.5 (s, C_{quat}), 140.5 (d, *J*(C,P)=1.5 Hz, C_{quat}), 140.0 (d, *J*(C,P)=6.1 Hz, C_{quat}), 136.8 (s, C_{quat}), 136.7 (d, *J*(C,P)=11.4 Hz, =*C*H), 136.5 (d, *J*(C,P)=3.0 Hz, C_{quat}), 136.4, 135.9 and 136.8 (s, C_{quat}), 136.6, 132.8, 132.4, 130.3, 129.8, 129.7, 128.9, 128.7, 128.5 and 128.1 (s, *C*H$_{arom}$), 127.7 (d, *J*(C,P)=3.0 Hz, *C*H$_{arom}$); MS (70 eV): *m*/*z* (%): 388 (100) $[M]^+$.

4.3.3. Compound 10a. From 0.200 g of complex **8a** (0.360 mmol) was isolated 0.045 g (0.130 mmol, 38%) of **10a** as an orange oil.

^1H NMR (200 MHz, C_6D_6) δ=7.91 (s, 1H, =CH), 7.46–7.01 (m, CH_{arom}), 0.45 (s, 6H, (CH_3)$_2$Si); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=160.1 (s, C_{quat}), 148.1 (s, =*C*H), 144.6, 144.3, 141.7, 140.5 and 137.7 (s, C_{quat}), 131.1, 130.7, 129.0, 128.9, 128.6, 128.5, 128.2, 128.1, 127.4 and 127.3 (s, *C*H$_{arom}$), −0.51 (s, (*C*H$_3$)$_2$Si); MS (70 eV): *m*/*z* (%): 338 (100) $[M]^+$.

4.3.4. Compound 10b. From 0.370 g of zirconacycle **8b** (0.540 mmol) was isolated 0.150 g (0.320 mmol, 59%) of **10b** as a yellow oil.

^1H NMR (200 MHz, C_6D_6) δ=8.24–8.10 (m, 5H, CH_{arom}), 7.47–6.22 (m, 20H, CH_{arom}), 6.21 (s, 1H, =C*H*); $^{13}C\{^1H\}$ NMR (125 MHz, C_6D_6): δ=158.4 (s, C_{quat}), 151.8 (s, =*C*H), 144.1, 142.6, 141.6, 141.4, 138.0 and 131.1 (s, C_{quat}), 129.3, 129.1, 128.8, 128.7, 128.65, 128.6, 128.5, 128.4, 128.3, 127.7, 127.5 and 125.7 (s, *C*H$_{arom}$); MS (70 eV): *m*/*z* (%): 462 (2) $[M]^+$.

4.4. Preparation of heterocycles 11–15

A solution of ECl_2 (E=Et_2Ge, Me_2Sn, PhP) in THF was added dropwise to a suspension of complex **5** or **8** and CuCl (10 mol%) in THF at room temperature. The reaction mixture was stirred for 4 h (**13**, **14**) or 20 h (**11**, **12**, **15**). After removal of the solvent in vacuo, the residue was extracted with ether (**11**, **12**, **14**, **15**) or pentane (**13**) and purified by column chromatography (SiO_2, ether) to afford the expected derivative.

4.4.1. Compound 11. Et_2GeCl_2 (0.10 mL, 0.600 mmol) and CuCl (0.006 g, 0.060 mmol) in THF (5 mL) and a solution of **5b** (0.379 g, 0.600 mmol) in THF (15 mL) gave **11** as a yellow powder.

$^{31}P\{^1H\}$ (81 MHz, C_6D_6): δ=43.4 (s); ^1H NMR (200 MHz, C_6D_6): δ=7.60–7.11 (m, CH_{arom}), 1.57 and 1.31 (q, 2H, GeCH_2CH$_3$), 1.28 and 1.21 (t, 3H, GeCH$_2$CH_3); MS (70 eV): *m*/*z* (%): 519 (2) $[M]^+$.

4.4.2. Compound 12. Et_2GeCl_2 (0.05 mL, 0.370 mmol) and CuCl (0.004 g, 0.037 mmol) in THF (5 mL) and a solution of **8a** (0.210 g, 0.370 mmol) in THF (15 mL) gave **12** as a yellow powder.

^1H NMR (200 MHz, C_6D_6): δ=7.74–7.10 (m, CH_{arom}), 1.64 (q, 4H, GeCH_2CH$_3$), 1.33 (t, 6H, GeCH$_2$CH_3), 0.22 (s, 6H, (CH_3)$_2$Si); MS (70 eV): *m*/*z* (%): 468 (29) $[M]^+$.

4.4.3. Compound 13. Me_2SnCl_2 (0.210 g, 0.950 mmol) and CuCl (0.010 g, 0.095 mmol) in THF (7 mL) and a solution of **5b** (0.582 g, 0.950 mmol) in THF (20 mL) gave **13** as a yellow powder.

$^{31}P\{^1H\}$ (81 MHz, C_6D_6): δ=47.8 (s); ^1H NMR (200 MHz, C_6D_6): δ=7.78–6.86 (m, CH_{arom}), 0.47 and 0.29 (s, 3H, (CH_3)$_2$Sn); MS (70 eV): *m*/*z* (%): 536 (45) $[M]^+$.

4.4.4. Compound 14. Me_2SnCl_2 (0.079 g, 0.360 mmol) and CuCl (g, 0.036 mmol) in THF (3 mL) and a solution of **8a** (0.200 g, 0.360 mmol) in THF (10 mL) gave **14** as a yellow powder.

^1H NMR (200 MHz, C_6D_6): δ=7.74–7.10 (m, CH_{arom}), 0.65 and 0.33 (s, 6H, (CH_3)$_2$Sn); MS (70 eV): *m*/*z* (%): 486 (85) $[M]^+$.

4.4.5. Compound 15. $PhPCl_2$ (4.08 mL, 0.600 mmol) and CuCl (0.006 g, 0.060 mmol) in THF (10 mL) and a solution of **8a** (0.336 g, 0.600 mmol) in THF (15 mL) gave **15** as a yellow powder.

$^{31}P\{^1H\}$ (81 MHz, C_6D_6): δ=49.8 (s); ^1H NMR (200 MHz, C_6D_6): δ=8.36–8.32 (m, CH_{arom}), 8.06–8.02 (m, CH_{arom}), 7.82–7.78 (m, CH_{arom}), 7.40–7.14 (m, CH_{arom}), 6.99–6.84 (m, CH$_{arom}$), 0.28 and 0.15 (s, 3H, (CH_3)$_2$Si); MS (70 eV): *m*/*z* (%): 444 (100) $[M]^+$.

4.5. Preparation of heterocycles 16–18

A solution of ECl_2 (E=PhAs, PhSb) in toluene was added dropwise to a solution of complex **5** or **8** in toluene cooled to −30 °C. The reaction mixture was left to warm slowly to room temperature and stirred for 20 h. After removal of the solvent in vacuo, the residue was extracted with pentane and purified by column chromatography (SiO_2, pentane) to afford the expected compound.

4.5.1. Compound 16a. $PhAsCl_2$ (0.110 g, 0.520 mmol) in toluene (5 mL) and a solution of **8a** (0.290 g, 0.520 mmol)

in toluene (7 mL) gave **16a** as a yellow powder. Yield: 71% (0.180 g, 0.360 mmol).

^{1}H NMR (200 MHz, C_6D_6): δ=7.70–6.84 (m, CH_{arom}), 0.27 and 0.22 (s, 3H, (CH_3)$_2$Si); ^{13}C{^{1}H} (50 MHz, $CDCl_3$): δ=168.0, 157.5, 145.2, 143.0, 142.1, 138.3 and 137.5 (s, C_{quat}), 136.3 (s, CH$_{arom}$), 136.2 and 136.0 (s, C_{quat}), 132.8, 129.7, 129.3, 129.2, 129.1, 129.0, 128.6, 128.4, 128.3, 127.2 and 126.8 (s, CH$_{arom}$), −0.3 and −1.2 (s, (CH$_3$)$_2$Si); MS (70 eV): *m*/*z* (%): 488 (100) [M]$^+$. Anal. calcd for $C_{30}H_{25}AsSi$ (488.5): C 73.76, H 5.16; found C 73.66, H 5.12.

4.5.2. Compound 16b. $PhAsCl_2$ (0.220 g, 0.990 mmol) in toluene (10 mL) and a solution of **8b** (0.670 g, 0.990 mmol) in toluene (17 mL) gave **16b** as a yellow powder. Yield: 76% (0.463 g, 0.760 mmol).

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.67–7.53 (m, CH_{arom}), 7.46–7.14 (m, CH_{arom}); ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ= 165.2, 162.0, 143.2, 142.2, 141.5, 138.0, 137.5 and 138.2 (s, C_{quat}), 136.0, 135.6, 135.5, 135.4, 135.3, 135.0, 134.8 and 134.5 (s, CH$_{arom}$), 133.6, 133.1 and 133.0 (s, C_{quat}), 132.4, 130.8, 130.3, 130.2, 129.8, 129.4, 129.3, 128.9, 128.8, 128.6, 128.3, 128.2, 128.1, 128.0 and 127.7 (s, CH$_{arom}$); MS (70 eV): *m*/*z* (%): 612 (100) [M]$^+$. Anal. calcd for $C_{40}H_{29}AsSi$ (612.7): C 78.42, H 4.77; found C 78.23, H 4.89.

4.5.3. Compound 17a. $PhSbCl_2$ (0.303 g, 1.112 mmol) in toluene (10 mL) and a solution of **5a** (0.660 g, 1.124 mmol) in toluene (15 mL) gave **17a** as a yellow powder. Yield: 28% (0.175 g, 0.309 mmol).

^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$): δ=73.7 (s); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.83–7.78 (m, 2H, CH_{arom}), 7.59–7.06 (m, CH_{arom}), 0.66 (d, J(H,P)=12.0 Hz, 9H, (CH_3)$_3$CP); ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ=163.3 (d, J(C,P)=5.8 Hz, C_{quat}), 146.9 (d, J(C,P)=6.9 Hz, C_{quat}), 140.7 (s, C_{quat}), 140.2 (d, J(C,P)=3.5 Hz, C_{quat}), 140.1 (s, CH$_{arom}$), 137.5–137.3 (2d overlapped, C_{quat}), 137.1 (d, J(C,P)=8.1 Hz, C_{quat}), 136.7 (s, CH$_{arom}$), 135.1 (d, J(C,P)=2.3 Hz, C_{quat}), 133.9 (s, C_{quat}), 131.3, 129.6, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.6, 127.8, 127.2, 127.1 and 127.0 (s, CH$_{arom}$), 33.4 (d, J(C,P)=27.0 Hz, (CH$_3$)$_3$$C$P), 27.6 (d, J(C,P)=12.3 Hz, (CH$_3$)$_3$CP); MS (DCI/CH_4): *m*/*z* (%): 565 (100) [M+1]$^+$, 564 (49) [M]$^+$. Anal. calcd for $C_{32}H_{28}PSb$ (565.3): C 67.99, H 4.99; found C 67.52, H 5.27.

4.5.4. Compound 17b. $PhSbCl_2$ (0.183 g, 6.780 mmol) in toluene (10 mL) and a solution of **5b** (0.412 g, 0.670 mmol) in toluene (20 mL) gave **17b** as a yellow powder. Yield: 67% (0.260 g, 0.450 mmol). Recrystallization from pentane/ether (1/1) afforded **17b** as yellow crystals (0.100 g, 0.170 mmol, 25%).

^{31}P{^{1}H} (81 MHz, $CDCl_3$): δ=42.2 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.75–7.73 (m, 2H, CH_{arom}), 7.60–7.58 (m, 2H, CH_{arom}), 7.39–7.11 (m, CH_{arom}); ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ=161.9 (s, C_{quat}), 148.4 (d, J(C,P)= 7.6 Hz, C_{quat}), 140.1 (d, J(C,P)=2.3 Hz, C_{quat}), 139.4 (s, CH$_{arom}$), 138.9 (d, J(C,P)=4.5 Hz, C_{quat}), 137.7 (d, J(C,P)= 6.1 Hz, C_{quat}), 136.8 (d, J(C,P)=6.1 Hz, C_{quat}), 136.6 (d, J(C,P)=4.5 Hz, C_{quat}), 136.4 (s, CH$_{arom}$), 135.8, 135.7 and 134.4 (s, C_{quat}), 133.0, 132.8, 130.5, 129.9, 129.6 and 129.5 (s, CH$_{arom}$), 129.4 (d, J(C,P)=1.4 Hz, CH$_{arom}$), 129.2 (s, CH$_{arom}$), 129.1 (d, J(C,P)=1.5 Hz, CH$_{arom}$), 128.6, 128.5, 128.3, 127.4, 127.3, 126.7 and 126.6 (s, CH$_{arom}$); MS (70 eV): *m*/*z* (%): 584 (100) [M]$^+$. Anal. calcd for $C_{34}H_{24}PSb$ (585.3): C 69.77, H 4.13; found C 69.69, H 4.06.

4.5.5. Compound 18a. $PhSbCl_2$ (0.125 g, 0.460 mmol) in toluene (5 mL) and a solution of **8a** (0.256 g, 0.460 mmol) in toluene (10 mL) gave **18a** as yellow powder. Yield: 97% (0.240 g, 0.448 mmol).

^{1}H NMR (200 MHz, $CDCl_3$): δ=7.78–7.68 (m, CH_{arom}), 7.59–7.15 (m, CH_{arom}), 0.47 and 0.37 (s, 3H, (CH_3)$_2$Si); ^{13}C{^{1}H} (50 MHz, $CDCl_3$): δ=172.5, 157.5, 146.0, 144.0 and 139.7 (s, C_{quat}), 139.4 (s, CH$_{arom}$), 139.0 and 137.4 (s, C_{quat}), 135.7 (s, CH$_{arom}$), 135.1 and 133.4 (s, C_{quat}), 130.4, 129.6, 129.1, 129.0, 128.8, 128.4, 128.3, 128.0 and 126.8 (s, CH$_{arom}$), −0.4 and −1.0 (s, (CH$_3$)$_2$Si); MS (70 eV): *m*/*z* (%): 534 (62) [M]$^+$. Anal. calcd for $C_{30}H_{25}SbSi$ (535.4): C 67.30, H 4.71; found C 67.19, H 4.58.

4.5.6. Compound 18b. $PhSbCl_2$ (0.139 g, 0.510 mmol) in toluene (10 mL) and a solution of **8b** (0.352 g, 0.51 mmol) in toluene (15 mL) gave **18b** as yellow crystals. Yield: 72% (0.242 g, 0.367 mmol).

^{1}H NMR (200 MHz, C_6D_6): δ=8.25–8.08 (m, CH_{arom}), 7.81–7.65 (m, CH_{arom}), 7.56–7.34 (m, CH_{arom}), 7.27–6.75 (m, CH_{arom}); ^{13}C{^{1}H} (50 MHz, $CDCl_3$): δ=169.0, 146.4, 144.2, 143.8, 143.4, 140.8 and 138.2 (s, C_{quat}), 136.0, 135.6, 135.5, 135.4, 135.3, 135.0, 134.8 and 134.5 (s, CH$_{arom}$), 133.6, 133.1 and 133.0 (s, C_{quat}), 132.4, 130.8, 130.3, 130.2, 129.8, 129.4, 129.3, 128.9, 128.8, 128.6, 128.3, 128.2, 128.1, 128.0 and 127.7 (s, CH$_{arom}$); MS (70 eV): *m*/*z* (%): 658 (5) [M]$^+$. Anal. calcd for $C_{40}H_{29}SbSi$ (659.5): C 72.85, H 4.43; found C 72.79, H 4.28.

4.5.7. Synthesis of phosphane 21a. A solution of (*t*BuCp)$_2$ $ZrPh_2$ **1′** (0.442 g, 0.910 mmol) in benzene (10 mL) was refluxed during 6 h. The reaction mixture was left to warm slowly to room temperature and *t*BuP(C≡CPh)$_2$ **4a** (0.264 g, 0.910 mmol) in benzene (10 mL) was added dropwise. Then after 15 h of stirring at room temperature, the reaction mixture was cooled to −30 °C and a solution of HCl in toluene (C=0.3 mol L^{-1}, 6.05 mL, 1.810 mmol) was added dropwise and the reaction mixture was stirred for 2 h at room temperature. After removal of the solvent in vacuo the residue was extracted by pentane and purified by column chromatography (SiO_2, pentane) to afford **21a** as a yellow oil. Yield: 70% (0.140 g, 0.380 mmol).

^{31}P{^{1}H} (81 MHz, $CDCl_3$): δ=−34.8 (s); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.59–7.55 (m, CH_{arom}), 7.48–7.42 (m, CH_{arom}), 6.87 (d, J(H,P)=3.9 Hz, 1H, CH=), 1.35 (d, J(H,P)=13.4 Hz, 9H, (CH_3)$_3$CP); ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ=157.7 (d, J(C,P)=26.6 Hz, =CPh$_2$), 142.9 (d, J(C,P)=7.9 Hz, C_{quat}), 140.4 (d, J(C,P)=5.9 Hz, C_{quat}), 132.2 and 131.9 (s, CH_{arom}), 130.8 (d, J(C,P)=3.9 Hz, CH_{arom}), 128.6, 128.5, 128.1, 127.4 and 123.8 (s, CH_{arom}), 123.6 (d, J(C,P)=3.9 Hz, CH=), 104.3 (d, J(C,P)=2.0 Hz, ≡C–Ph), 88.7 (d, J(C,P)=20.7 Hz, P–C≡), 32.1 (d,

J(C,P)=5.9 Hz, $(CH_3)_3CP$), 27.8 (d, J(C,P)=14.7 Hz, $(CH_3)_3CP$); IR (KBr): ν=2163 cm^{-1} (C≡C); MS (70 eV): m/z (%): 368 (91) $[M]^+$.

4.5.8. Synthesis of heterocycle 24b. A solution of Cp_2ZrPh_2 **1** (0.260 g, 0.700 mmol) and $PhP(C{\equiv}CPh)_2$ **4b** (0.220 g, 0.700 mmol) in toluene (20 mL) was heated to 80 °C for 20 h. Then the reaction mixture was cooled to −35 °C and a solution of $PhSbCl_2$ (0.190 g, 0.700 mmol) in THF (10 mL) was added dropwise and the reaction mixture was stirred for 20 h at room temperature. After removal of the solvent in vacuo, the residue was extracted by pentane and purified by column chromatography (SiO_2, pentane). Fractional recrystallization from ether/pentane (1/1) afforded **24b** as orange crystals. Yield: 11% (0.050 g, 0.08 mmol).

$^{31}P\{^1H\}$ (81 MHz, C_6D_6): δ=−57.4 (s); ^1H NMR (200 MHz, C_6D_6): δ=8.48–8.44 (m, CH_{arom}), 7.85–7.78 (m, CH_{arom}), 7.39–7.27 (m, CH_{arom}), 7.10–6.88 (m, CH_{arom}); MS (70 eV): m/z (%): 584 (5) $[M]^+$; IR (KBr): ν=2150 cm^{-1} (C≡C). Anal. calcd for $C_{34}H_{24}PSb$ (585.3): C 69.77, H 4.13; found C 69.48, H 4.35.

5. X-Ray analyses

5.1. Crystal data for 8a

$C_{34}H_{30}SiZr$, M=557.89, triclinic, space group P-1, a=8.0851(9) Å, b=11.098(2) Å, c=15.466(2) Å, α=92.92(2)°, β=91.43(2)°, γ=105.41(2)°, Z=2, V=1335.1(3) Å^3, D_c=1.388 mg m^{-3}, Mo Kα radiation (λ=0.71073 Å), μ=0.478 mm^{-1}, crystal dimensions 0.40×0.12×0.08 mm^3, F(000)=576, T=180(2) K. From 7893 reflections, 3929 were unique (R_{int}=0.0344). 3929 with $I>2\sigma(I)$ were used in refinement. Data/parameters ratio 3929/327, R=0.0252, $R\omega$=0.0604.

5.2. Crystal data for 17b

$C_{34}H_{24}PSb$, M=585.25, triclinic, space group P-1, a=11.191(2) Å, b=11.218(2) Å, c=12.535(3) Å, α=99.18(2)°, β=114.43(2)°, γ=107.95(2)°, Z=2, V=1286.2(4) Å^3, D_c=1.511 mg m^{-3}, Mo Kα radiation (λ=0.71073 Å), μ=1.156 mm^{-1}, crystal dimensions 0.25×0.20×0.07 mm^3, F(000)=588, T=160(2) K. From 9429 reflections, 3486 were unique (R_{int}=0.0427). 3486 with $I>2\sigma(I)$ were used in refinement. Data/parameters ratio 3486/325, R=0.0314, $R\omega$=0.0673.

5.3. Crystal data for 24b

$C_{34}H_{24}PSb$, M=585.25, triclinic, space group P-1, a=9.9506(13) Å, b=11.8836(17) Å, c=12.4912(16) Å, α=81.650(16)°, β=69.084(15)°, γ=73.579(16)°, Z=2, V=1321.8(3) Å^3, D_c=1.470 mg m^{-3}, Mo Kα radiation (λ=0.71073 Å), μ=1.125 mm^{-1}, crystal dimensions 0.20×0.15×0.12 mm^3, F(000)=588, T=160(2) K. From 12843 reflections, 4739 were unique (R_{int}=0.0276). 4739 with $I>2\sigma(I)$ were used in refinement. Data/parameters ratio 4739/325, R=0.0207, $R\omega$=0.0540.

For the three compounds, the data were collected on a IPDS STOE diffractometer. The structures were solved by direct methods with the program SIR92[24] and refined by least squares procedures on F with the CRYSTAL package.[25] The molecules were plotted with CAMERON.[26] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-192764 (**8a**), CCDC-192765 (**17b**), CCDC-192766 (**24b**). 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).

Acknowledgements

This work was supported by the CNRS (France) and the Conseil Régional de Bourgogne (France) for financial support. The authors also wish to thank S. Royer and G. Delmas for technical assistance.

References and notes

1. (a) Erker, G. *Pure Appl. Chem.* **1991**, *63*, 797–806. (b) Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696–1701. (c) Gautheron, B.; Broussier, R.; Meunier, P. In *Encyclopedia of Inorganic Chemistry*; King, R. B., Ed.; Wiley: Chichester, 1994; pp 4488–4506. (d) Lappert, M. F. In *Comprehensive Organometallic Chemistry II: A Review of the Literature 1982–1994*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; pp 433–632. (e) Majoral, J.-P.; Meunier, P.; Igau, A.; Pirio, N.; Zablocka, M.; Skowronska, A.; Bredeau, S. *Coord. Chem. Rev.* **1998**, *178–180*, 145–167.
2. (a) Negishi, E.; Takahashi, T. *Synthesis* **1988**, *1*, 1–19. (b) Negishi, E. *Chem. Scr.* **1989**, *29*, 457–468.
3. (a) Rosenthal, U.; Ohff, A.; Baumann, W.; Kempe, R.; Tillack, A.; Burlakov, V. V. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1605–1607. (b) Rosenthal, U.; Pellny, P. M.; Kirchbauer, F. G.; Burlakov, V. V. *Acc. Chem. Res.* **2000**, *33*, 119–129.
4. Hsu, D. P.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10394–10395.
5. Fagan, P. J.; Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 1880–4995.
6. (a) Takahashi, T.; Tsai, F.-Y.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994–4995. (b) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059–5067.
7. Cadierno, V.; Zablocka, M.; Donnadieu, B.; Igau, A.; Majoral, J.-P. *J. Am. Chem. Soc.* **1999**, *50*, 11086–11092.
8. Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Huo, S.; Hara, R. *Organometallics* **2001**, *201*, 4122–4125.
9. Takahashi, T.; Huo, S.; Hara, R.; Noguchi, Y.; Nakajima, K.; Sun, W.-H. *J. Am. Chem. Soc.* **1999**, *121*, 1094–1095.
10. Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047–1058.
11. (a) Zablocka, M.; Igau, A.; Donnadieu, B.; Majoral, J.-P.; Skowronska, A.; Meunier, P. *Chem. Commun.* **1997**, 1239–1240. (b) Miquel, Y.; Igau, A.; Donnadieu, B.; Majoral, J.-P.; Dupuis, L.; Pirio, N.; Meunier, P. *Chem. Commun.* **1997**, 279–280.

12. Majoral, J.-P.; Igau, A.; Cadierno, V.; Zablocka, M. *Top. Curr. Chem.* **2002**, *220*, 53–77.
13. Dupuis, L.; Pirio, N.; Meunier, P.; Igau, A.; Donnadieu, B.; Majoral, J.-P. *Angew. Chem., Int. Ed. Engl.* **1997**, *9*, 987–989.
14. (a) Mike, C. A.; Nelson, T.; Graham, J.; Cordes, A. W.; Allison, N. T. *Organometallics* **1988**, *7*, 2573–2575. (b) Xi, Z.; Fischer, R.; Hara, R.; Sun, W.-H.; Obora, Y.; Suzuki, N.; Nakajima, K.; Takahashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 12842–12848, and references quoted herein.
15. For phosphacyclobutenes see for example: (a) Doxsee, K. M.; Hanawalt, E. M.; Shen, G. S.; Weakley, T. J. R.; Hope, H.; Knobler, C. B. *Inorg. Chem.* **1991**, *30*, 3381–3389, and references quoted herein. (b) Weber, L.; Kaminski, O.; Stammler, H.-G.; Neumann, B. *Organometallics* **1995**, *14*, 581–583, For silacyclobutenes see for example Ref. 13b and references quoted herein.
16. Fagan, P. J.; Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 1880–1889.
17. Ura, Y.; Li, Y.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1998**, *39*, 2787–2790.
18. (a) Adams, E. A.; Kolis, J. W.; Pennington, W. T. *Acta Crystallogr. Sect. C* **1990**, *46*, 917–919. (b) Vela, J.; Sharma, P.; Cabrera, A.; Alverez, C.; Rosas, N.; Hernandez, S.; Toscano, A. *J. Organomet. Chem.* **2001**, *634*, 5–11.
19. (a) Erker, G.; Mühlenbernd, T. *J. Organomet. Chem.* **1987**, *319*, 201–211. (b) Legrand, C.; Meunier, P.; Petersen, J. L.; Tavares, P.; Bodiguel, J.; Gautheron, B.; Dousse, B. *Organometallics* **1995**, *14*, 162–169.
20. Mahieu, A.; Miquel, Y.; Igau, A.; Donnadieu, B.; Majoral, J.-P. *Organometallics* **1997**, *16*, 3086–3088.
21. Escudie, J.; Ranaivonjatovo, H.; Rigon, L. *Chem. Rev.* **2000**, *100*, 3639–3696.
22. Samuel, E.; Rausch, M. D. *J. Am. Chem. Soc.* **1973**, *95*, 6263–6267.
23. Gautheron, B.; Tainturier, G.; Pouly, S.; Theobald, F.; Vivier, H.; Laarif, A. *Organometallics* **1984**, *3*, 1495–1499.
24. Altomare, A.; Cascarano, G.; Giacovazzo, G.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. SIR92, a program for automatic solution of crystal structures by direct methods. *J. Appl. Crystallogr.* **1994**, *27*, 435.
25. Watkin, D. J.; Prout, C. K.; Carruthers, R.; Betteridge, P. *CRYSTALS issue 10*; Chemical Crystallography Laboratory, University of Oxford: Oxford, 1996.
26. Watkin, D. J.; Prout, C. K.; Pearce, L. *CAMERON*; Chemical Crystallography Laboratory, University of Oxford: Oxford, 1996.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1329–1337
Tetrahedron

From vinyl sulfides, sulfoxides and sulfones to vinyl zirconocene derivatives

Shahera Farhat, Irena Zouev and Ilan Marek*

Department of Chemistry, Institute of Catalysis Science and Technology, Technion-Israel Institute of Technology, Technion City, Haifa 32000, Israel

Received 11 July 2003; accepted 6 August 2003

Abstract—An easy and straightforward new method for the preparation of sp^2 zirconocene derivatives from a wide range of heterosubstituted alkenes such as vinyl sulfides, sulfoxides and sulfones is described. In all cases, a complete isomerization of the stereochemistry is observed and only the *E*-isomer is obtained. The reactivity of the resulting vinylic organometallic can be increased by a transmetalation reaction into organocopper, organozinc or organopalladium species and, therefore, several carbon–carbon formation were easily realized.

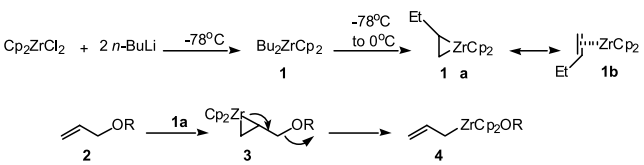
1. Introduction

Although numerous methods for the preparation of sp^2 organometallic derivatives are known in the literature and widely used in synthesis,[1] there are still some very challenging synthetic transformations such as the preparation of vinylic organometallics from oxygen- and sulfur heterosubstituted alkenes. As the importance of the sulfoxide and sulfone moieties stem from their application in carbon–carbon bond formations, including asymmetric synthesis, and this in turn derive from key aspects of their properties and reactivity, outstanding applications were found in organic synthesis.[2] In these applications, sulfoxides and sulfones are, therefore, mostly synthetic tools, which must be disposed of at the end of the sequence.[3] As a potentially very interesting transformation, the preparation of organometallic derivatives from vinyl sulfoxides or sulfones should be synthetically very useful since further functionalization will increase the complexity of the carbon skeleton. The only reported example was the transformation of vinyl phenyl sulfide into vinyl lithium derivatives via reductive metalation.[4] This method involves the reductive lithiation of alkenyl phenyl sulfides by means of either a stoichiometric amount of radical anion lithium *p*,*p*′-di-*tert*-butylbiphenylide (LDBB) or an excess of lithium metal in the presence of a catalytic amount of *p*,*p*′-di-*tert*-butylbiphenyl (DBB; 5% mol).[5] Such transformations failed on vinyl alkyl sulfides.[5,6] Although conceptually simple, the transformation of sulfur heterosubstituted alkenes into organometallic derivatives was not addressed (except for vinyl aryl sulfide) and was therefore a very interesting challenge to solve.

In this paper, we would like to report in full our results concerning these transformations.[6]

Over the past two or three decades, organozirconium derivatives have emerged as being synthetically useful reagents or intermediates in organic synthesis and their incredible efficiency, coupled to their unique ability to promote unusual transformations have aroused the imagination of chemists.[7] As particular example, we were recently interested by a side product, originally described by Negishi,[8] obtained when the diallyl ether **2** ($R=C_3H_5$) was treated with the zirconacyclopropane **1a** (easily prepared by the treatment of Cp_2ZrCl_2 with two equiv of *n*-BuLi in THF, and also called Negishi Reagent).[9] Instead of producing the desired zirconabicycle, the reaction gave the allylzirconocene derivative **4** via the addition product **3** followed by a β-elimination as described in Scheme 1.

This originally unwanted side reaction has proved to be a synthetically useful route to allylzirconocene derivatives, as nicely demonstrated by Hanzawa and Taguchi.

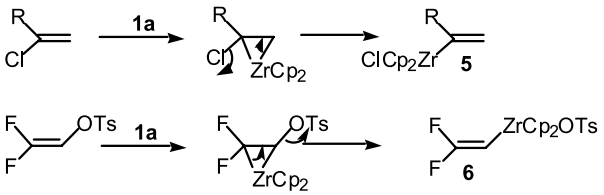


Scheme 1.

* Corresponding author. Tel.: +972-4-829-3709; fax: +972-4-829-3709; e-mail address: chilanm@tx.technion.ac.il

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.08.074

Therefore, several allylic,[10] allenic,[11] γ[12]- and γ,γ-alkoxy allylic[13] zirconium species were prepared.[14] So, although the direct insertion of organometallic derivatives into the carbon-ether bond is impossible, a two-step mechanism allows their easy preparations. This strategy was also developed for the selective cleavage of allylic ether derivative.[15] However, this concept of addition-β-elimination was only sporadically used for the preparation of vinyl zirconium derivatives. The initial report, published by Takahashi et al., was the preparation of **5** by reaction of 2-chloroalkene derivatives[16] with **1a**. Recently, Ichikawa and Minami successfully applied this strategy[17] for the synthesis of fluorinated vinyl zirconium moieties **6** (Scheme 2).



Scheme 2.

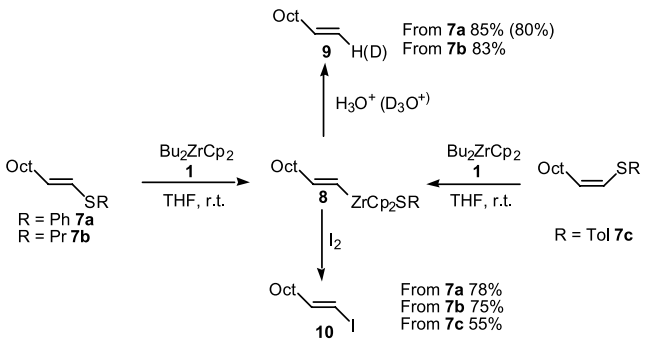
In both cases, a good leaving group was used (halide or tosyloxy groups) for the β-elimination reaction and no information on the stereochemical outcome of this reaction was disclosed.[18] On the other hand, when the difluoroolefin bears a substituent with a lower leaving-group propensity than that a fluorine (i.e., OPh or OMEM), the preferential elimination of fluoride occurs in low yield (respectively, 17 and 32% yield).[17]

2. Results and discussions

So, we reasoned that the combined addition–β-elimination mechanism could be an interesting way to prepare specific vinylic organometallic derivatives from sulfur-heterosubstituted olefins. Indeed, from the mechanistic interpretation given in Scheme 2, the combination of an olefinic moiety (complexation with **1a**) with a vinylic heteroatom (leaving group present in the β-position of the zirconacyclopropane) should lead to the corresponding sp^2 organometallic derivatives via an addition–elimination sequence.

Our first attempt was directed to the preparation of vinylic zirconocene from vinyl phenyl sulfide; when **7a** was added to a slight excess of **1a**, generated by thermal decomposition of **1** in THF, and stirred at room temperature for few hours, the expected vinyl zirconocene **8** was obtained in excellent yield as determined by its hydrolyzed product **9**.

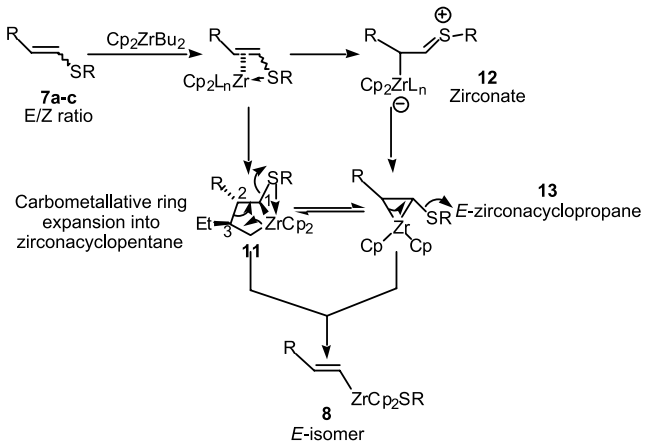
The formation of a discrete organometallic was first checked by deuteriolysis and iodinolysis to give **9** and **10** in 80 and 78% yields, respectively (Scheme 3). The reaction also proceeds efficiently from the alkyl vinyl sulfide **7b**, and **9** and **10** are respectively obtained in 83 and 75% yields after hydrolysis or iodinolysis. Thus, no difference has been found in this reaction between alkyl and aryl sulfide. When the same reaction was now performed on the *Z*-isomer of the aryl vinyl sulfide **7c**, followed by the addition of iodine, only the *E*-vinyl iodide **10** was obtained. So, whatever be the



Scheme 3.

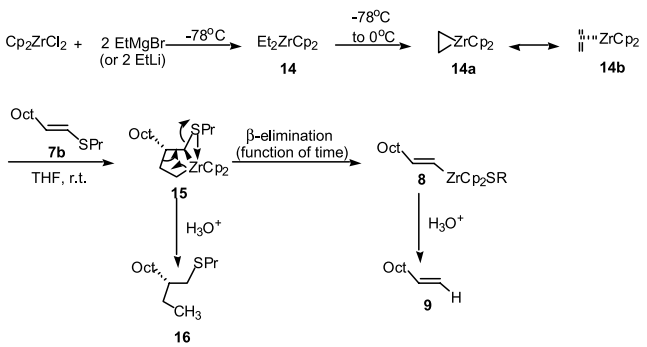
stereochemistry of the initial vinyl sulfide, the reaction is >99% stereoselective but not stereospecific, producing only the *E*-vinyl zirconium in good overall yields. No, stereoisomerization of **7c** into **7a** was observed in the process, which indicates that zirconocene **1a** is not a catalyst for the isomerization of thioenol ether. This isomerization can be explained by a carbometallative ring expansion between **1a** and **7a–c** to lead to the corresponding five-membered ring zirconacycle **11** which may produce the three-membered zirconacyclopropane **13**, since facile equilibration among three- and five-membered zirconacycle have been already discussed for skeletal rearrangements.[19] If we consider the ligand exchange described in Scheme 2, the addition–β-elimination should lead to different geometrical isomers of the corresponding vinyl zirconium derivatives **8** when starting from the *E*- or *Z*-isomers of vinyl sulfides (**7a** and **7c**, respectively). Therefore, more complicated intermediates are most probably involved during the complexation between the thioenol ethers **7a–c** and the zirconocene **1a** since we have a complete isomerization reaction. Our first hypothesis was that the initial step proceeds via a dipolar zirconate species[20] represented by **12**, followed by an isomerization reaction leading to the *trans* zirconacyclopropane **13**.[21] Then, after a β-elimination step, the corresponding *E*-vinyl zirconium should be obtained. Although this mechanistic interpretation was attractive, a stereochemical problem remains for the elimination reaction since an angle of 180° (*anti*-elimination) or 0° (*syn*-elimination) is usually required for an elimination reaction. In this case, an angle of 120° is expected in the zirconacyclopropane **13** (Scheme 4).

Now, if we consider the carbometallative ring expansion to produce the corresponding five-membered zirconacycle **11**, the carbon–heteroatom bond of the sp^3 metallated center C_1 should isomerize to produce the most stable intermediate. Such isomerization could be due to an interaction between the sulfur moiety and the zirconium atom,[22] which would produce a weakness of the C_1–Zr bond and would facilitate the isomerization. Thus, whatever the stereochemistry of the starting material, a conformation is always possible in which C_1–SR is antiperiplanar to C_2–C_3 in **11**. The elimination reaction or decarbozirconation, occurs in a concerted way to give the *E*-vinyl zirconium **8**. Unfortunately, neither the zirconacyclopentane nor the zirconacyclopropane have been trapped as intermediates. On the other hand, Cp_2ZrEt_2 **14** is known to give zirconocene-ethylene complex $Cp_2Zr(CH_2{=}CH_2)$ **14a** in a similar way to **1a**, but



Scheme 4.

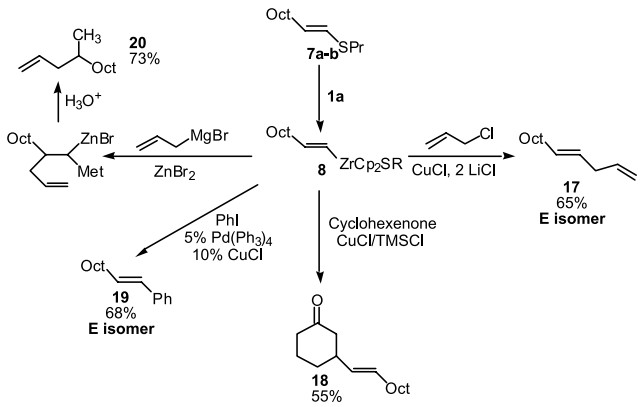
the behavior of the ethylene ligand is very different, in most cases, from the butene moiety of the zirconocene–butene complex **1b**.[23] Indeed, the ethylene ligand reacts with various unsaturated compounds and as it is usually incorporated in the reaction products, we were interested to see if it could be also incorporated into the vinyl sulfide **7b**. Cp_2ZrEt_2 was easily prepared by treatment of 2 equiv. of EtMgBr (and by also 2 equiv. of EtLi to check that there is no salt effects) with Cp_2ZrCl_2 to furnish **14**, which was then treated with **7b** at room temperature. The addition product **15** is rapidly observed by analysis by gas chromatography of aliquots after hydrolysis, which is followed by the elimination reaction to give the vinyl zirconium species **8** and ethylene. Both of the intermediates and the product were trapped by hydrolysis (Scheme 5). Although the formation of the vinyl zirconium **8** is slower in this particular case (only 2–3 h were necessary for the formation of **8** from **7b** and **1a**), we can clearly see that the addition product **15** undergoes a subsequent β-elimination reaction to give the expected product **8** (Table 1).



Scheme 5.

Table 1. Apparition of **9** after β-elimination of **15** followed by hydrolysis

Reaction time	**16** (%)	**9** (%)
20 min	90	10
2 h	70	30
3 h	50	50
10 h	30	70



Scheme 6.

Thus, from these mechanistic studies, we believe that the unique formation of the *E*-isomer results from a carbometallative ring expansion into zirconacyclopentane followed by an elimination reaction.

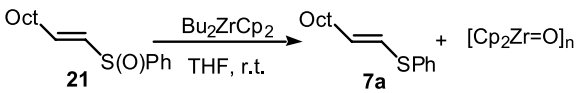
The scope of the reaction can be broader since vinyl zirconocenes can be transmetallated into more reactive species as described in Scheme 6.[24]

Indeed, addition of a catalytic amount of copper chloride in the presence of lithium chloride[25] leads to the corresponding *E*-vinyl copper derivative. The latter reacts either via a S_N2' process with allyl chloride (**17** in 65% yield) or in a 1,4-addition manner with cyclohexanone in the presence of TMSCl[26] (**18** in a non-optimized 55% yield). The palladium-catalyzed cross-coupling reaction of **8** with aryl iodide opens a new route to further functionalization as shown by the formation of **19** in 68% yield. Finally, the transmetalation of the vinyl zirconium **8** to zinc bromide followed by the addition of allylmagnesium bromide leads to new bismetallated species (**20** after hydrolysis in 73% yield).[27]

We were then interested to extend this methodology to the transformation of vinyl sulfoxides into vinylic organometallic derivatives. Indeed, the stereogenic sulfur atom in sulfoxides is configurationally stable at room temperature and thus sulfoxides may be chiral based on this property alone.[28] Therefore, reactions of chiral sulfoxides found extensive applications in Asymmetric Synthesis.[29] However, in most cases, once the new chiral centers are created, sulfoxides have to be removed in subsequent chemical steps. Although the replacement of sulfoxide moiety in vinyl sulfoxide by hydrogen atom can be performed by using different metals such as Na/Hg or activated zinc,[30] the transformation of vinyl sulfoxide into vinylic organometallic derivatives was unknown.

When *E*-vinyl sulfoxide **21** was treated with 1.5 equiv. of **1a** in THF at −78 °C and warning up the reaction mixture to room temperature, we obtained the corresponding sulfides **7a** instead of the expected vinyl zirconium derivative **8**. Therefore, vinyl sulfoxides are reduced with **1a** into the corresponding vinyl sulfide with concomitant formation of the insoluble polymer $[Cp_2Zr{=}O]_n$ (Scheme 7).

Low-valent group 4 organometallic derivatives such as



Scheme 7.

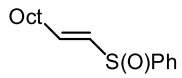
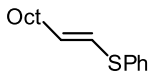
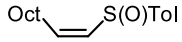
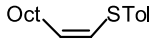
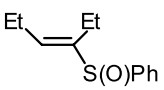
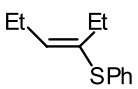
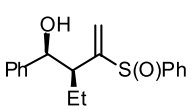
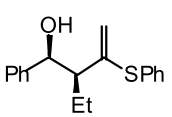
bis(trimethyl)phosphine zirconium derivatives are know to reduce CO_2 into CO and Cp_2ZrO polymer.[31] Thus, Bu_2ZrCp_2 **1** is also a very mild reducing agent of sulfoxides into sulfides with formation of the easily removable $[Cp_2ZrO]_n$ by simple filtration at the end of the sequence. As shown in Table 2, the scope of the reaction is relatively broad.

Diaryl, aryl–vinyl, aryl–alkyl sulfoxides were reduced in 1 to 2 h at room temperature in good to excellent yields (entries 1–6). Trisubstituted vinyl sulfoxides undergo also the transformation in good isolated yield. Whatever the stereochemistry of the vinyl sulfoxide (compare entries 2 and 3), the reduction occurs into the corresponding vinyl sulfide without isomerization of the double bond. Finally, even sulfoxide bearing two stereogenic centers on its carbon skeleton as in entry 5 can be reduced without any change in the stereochemical purity of the substrate. In this particular case, 2 equiv. of **1a** were used.

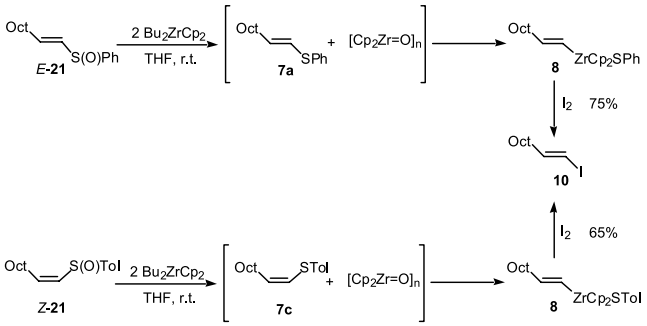
However, our main research goal was the preparation of vinyl zirconocene derivatives from vinyl sulfoxides and not its reduction. As sulfoxides can be easily transformed into sulfides and sulfides can be further transformed into vinylic organometallics, the expected vinylic organometallic derivatives have been obtained in a single-pot operation from sulfoxides by treatment with 2 equiv. of Bu_2ZrCp_2 as described in Scheme 8.

The first equivalent of **1a** reduces the vinyl sulfoxides *E*-

Table 2. Reduction of sulfoxides into sulfides with Bu_2ZrCp_2

Entry	Sulfoxides	Sulfides	Yield[a]%
1	PhS(O)Ph	PhSPh	95
2			80
3			81
4			85
5	$C_{12}H_{25}S(O)Tol$	$C_{12}H_{25}STol$	73
6			92

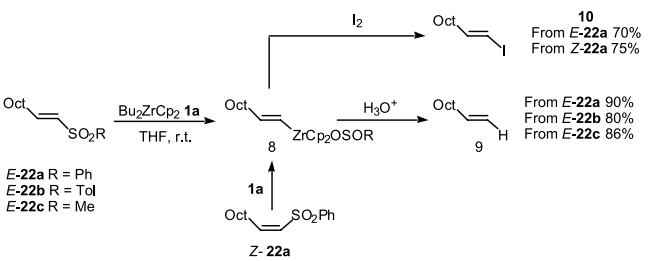
[a] Yield of isolated products after purification by column chromatography.



Scheme 8.

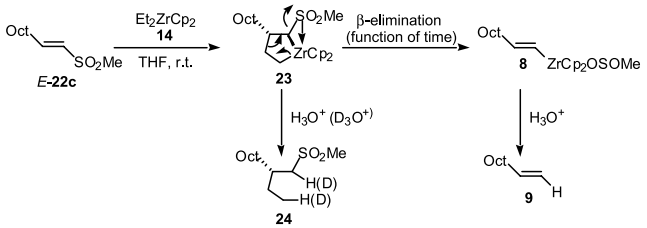
and *Z*-**21** into the vinyl sulfide **7a** and **7c**, respectively, without any isomerization of the double bond and then, the second equivalent of **1a** transforms the vinyl sulfides **7a**,**c** into the corresponding organometallics with a complete isomerization of the double bond as discussed in Schemes 3 and 4. Reaction of *E*-**8** with iodine led in both cases to the *E*-vinyl iodide **10** in good overall yields.

Finally, we turned our attention to vinyl sulfones. Indeed, although sulfones were extensively used for the creation of carbon–carbon bonds, the transformation into vinylic organometallic derivatives was simply unknown. To date, the available method for the replacement of sp^2 sulfone falls roughly into three categories: those resulting in replacement of the sulfone by hydrogen (reductive desulfonylation),[32] those in which the sulfone removal is accompanied by a C–C bond formation (alkylative desulfonylation)[33] and finally those in which the sulfone is a good leaving group towards β-elimination reaction with formation of the sulfinate moiety (RSO_2^-).[34] When *E*-**22a–c** were treated with Bu_2ZrCp_2 **1a** in THF at room temperature, a very fast reaction was observed which lead to the expected alkenes **9** in excellent isolated yields after hydrolysis, whatever the nature of the group on the starting sulfone (R=Ph, Tol, Me, Scheme 9). By reaction with iodine, *E*-**10** was isolated from *E*-**22a** in 70% yield.



Scheme 9.

When the *Z*-vinyl sulfone **22a** is treated with **1a**, a complete isomerization also occurs as determined by the reaction of the resulting vinyl organometallic derivatives with iodine. Only the *E*-isomer of **10** was isolated with good chemical yield. In order to probe the formation of zirconacyclopentane **23** as reactive intermediates, the same reaction between *E*-**22c** and Et_2ZrCp_2 **14** was repeated (as described in Scheme 4 but with sulfone instead of sulfide). Here again, the addition product **23** was rapidly formed at room temperature as determined by its hydrolyzed or deuteriolysis products **24** and **24**(*d*), respectively. Then, **23** disappear over time in favor of **8** (Scheme 10).



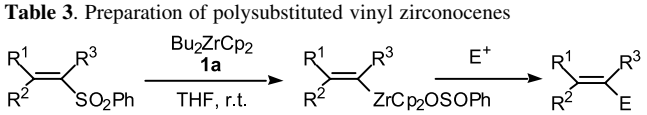
Scheme 10.

In order to extend the scope of the reaction, several polysubstituted vinyl sulfones were prepared and transformed into the corresponding vinylic organometallic derivatives as described in Table 3.

When β,β-disubstituted vinyl sulfones were treated with zirconocene **1a**, the expected products **25**, **27** and **29** were obtained in reasonably good yields (Table 3, entries 1, 3 and 5, respectively). The presence of an organometallic species was proved by trapping experiments either with MeOD (Table 1, entry 2 of unknown stereochemistry) or with iodine (Table 3, entry 4). Two geometrical isomers were obtained for the vinyl iodide **28** starting from two isomers for the corresponding vinyl sulfones. α,β-Disubstituted vinyl sulfones also undergo the transformation but only when one of the substituents is an aromatic group (either in α- or β-position as described in Table 3, entries 6–8). Only the *E*-isomer is obtained in these three cases. When the two substituents are alkyl groups, the reaction leads to several isomers, most probably due to subsequent isomerization of the resulting olefin (Table 3, entry 9). Interestingly, among all the isomers formed, no terminal double bond was detected. Finally, when cyclohexenyl sulfone was treated with **1a**, only a 40% yield of the cyclic organometallic was formed after iodinolysis (Table 3, entry 10).

From this study, we can deduce that β,β′-disubstituted—as well as α,β-disubstituted vinyl sulfones (but only when one substituent is aromatic) undergo the transformation but surprisingly not when substituents are alkyl groups. Apparently, the phenyl group induces a particular stabilization of the zirconacycle intermediate that leads to a complete stereoselective formation of the *E*-vinyl zirconium whereas in its absence, an isomerization occurs and, therefore, a loss of stereoselectivity.

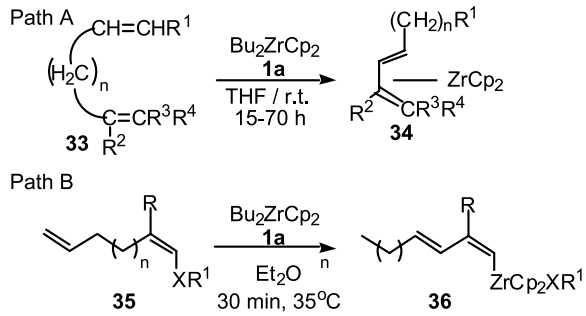
Table 3. Preparation of polysubstituted vinyl zirconocenes



Entry	R^1	R^3	R^2	E^+	Products	Yield (%)[a]
1	Oct	H	Bu	H_3O^+	**25**	70
2	Oct	H	Bu	MeOD	**26**	60
3	Oct	H	Me	H_3O^+	**27**	68
4	Oct	H	Me	I_2	**28**	67
5	Ph	H	Bu	H_3O^+	**29**	64
6	Ph	Me	H	H_3O^+	**30**	70
7	Me	Ph	H	H_3O^+	**30**	60
8	Ph	Et	H	H_3O^+	**31**	65
9	hept	Me	H	H_3O^+	/	/
10	$(CH_2)_4$	$(CH_2)_4$	H	I_2	**32**	40

[a] Yields after purification by column chromatography.

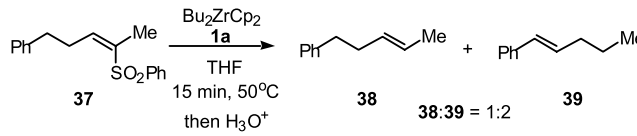
On the other hand, it is well known that transition metal catalyzed isomerization of terminal olefins into internal olefins and in general a mixture of 1-alkenes, (*E*)- and (*Z*)-2-alkenes, reflecting the thermodynamic equilibrium, is obtained.[35] Some low-valent titanocene derivatives are highly effective and stereoselective in favor of the (E)-2-isomer.[36] When non-conjugated dienes such as **33** containing one or two substituted vinyl groups are treated with zirconocene **1a**, a regioisomerization of the less-substituted double bond occurs and lead to the formation of the conjugated diene–zirconocene complexes **34** (Scheme 11, path A).[37]



Scheme 11.

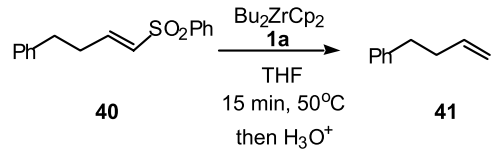
We have recently used this concept of isomerization for the stereoselective preparation of dienyl zirconocene **36** derivatives in a single-pot operation for substituted enol ether **35** (Scheme 11, Path B).[38]

Therefore, we have examined the case of 4-phenyl-sulfonyl-pent-3-enylbenzene **37**, as dialkyl substituted vinyl sulfone, but with also an aromatic group in a remote position of the alkyl chain to see if we have an isomerization reaction. The reaction of **37** with **1a** lead to the expected *trans* isomer **38** but also to the isomerized product **39** in a 1:2 ratio, respectively, in 60% combined yield as described in Scheme 12.



Scheme 12.

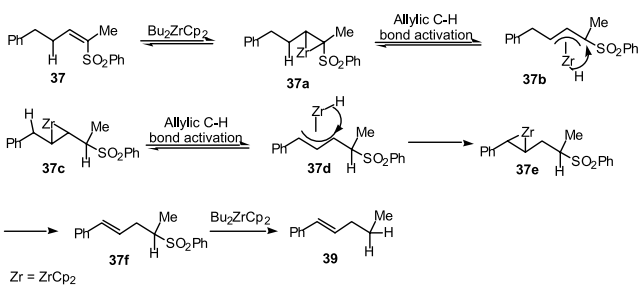
Here again, no traces of terminal olefin that could result from the isomerization to the opposite side of the molecule were detected. The isomerization occurs towards the most stable isomer in which the double bond is conjugated with the phenyl ring. More surprisingly, when iodine was added at the end of the reaction to potentially trap organometallic derivatives, no iodinated products were detected. On the other hand, when terminal vinyl sulfone **40** with the same remote aromatic ring was treated with **1a**, no isomerization reaction was found; only **41** was formed in 67% yield (Scheme 13).



Scheme 13.

From this experiment, we can conclude that alkyl substituents in α- and β-position of the olefin induce the isomerization process. As nothing is known on the exact nature of our intermediate, we must await further investigations to elucidate completely the mechanism of this reaction, but should arise most probably from the destabilization of the zirconacyclopropane intermediate (such as **13** in Scheme 4, compare Schemes 12 and 13).

Based on the reported data, we reasoned that α-substituted vinyl sulfones might undergo the isomerization towards the most stable alkene via a mechanism similar to the one described in Scheme 11. Indeed, **37** can react with **1a** to form the zirconacyclopropane **37a**, which undergo via a double allylic C–H bond activation (transformation of **37a** to **37e** by formation of two η^3-allyl intermediates **37b**,**d**). Once **37e** is formed, the zirconocene must be released (the sulfonyl moiety can eventually induce this release by intramolecular chelation) and induce the reduction of the sp^3 alkyl sulfone into **39** (see Scheme 14).



Scheme 14.

Although several pendant questions have to be solved to confirm this mechanistic hypothesis, we have already confirmed that zirconocene **1a** reduces efficiently primary sp^3 alkyl sulfone into the corresponding alkane. When iodine was added at the end of the reaction, minor amount of the alkyl iodide was formed confirming that primary alkyl sulfone undergo reductive desulfonylation most probably via single-electron transfer process.

In conclusion, by using zirconocene **1a**, we have been able for the first time to develop an easy and straightforward new method for the preparation of sp^2 zirconocene derivatives from a wide range of heterosubstituted alkenes such as vinyl sulfides, sulfoxides and sulfones. In all cases, a complete isomerization of the stereochemistry is observed and only the *E*-isomer is obtained. The reactivity of the resulting vinylic organometallic can be increased by a transmetalation reaction into organocopper, organozinc or organopalladium species and therefore, several carbon–carbon formation were easily realized. When more substituted vinyl sulfones such as β,β′-disubstituted- or α,β-disubstituted (with at least one substituent aromatic) were used, this method also leads to the corresponding organometallic derivatives. On the other hand, when α,β-disubstituted vinyl sulfones have only alkyl groups, an isomerization occurs to give a mixture of isomers. This isomerization can be used for the preparation of the most stable olefin if an aromatic group is present in the carbon skeleton.

3. Experimental

All our starting materials (vinyl sulfides,[39] vinyl sulfoxides[40] and vinyl sulfones[41]) were prepared by conventional methods described in the above references.

3.1. General procedure for the transformation of heterosubstituted alkenes into vinylic zirconocenes

A solution of *n*-butyllithium in hexane (1.6 M, 3.4 equiv., 3.4 mmol) was added slowly to a solution of bis(cyclopentadienyl)zirconium dichloride (1.7 equiv., 1.4 mmol) in dry THF (7 ml) at −78 °C. After the solution was stirred for 1 h at −78 °C, heterosubstituted alkene was added (1 equiv., 1 mmol) as solution in 3 ml of dry THF at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3–5 h. The quantitative formation of the adduct was checked by gas chromatography. Then, the solution was cooled to −20 °C, and the electrophile was added. The reaction was warmed to room temperature and the mixture was diluted with ether and with an aqueous solution of HCl (1 M) [in case of transmetalation with CuCl, a mixture of saturated aqueous solution of NH_4Cl (2 equiv.) and aqueous solution of NH_4OH (25%, 1 equiv.) was used]. The aqueous phase was then extracted three times with ether. The combined organic phases were then washed successively with a solution of saturated aqueous sodium hydrogen carbonate, brine and water (in case of addition of iodine as electrophile, aqueous $Na_2S_2O_3$ was used), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was finally purified by column chromatography on silica gel.

Note. Reaction of vinyl sulfoxides *E*-**21** and *Z*-**21** according to the above mentioned procedure produced the corresponding vinyl sulfide.**7a**,**c**. By using 2.5 equiv. of Cp_2ZrCl_2 and 5 equiv. of *n*-BuLi, the desired vinyl zirconium derivative is obtained.

The reaction of β,β′- and α,β-disubstituted vinyl sulfones was carried out by using an excess of Cp_2ZrCl_2 (2 equiv.) with 4 equiv. of *n*-BuLi.

1-Decene (**9**). Purification by column chromatography on silica gel (eluent: hexane) gave a colorless liquid in 85% yield, spectrally identical with an authentic sample commercially available. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.86 (t, 3H, J=6.4 Hz), 1.42 (m, 12H), 2.00 (m, 2H), 4.93 (m, 2H), 5.78 (m,1H).

(*E*)-1-Deuterio-1-decene (**9d**).[42] Purification by column chromatography on silica gel (eluent: hexane) gave a colorless liquid in 83% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.87 (t, 3H, J=6.56 Hz), 1.25 (m, 12H), 1.97–2.07 (m, 2H), 4.87–5.00 (d, 1H, J=16.85 Hz), 5.72–5.87 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 14.21, 22.84, 29.16–29.86 (4C), 32.07, 33.92, 113.47 (t), 139.27.

(*E*)-1-Iodo-1-decene (**10**).[43] Purification by column chromatography on silica gel (eluent: hexane) gave a yellow liquid in 55–78% yield, spectrally identical with an authentic sample. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm)

0.86 (t, 3H, J=5.89 Hz), 1.09–1.34 (m, 12H), 1.96–2.15 (m, 2H), 5.98 (d, 1H, J=15.3 Hz), 6.41–6.56 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 14.19, 22.79, 28.51–29.83 (4C), 32.03, 36.16, 74.29, 146.98.

(*E*)-1,4-Tridecadiene (**17**).[44] The general procedure was performed as described above. When the formation of the vinyl zirconium was complete (checked by GC), 0.12 ml of allyl chloride (1.5 mmol, 1.5 equiv.), copper chloride (0.1 mmol, 10 mg, 0.1 equiv.) and lithium chloride (2 mmol, 85 mg, 2 equiv.) were added at 0 °C. Then, the solution was stirred at 50 °C for 5 h. After usual treatment, the residue was purified by column chromatography on silica gel (eluent: hexane) to give a colorless liquid in 65%. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.88 (t, 3H, J=6.56 Hz), 1.11–1.25 (m, 12H), 1.98 (m, 2H), 2.73 (m, 2H), 4.89–5.05 (m, 3H), 5.34–5.45 (m, 1H), 5.71–5.83 (m, 1H).

(*E*)-1-Cyclohexanone-1-decene (**18**). The general procedure was performed as described above. When the formation of the vinyl zirconium was complete (checked by GC), 2-cyclohexene-1-one (2.5 equiv., 1.35 mmol, 0.13 ml), TMSCl (2.6 equiv., 1.41 mmol, 0.18 ml), copper chloride (0.1 equiv., 0.054 mmol, 5 mg) and lithium chloride (2 equiv., 1.08 mmol, 46 mg) were added at room temperature. Then, the solution was stirred at 60 °C for 6 h. After usual treatment, the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate (30:1) to give a colorless liquid in 50% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.85 (t, 3H, J=6.79 Hz), 1.23 (m, 12H), 1.68 (m, 4H), 1.83–2.14 (m, 3H), 2.15–2.41 (m, 4H), 5.33–5.40 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 14.048, 22.63, 23.87, 28.84–29.67 (4C), 31.34, 31.62, 31.86, 41.51, 41.54, 47.71, 130.02, 132.93, 211.27.

(*E*)-1-Phenyl-1-decene (**19**).[45] The general procedure was performed as described above. When the formation of the vinyl zirconium was complete (checked by GC), phenyl iodide (0.26 g, 1.3 mmol, 1.3 equiv.), copper chloride (0.15 g, 1.5 mmol, 1.5 equiv.) and 5% of $Pd(PPh_3)_4$ (60 mg, 0.05 mmol) were added at room temperature. The solution was heated for 3 hr at 50 °C. After usual treatment, the residue was purified by column chromatography on silica gel (eluent: hexane) to give a colorless liquid in 68% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.88 (t, 3H, J=7.1 Hz), 1.29–1.52 (m, 12H), 2.15–2.25 (m, 2H), 6.17–6.29 (m,1H), 6.34–6.42 (d, 1H, J=15.99 Hz), 7.17–7.37 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 14.06, 22.67, 29.26, 29.28, 29.41, 29.50, 31.91, 33.05, 125.92 (2C), 126.72, 128.44 (2C), 129.75, 131.24, 138.04.

4-Methyl-1-dodecene (**20**).[46] The general procedure was used as described above. When the formation of the vinyl zirconium was complete (checked by GC), zinc dibromide (1.9 equiv., 1.9 mmol, 0.43 g) was added at room temperature followed by addition of allylmagnesium bromide (1.9 equiv., 1.9 mmol, 0.85 M in ether, 2.24 ml) at −30 °C. Then, the mixture was warmed to room temperature for 3 h. After usual treatment, the residue was purified by column chromatography on silica gel (eluent: hexane) to give a colorless liquid in 73% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.83 (t, 3H, J=3.39 Hz), 0.86 (t, 3H, J=6.69 Hz), 1.24 (m, 15H), 1.77–2.11 (m, 2H), 4.88–5.02 (m, 2H), 5.64–5.87 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 14.07, 22.67, 29.34–31.92 (8C), 31.92, 117.5, 135.6.

1-(Propylthio)-2-ethyl-decane (**16**). The general procedure was performed using EtLi or EtMgBr instead of *n*-BuLi. The starting material was the vinyl propyl sulfide **7b**. The reaction mixture was quenched with aqueous solution of HCl (1 M) after 1 h stirring at room temperature. The major product, 3-(propylthio)-ethyl-decane **16**, was purified by column chromatography on silica gel (eluent: hexane) to give a yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.81–1.00 (m, 9H), 1.25–1.64 (m, 19H), 2.41–2.48 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 10.83, 13.51, 14.07, 22.67, 23.12, 25.66, 26.73, 29.36, 29.64, 29.99, 31.92, 32.82, 35.03, 36.83, 39.54.

2-(2′-Deuterioethyl)-1-(1′-deuteriodecyl) methyl sulfone (**24**). The general procedure was performed using EtLi or EtMgBr instead of *n*-BuLi. The starting material was the vinyl methyl sulfone *E*-**22c**. The reaction mixture was quenched with MeOD after stirring for 1 h at room temperature after adding the starting material at −78 °C. After usual work up, two products were obtained. The minor product was *E*-1-deuterio-1-decene **9d** and the major product was 2-(2′-deuterioethyl)-1-(1′-deuteriodecyl) methyl sulfone **24**, which was purified by column chromatography on silica gel (hexane/ethyl acetate, 4/1) to give a yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.84 (t, 5H, J=6.54 Hz), 1.07–1.55 (m, 17H), 1.96–2.05 (m, 1H), 2.86 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 9.83 (t), 13.98–34.91 (9C), 41.71, 57.99 (t). HRMS (ESI, methanol) Calcd for $C_{13}H_{26}D_2O_2S$ (MH+) 273.432, Found 273.4453.

Butyl-1-decene (**25**).[47] Purification by column chromatography on silica gel (eluent: hexane) gave a yellow liquid in 70% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.86 (t, 6H, J=6.67 Hz), 1.14–1.51 (m, 16H), 1.93–1.97 (m, 4H), 4.67 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 22.50–42.78 (12C), 108.34, 150.39.

2-Butyl-1-deuterio-1-decene (**26**). Purification by column chromatography on silica gel (eluent: hexane) gave a yellow liquid in 60% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.87 (t, 6H, J=5.06 Hz), 1.24 (m, 16H), 1.94–2.01 (m, 4H), 4.69 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 14.08–42.72 (12C), 108.37 (t), 150.37.

2-Methyl-1-decene (**27**).[48] Purification by column chromatography on silica gel (eluent: hexane) gave a yellow liquid in 68% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.86 (t, 3H, J=6.93 Hz), 1.17–1.50 (m, 12H), 1.69 (s, 3H), 1.98 (t, 2H, J=7.59 Hz), 4.65 (s, 2H).

2-Methyl-1-iodo-1-decene (**28**).[49] Purification by column chromatography on silica gel (eluent: hexane) gave a yellow liquid in 67% yield as a mixture of two isomers in a 1 to 1 ratio. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.86 (t, 3H, J=6.46 Hz), 1.17–1.38 (m, 12H), 1.79 (s, 3H, the second isomer was singlet at 1.85 ppm), 2.17 (t, 2H, J=7.82 Hz), 5.79 (s, 1H, the second isomer was singlet at 5.82 ppm).

α-Butylstyrene (**29**).[50] Purification by column chromatography on silica gel (eluent: hexane) gave a yellow liquid in 64% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.86 (m, 3H), 1.07–1.53 (m, 4H), 2.49 (t, 2H, J=6.98 Hz), 5.05 (s, 1H), 5.25 (s, 1H), 7.13–7.43 (m, 5H).

***E*-β-Methylstyrene** (**30**).[51] Purification by column chromatography on silica gel (eluent: hexane) gave a colorless liquid in 70% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.87–1.90 (d, 3H, J=5.92 Hz), 6.15–6.32 (m, 1H), 6.37–6.46 (d, 1H, J=16.03), 7.15–7.36 (m, 5H).

***E*-β-Ethyl styrene** (**31**).[52] Purification by column chromatography on silica gel (eluent: hexane) gave a colorless liquid. Isolated yield 65% (0.095 g).^{1}H NMR: δ 7.21 (d, J=7 Hz, 2H), 7.09 (d, J=7 Hz, 2H), 6.33 (d, J=16 Hz, 1H) 6.25–6.11 (m, 1H), 2.19 (q, J=6.8 Hz, 2H), 0.95 (t, 6.8 Hz, 3H).

1-Iodo-1-cyclohexene (**32**).[53] The general procedure was performed. With an excess of Cp_2ZrCl_2 (3 equiv.) and *n*-BuLi (6 equiv.). After usual work up the residue was purified by column chromatography on silica gel (eluent: hexane) to give yellow liquid in 40% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.79–0.90 (m, 2H), 1.58–1.73 (m, 2H), 2.06–2.11 (m, 2H), 2.47 (m, 2H), 6.29–6.32 (m, 1H).

Pentyl-3-enylbenzene (**38**).[54] Colorless liquid. ^{1}H NMR: δ 7.19–7.07 (m, 5H), 5.34–5.26 (m, 1H), 2.52–2.69 (m, 2H), 2.32 (q, J=6.5 Hz, 2H), 1.62 (d, J=4.8 Hz, 3H).

Propyl-1-enylbenzene (**39**).[55] Colorless liquid. ^{1}H NMR: δ 7.24–7.21 (m, 5H), 6.22 (d, J=15.9 Hz, 1H), 6.16–6.11 (m, 1H), 2.28–2.37 (m, 4H), 0.88 (t, J=6 Hz, 3H).

Butyl-3-enyl-benzene (**41**).[56] Slight yellow liquid. Isolated yield 67% (0.085 g).^{1}H NMR: δ 7.26–7.15 (m, 5H), 5.85–5.83 (m, 1H), 5.06–4.94 (m, 2H), 2.67 (t, J=7.2 Hz, 2H), 2.34 (q, J=7.2 Hz, 2H).

Reduction of sulfoxides into sulfides

Diphenyl sulfide (Table 2, entry 1). Purification by column chromatography on silica gel (eluent: hexane) gave a colorless liquid in 95% yield, spectrally identical with an authentic sample. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.24–7.38 (m). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 127.07 (2C), 129.22 (4C), 131.18 (4C), 131.23 (2C).

3-Phenylthio-3-hexene (Table 2, entry 4). Purification by column chromatography on silica gel (eluent: hexane) gave colorless liquid in 85% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.97–1.06 (m, 6H), 2.06–2.30 (m, 4H), 5.81 (t, 1H, J=7.32 Hz), 7.13–7.31 (m, 5H).

Dodecyl tolyl sulfide (Table 2, entry 5).[57] Purification by column chromatography on silica gel (eluent: hexane) gave a colorless liquid in 73% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.87 (t, 3H, J=6.74 Hz), 1.20–1.63 (m, 20H), 2.30 (s, 3H), 2.77–2.89 (m, 2H), 7.05–7.25 (m, 4H).

2-Phenylthio-3-ethyl-4-hydroxyl-4-phenyl-1-butene (Table 2, entry 6). The general procedure was used as described above, 2.5 equiv. of Cp_2ZrCl_2 and 5 equiv. of *n*-BuLi were used. After usual work up the residue was purified by column chromatography on silica gel (eluent: hexane/ ethyl acetate, 3/1) to give yellow liquid in 92% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.87 (t, 3H, J=7.25 Hz), 1.60–1.80 (m, 2H), 2.13 (s, 1H), 2.39–2.49 (m, 1H), 4.64 (s, 1H), 4.89–4.92 (d, 1H, J=5.92 Hz), 4.99 (s, 1H), 7.24–7.36 (m, 10H).

Acknowledgements

This research was supported by the Israel Science Foundation (grant 79/01-2) and by the Fund for the Promotion of Research at the Technion.

References and notes

1. For monographs, see (a) Schlosser, M. *Organometallics. Synthesis*; 2002. (b) Furstner, A. *Active Metals*. VCH: Weinheim, 1996. (c) Negishi, E. *Organometallics in Organic Synthesis*. Wiley-Interscience: New York, 1980.
2. (a) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. (b) Patai, S.; Rappoport, Z.; Stirling, C. J. M. *The Chemistry of Sulphones and Sulphoxides*. Wiley: Chichester, 1988. (c) Simpkins, N. S. *Sulphones in Organic Synthesis*. Pergamon, 1993.
3. (a) Cuvigny, T.; Herve du Penhoat, C.; Julia, M. *Tetrahedron Lett.* **1983**, *24*, 4311. (b) Julia, M.; Lauron, H.; Stacino, J. P.; Verpeaux, J. N.; Jeannin, Y.; Dromzee, Y. *Tetrahedron* **1986**, *42*, 2475. (c) Fabre, J. L.; Julia, M.; Verpeaux, J. N. *Bull. Soc. Chim. Fr.* **1985**, 762. (d) Baldwin, J. E.; Adlington, R. M.; Ichikawa, Y.; Kneale, C. J. *J. Chem. Soc. Chem. Commun.* **1988**, 702. (e) Trost, B. M. *Bull. Chem. Soc. Jpn* **1988**, *61*, 107. (f) Backvall, J. E.; Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291.
4. (a) Cohen, T.; Doubleday, M. D. *J. Org. Chem.* **1990**, *55*, 4784. (b) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.
5. (a) Foubelo, F.; Gutierrez, A.; Yus, M. *Tetrahedron Lett.* **1990**, *40*, 8173. (b) Yus, M. *Chem. Soc. Rev.* **1996**, 155.
6. Farhat, S.; Marek, I. *Angew. Chem. Int. Ed.* **2002**, *41*, 1410.
7. Titanium and Zirconium in Organic Synthesis. Marek, I., Ed.; Wiley-VCH: Weinheim, 2002.
8. Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5105.
9. For reviews, see (a) Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn* **1988**, *71*, 755. (b) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. (c) Negishi, E.; Kondakov, D. Y. *Chem. Soc. Rev.* **1996**, *26*, 417.
10. (a) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295. (b) Hanzawa, Y.; Kiyono, H.; Tanaka, N.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 4615.
11. (a) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 3769. (b) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835. (c) Ito, H.; Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y.; Shiro, M. *J. Am. Chem. Soc.* **1994**, *116*, 5469. (d) Hanzawa, Y.; Kiyono, H.; Tanaka, N.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 4615.

12. Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 7873.
13. (a) Ito, H.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 5829. (b) Sato, A.; Ito, H.; Taguchi, T. *J. Org. Chem.* **2000**, *65*, 918. (c) Ito, H.; Kuroi, H.; Ding, H.; Taguchi, T. *J. Am. Chem. Soc.* **1998**, *120*, 6623. (d) Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 3217.
14. (a) Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299. (b) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* **1995**, *51*, 4507.
15. Ito, H.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **1993**, *58*, 774.
16. Takahashi, T.; Kotora, M.; Fischer, R.; Nishihara, Y.; Nakajima, K. *J. Am. Chem. Soc.* **1995**, *117*, 11039.
17. (a) Ichikawa, J.; Fujiwara, M.; Nawata, H.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1996**, *37*, 8799. (b) Fujiwara, M.; Ichikawa, J.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 7261.
18. The only available information was found in a footnote (Ref. [16]) in which a *J* value of 19 Hz was described (*trans* configuration) for a vinyl zirconium without describing the stereochemistry of the starting material.
19. Takahashi, T.; Fujimoto, T.; Seki, T.; Saburi, M.; Uchida, Y.; Rousset, C. J.; Negishi, E. *J. Chem. Soc. Chem. Commun.* **1990**, 182.
20. Negishi, E.; Choueiry, D.; Nguyen, T. B.; Swanson, D. R.; Suzuki, N.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 9751.
21. Liard, A.; Marek, I. *J. Org. Chem.* **2000**, *65*, 7218.
22. (a) Mintz, E. A.; Ward, A. S.; Tice, D. S. *Organometallics* **1985**, *4*, 1308. (b) Ward, A. S.; Mintz, E. A.; Kramer, M. P. *Organometallics* **1988**, *7*, 8.
23. (a) Takahashi, T.; Suzuki, N.; Kageyama, M.; Nitto, Y.; Saburi, M.; Negishi, E. *Chem. Lett.* **1991**, 1579. (b) Takahashi, T.; Nitto, Y.; Seki, T.; Saburi, M.; Negishi, E. *Chem. Lett.* **1990**, 2259.
24. Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853.
25. Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Tetrahedron Lett.* **1994**, *35*, 5685.
26. (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 214.
27. Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241.
28. Mislow, K.; Siegel, J. *J. Chem. Soc.* **1984**, *106*, 3319.
29. Carreno, C. M. *Chem. Rev.* **1995**, *95*, 1717.
30. Holton, R. A.; Crouse, D. J.; Williams, A. D.; Kennedy, R. M. *J. Org. Chem.* **1987**, *52*, 2317.
31. Howard, W. A.; Parkin, G. *J. Am. Chem. Soc.* **1994**, *116*, 606.
32. Cuvigny, T.; Herve du Penhoat, C.; Julia, M. *Tetrahedron Lett.* **1983**, *24*, 4311.
33. (a) Fabre, J. L.; Julia, M.; Verpeaux, J. N. *Bull. Soc. Chim. Fr.* **1985**, 762. (b) Fabre, J. L.; Julia, M.; Verpeaux, J. N. *Bull. Soc. Chim. Fr.* **1985**, 772. (c) Baldwin, J. E.; Adlington, R. M.; Ichikawa, Y.; Kneale, C. J. *J. Chem. Soc. Chem. Commun.* **1988**, 702.
34. (a) Trost, B. M. *Bull. Chem. Soc. Jpn* **1988**, *61*, 107. (b) Backvall, J. E.; Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291.
35. (a) Tolman, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 2994. (b) Bingham, D.; Hudson, B.; Webster, B. D. E.; Wells, P. B. *J. Chem. Soc., Dalton Trans.* **1974**, 1521. (c) Bingham, D.; Webster, D. E.; Wells, P. B. *J. Chem. Soc., Dalton Trans.* **1974**, 1514.
36. Akita, M.; Yasuda, H.; Nagasuna, K.; Nakamura, A. *Bull. Chem. Soc. Jpn* **1983**, *56*, 554.
37. (a) Swanson, D. R.; Negishi, E. *Organometallics* **1991**, *10*, 825. (b) Maye, J. P.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 3359. (c) Negishi, E.; Maye, J. P.; Choueiry, D. *Tetrahedron* **1995**, *51*, 4447.
38. Chinkov, N.; Majumbar, S.; Marek, I. *J. Am. Chem. Soc.* **2002**, *124*, 10282.
39. Normant, J. F.; Alexakis, A.; Commercon, A.; Cahiez, G.; Villieras, J. *C.R. Acad. Sci.* **1974**, *279*, 763.
40. (a) Vermeer, P.; Meijer, J.; Eylander, C. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 240. (b) Truce, W. E.; Lusch, *J. Org. Chem.* **1974**, *39*, 3174.
41. Julia, M.; Lauron, H.; Stacino, J. P.; Verpeaux, J. N.; Jeannin, Y.; Dromzee, Y. *Tetrahedron* **1986**, *42*, 2475.
42. Hoshi, M.; Shirakawa, K. *Chem. Commun.* **2002**, 2146.
43. (a) Boothe, T.; Finn, R.; Vora, M. *J. Labelled Compd. Radiopharm.* **1985**, *22*, 1109. (b) Chen, D. W.; Ochiai, M. *J. Org. Chem.* **1999**, *64*, 6804.
44. Kasai, K.; Kotora, M.; Suzuki, N.; Takahashi, T. *J. Soc. Chem. Commun.* **1995**, 109.
45. Neumann, H.; Seebach, D. *Tetahedron Lett.* **1976**, 4839.
46. Marek, I.; Lefrancois, J. M.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1994**, *131*, 910.
47. Barber, J.; Willis, C.; Whitesides, G. *J. Org. Chem.* **1979**, *44*, 3603.
48. Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.
49. Ma, S.; Negishi, E. *J. Org. Chem.* **1977**, *62*, 784.
50. Itami, K.; Nokami, T.; Ioshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600.
51. Baxendale, I.; Lee, A.; Ley, S. *Synlett* **2002**, 516.
52. Yao, C.; Chu, C.; Liu, J. *J. Org. Chem.* **1998**, *63*, 719.
53. Lee, K.; Wiemer, D. *Tetrahedron Lett.* **1993**, *34*, 2433.
54. Kirmse, W.; Kopannia, S. *J. Org. Chem.* **1998**, *63*, 1178.
55. Wang, Q.; Deredas, D.; Huynh, C.; Schlisser, M. *Chem. A Eur. J.* **2003**, *9*, 570.
56. Grasa, G.; Moore, Z.; Martin, K.; Stevens, E.; Nolan, S.; Paquet, V.; Lebel, H. *J. Organomet. Chem.* **2002**, *658*, 126.
57. Furman, I.; Whitten, D.; Penner, T.; Ulman, A.; Geiger, H. *Langmuir* **1994**, *10*, 837.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1339–1344
Tetrahedron

Transformation of 1,5- and 1,6-dienes to carbocycles by hydrozirconation and oxidation with cerium(IV) compounds

Takushi Azemi, Mitsuru Kitamura and Koichi Narasaka*

Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

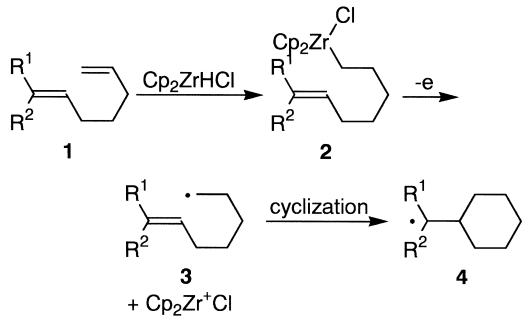
Received 15 July 2003; accepted 6 August 2003

Abstract—Cyclopentane and cyclohexane derivatives are prepared from 1,5- and 1,6-dienes in a one pot procedure by hydrozirconation, then oxidation of the generated 5- and 6-alkenylzirconocene chlorides with ammonium hexanitratocerate.

1. Introduction

Radical addition to the olefinic moiety is recognized as one of the general tools to construct molecular skeletons, particularly cyclopentane derivatives.[1] To generate radical species, one-electron oxidation of organometallic compounds has attracted considerable attention and has been utilized mostly to generate α-keto and β-keto radical species.[2] For example, Mn(III)-based oxidation is applied to the generation of keto radicals and the successive intra- and intermolecular addition to alkenes.[2a–e] Such oxidative methods, however, have found a quite limited application for the generation of alkyl radicals from organometallics. The dimerization of alkyl groups occurs by oxidation probably due to the aggregation of alkyl metals, as being exemplified by the dimerization of phenyl Grignard reagent by electrode oxidation.[3] Accordingly, the choice of alkyl metals seems to be crucial to prevent such a dimerization of alkyl groups to generate radical species by oxidation of organometals. Alkylzirconocenes are easily prepared by hydrozirconation of alkenes[4,5] and scarcely aggregate due to steric effects by of the cyclopentadienyl groups. We planed to examine the oxidation of alkylzirconocenes **2** having an internal olefinic moiety with the expectation that alkyl radical species **3** would be generated by oxidation and add to the olefinic moiety to give cyclization product **4** as shown in Scheme 1. The 6-alkenylzirconocenes **2** are readily prepared by the regioselective hydrozirconation of the less-hindered terminal vinyl group of 1,6-dienes **1**.[6]

Concerning the oxidation of alkylzirconocenes, the formation of alcohols was reported by the reaction of alkylzirconocenes with peroxides and peracids.[4a] The oxidation of benzylarylzirconocene with Cp_2FePF_6 caused the dimerization of benzyl groups to 1,2-diphenylethane.[7] The intramolecular cross-coupling of organic substituents on zirconium was accomplished by the oxidation of the alkenyl-alkynylzirconocenes with an oxovanadium(V) compound, giving the corresponding enynes.[8] In contrast, there has been no example for oxidative cyclization reaction of organozirconocenes.



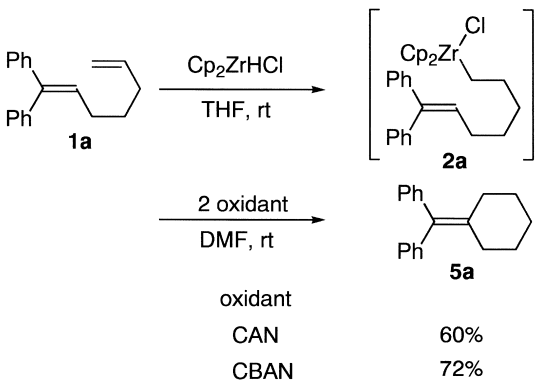
Scheme 1. Oxidative cyclization of alkenylzirconocenes.

2. Results and discussion

6-Heptenylzirconocene chloride **2a** was prepared in situ by hydrozirconation of 1,1-diphenyl-1,6-heptadiene (**1a**) with a slight excess of Cp_2ZrHCl. In fact, the quench of the generated alkenylziconocene with CD_3COOD gave only 7-deuterio-1,1-diphenyl-1-heptane. The in situ generated 6-alkenylzirconocene intermediate **2a** was submitted for the oxidation with Ce(IV) complexes as shown in Scheme 2. When a DMF solution of ammonium hexanitratocerate (CAN) was added to a THF solution of **2a**, the expected cyclization product **5a** was obtained in 60% yield whereas **5a** was not obtained by the oxidation with Cp_2FePF_6, $Mn(pic)_3$, $Ag(pic)_2$ (pic=2-pyridinecarboxylato), or

Keywords: 1,5- and 1,6-Dienes; Radical cyclization; Alkyl zirconocene; Cerium(IV).
* Corresponding author. Tel.: +81-3-5841-4343; fax: +81-3-5800-6891; e-mail address: narasaka@chem.s.u-tokyo.ac.jp

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.08.075

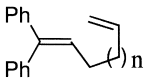
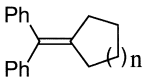
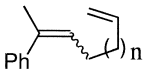
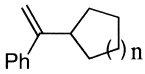
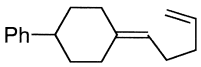
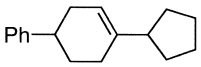
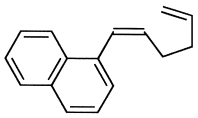
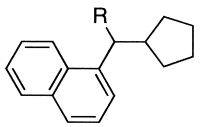
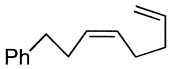
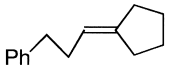
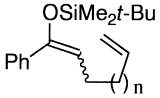
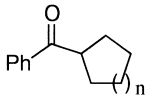
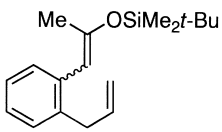
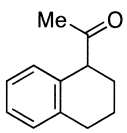
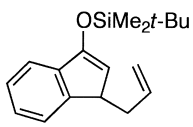
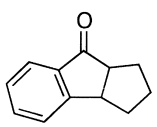


Scheme 2. Oxidation of alkenylzirconocene **2a** by using Ce(IV) salts.

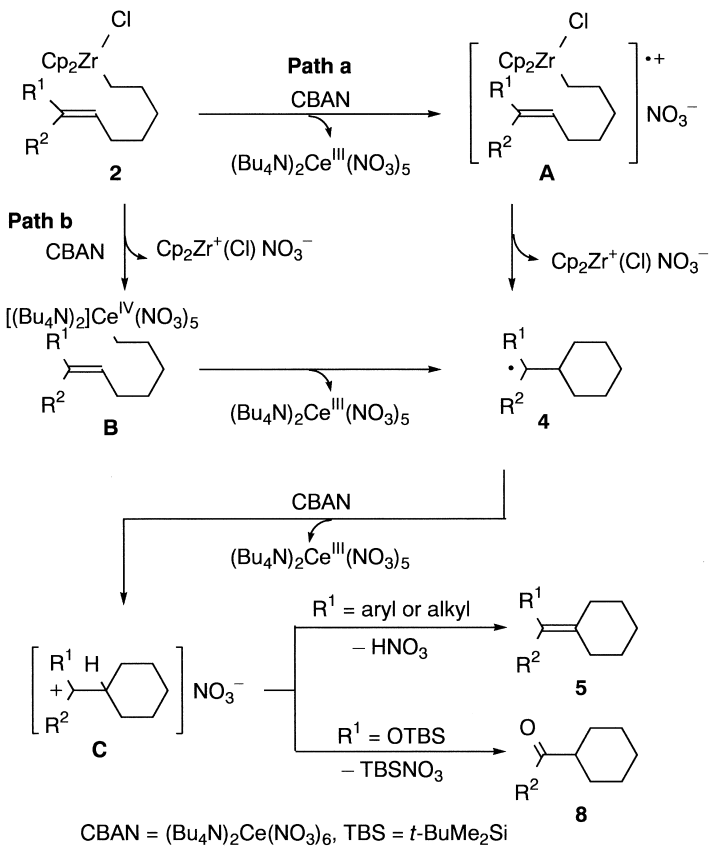
$Cu(OAc)_2$.[9] The yield of **5a** was increased to 72% by use of tetrabutylammonium hexanitratocerate (CBAN).

This oxidative method was applied to the cyclization of various 1,5- and 1,6-dienes, and the results are summarized in Table 1. Prior to the oxidation, the hydrozirconation of the teminal vinyl group of dienes (**1a**–**k**) was confirmed by quenching the in situ generated 5-or 6-alkenylzirconocene with CD_3COOD or D_2O, which gave the terminal monodeuterated alkenes in 76–92% yield. As compared to the formation of 6-membered ring derivatives from 1,6-dienes, 1,5-pentadienes are converted to the corresponding cyclopentane derivatives in better yields (run 1 vs. 2 and 3 vs. 4). Within the radical addition process, the 5-membered cyclization tend to proceed more efficiently than the 6-membered cyclization.[10] Diene having trialkyl substituted olefinic moiety **1e** gave the desired cyclopentane **5e** in 76% yield. In the case of naphthyl substituted 1,5-diene **1f**, alcohol **6** and formate **7** were formed exceptionally in 56% total yield. These compounds were formed by trapping the benzylic cation intermediate (vide infra: **C** in Scheme 3) with DMF. Dialkyl substituted alkene **1g** is not suitable for a radical accepter and the reduction product of **1g**, 1-phenyl-3-octene, was obtained in 83% yield (run 7). Thus, trisubstituted or aryl substituted olefinic moiety was found to be suitable as a radical acceptor. Particularly noteworthy is that various carbonyl compounds were prepared by this cyclization method from dienes bearing a siloxy olefinic moiety **1h**–**k**. For example, the cyclization of 1-phenyl-1-siloxy-1,6- and 1,5-dienes **1h** and **1i** proceeded smoothly to afford the corresponding cyclohexyl ketone **8h** and cyclopentyl ketone **8i** in high yield (runs 8 and 9). Bicyclic

Table 1. The oxidative intramolecular cycloaddition of various 1,5- and 1,6-dienes with CBAN[a]

Run	Substrates		Products		Yield (%)
1		n=2 **1a**		n=2 **5a**	72
2		n=1 **1b**		n=1 **5b**	83
3		n=2 **1c**[b]		n=2 **5c**	39
4		n=1 **1d**[b]		n=1 **5d**	72
5		**1e**		**5e**	76
6[c]		**1f**		R=OH **6** R=OCOH **7**	42 14
7[d]		**1g**			0
8		n=2 **1h**[e]		n=2 **8h**	71
9		n=1 **1i**[f]		n=1 **8i**	78
10		**1j**[b]		**8j**	36
11		**1k**		**8k**[g]	75

[a]*Reaction and conditions*: (1) diene, Cp_2ZrHCl (1 equiv.), THF, rt, 1 h, (2) CBAN (2 equiv.), DMF, rt, 12 h; [b]*E*, *Z* mixture. The stereochemistry is not determined; [c]Hydrozirconation was carried out at −10 °C for 5 h; [d]Hydrozirconation was carried out at −10 °C for 4 h; [e]*E*/*Z*=13:1; [f]*E*/*Z*=10:1; [g]Single diastereomer. The stereochemsitry is not determined.



Scheme 3. A plausible mechanism of the cyclization of alkenylzirconocene **2** with CBAN.

and tricyclic ketones **8j** and **8k** could be also synthesized from olefinic silyl enol ethers **1j** and **1k**, respectively (runs 10 and 11).

A plausible mechanism of the present cyclization of alkenylzirconocene **2** with CBAN is depicted in Scheme 3. Alkenylzirconocene **2** is oxidized with CBAN to give cation radical species **A** and the successive radical cyclization occurs to give radical intermediate **4** (Path a). **4** might be formed via alkenylcerium(IV) intermediate **B** generated by the transmetallation between **2** and CBAN (Path b). Further oxidation of the radical intermediate **4** with CBAN gives the corresponding cation species **C** and the successive deprotonation or desilylation from **C** affords cycloalkenes **5** or cycloalkyl ketones **8**.

In conclusion, we developed the method of the synthesis of cyclopentane and cyclohexane derivatives from 1,5- and 1,6-dienes in a one pot procedure by hydrozirconation, and the successive oxidation of the generated 5- and 6-alkenylzirconocene chlorides with Ce(IV) compounds.

3. Experimental

3.1. General

IR spectra were measured with a Horiba FT 300-S spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded on a Bruker DRX 500 or an Avance 500 spectrometer with $CHCl_3$ (δ=7.24 for ^{1}H NMR) and $CDCl_3$ (δ=77.0 for ^{13}C NMR) as an internal standard. High-resolution mass spectra were recorded on a JEOL MS-700P mass spectrometer (EI: operating at 70 eV). All melting points were uncorrected. Yields quoted are based on isolated mass. All reactions were carried out under an argon atmosphere. Et_2O and THF were dried by distillation from sodium and benzophenone. Dimethylformamide (DMF) was dried over by P_2O_5 for 24 h followed by distillation, then was distilled from CaH_2 and subsequently stored over 4 Å molecular sieves. Cp_2ZrHCl was purchased from Aldrich and was used as received. Ammonium hexanitratocerate [$(NH_4)_2Ce(NO_3)_6$, (CAN)] was dried under pressure (0.5 mmHg) for 6 h at 80 °C. Tetrabutylammonium hexanitratocerate [$(n\text{-}Bu_4N)_2Ce(NO_3)_6$, (CBAN)] was prepared according to the literature procedure.[11] Flash column chromatography was carried out on silica-gel [Kanto Chemical Co., Inc. Silica gel 60N (spherical, neutral)]. Preparative TLC was performed on silica-gel (Wakogel B-5F).

3.2. General procedure for oxidation of alkenyl-zirconocene

Freshly distilled dienes (0.20 mmol) were added to a THF suspension (2.0 mL) of Cp_2ZrHCl (114 mg, 0.21 mmol) under argon atmosphere at rt, and the suspension was stirred for 1 h (a white suspension turned to a yellow solution). To this solution was added CBAN (439 mg, 0.42 mmol) in DMF (4.5 mL) at rt, and the mixture was allowed to stir for 12 h. After the reaction was quenched with water, the mixture was filtered through a Celite pad. The filtrate was extracted with EtOAc, and the combined organic extracts were washed with water and brine, and dried over Na_2SO_4.

The solvent was evaporated in vacuo to give a crude product, which was purified by preparative TLC.

3.2.1. (Diphenylmethylene)cyclohexane (5a).[12] 72% Yield; mp 73–74 °C; ^{1}H NMR ($CDCl_3$) δ 1.56–1.60 (m, 6H), 2.23–2.25 (m, 4H), 7.10–7.29 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.8, 28.7, 32.4, 126.0, 127.8, 129.8, 134.5, 139.1, 143.1.

3.2.2. (Diphenylmethylene)cyclopentane (5b).[13] 83% Yield; mp 61–63 °C; ^{1}H NMR ($CDCl_3$) δ 1.65–1.71 (m, 4H), 2.23–2.25 (m, 4H), 7.15–7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.8, 33.2, 126.0, 127.9, 129.2, 134.3, 138.9, 143.5.

3.2.3. 1-Cyclohexyl-1-phenylethene (5c).[14] 39% Yield; ^{1}H NMR ($CDCl_3$) δ 1.19–1.38 (m, 6H), 1.80–1.88 (m, 4H), 2.42–2.48 (m, 1H), 5.04 (s, 1H),?5.16 (s, 1H), 7.28–7.37 (m, 5H).

3.2.4. 1-Cyclopentyl-1-phenylethene (5d).[15] 72% Yield; ^{1}H NMR ($CDCl_3$) δ 1.23–2.02 (m, 7H), 2.18–2.36 (m, 1H), 2.94 (q, J=8.1 Hz, 1H), 5.05 (d, J=1.1 Hz, 1H), 5.15 (d, J=1.1 Hz, 1H), 7.15–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.8, 32.0, 44.5, 110.0, 126.5, 126.9, 128.0, 143.1, 152.8.

3.2.5. (4-Cyclopentyl-3-cyclohexenyl)benzene (5e). 76% Yield; ^{1}H NMR ($CDCl_3$) δ 1.37–2.36 (m, 15H), 2.64–2.83 (m, 1H), 5.52 (d, J=5.1 Hz, 1H), 7.16–7.33 (m, 5H).

3.2.6. Cyclopentyl-(1-naphthyl)methanol (6). 42% Yield; IR (neat) 3390, 2950, 2870, 800, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23–1.28 (m, 1H), 1.41– 1.68 (m, 6H), 1.86–1.96, (m, 1H), 2.49–2.57 (m, 1H), 5.20 (d, J=7.6 Hz, 1H), 7.40–7.52 (m, 3H), 7.58 (d, J=7.0 Hz, 1H), 7.77 (d, J=8.2 Hz, 1H), 7.83–7.86 (m, 1H), 8.20–8.24 (m, 1H); ^{13}C NMR δ 25.6, 25.7, 29.0, 29.7, 46.5, 75.3, 123.6, 123.9, 125.3, 125.4, 125.8, 128.0, 128.8, 130.8, 133.9; FAB HRMS $(M+H)^+$ calcd for $C_{16}H_{19}O$ 227.1437, found 227.1428.

3.2.7. Cyclopentyl-(1-naphthyl)methylformate (7). 14% Yield; oil; IR (neat) 2960, 2870, 1720, 1170, 800, 780; ^{1}H NMR ($CDCl_3$) δ 1.15–1.87 (m, 8H), 2.65–2.73 (m, 1H), 6.45 (d J=8.6 Hz, 1H), 7.42–7.55 (m, 4H), 7.80 (d, J=8.0 Hz, 1H), 7.86 (d, J=8.1 Hz, 1H), 8.14 (s, 1H), 8.26 (d, J=8.1 Hz, 1H); ^{13}C NMR δ 25.2, 25.3, 29.4, 29.5, 45.1, 123.6, 125.0, 125.2, 125.6, 126.2, 128.6, 128.9, 130.6, 133.8, 135.8, 160.6; FAB HRMS $(M+H)^+$ calcd for $C_{17}H_{19}O_2$ 255.1380, found 255.1386.

3.2.8. Cyclohexyl phenyl ketone (8h).[16] 71% Yield; ^{1}H NMR ($CDCl_3$) δ 1.24–1.90 (m, 10H), 3.26 (m, 1H), 7.41 (m, 3H), 7.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.8, 25.9, 29.4, 45.6, 128.2, 128.5, 132.7, 136.3, 203.9.

3.2.9. Cyclopentyl phenyl ketone (8i).[17] 78% Yield; ^{1}H NMR ($CDCl_3$) δ 1.58–1.72 (m, 4H), 1.76–1.94 (m, 4H), 3.70 (q, J=7.8 Hz, 1H), 7.41–7.59 (m, 3H), 7.94–7.97 (m, 2H).

3.2.10. 1-(1,2,3,4-Tetrahydro-1-naphthyl)ethanone (8j).[18] 36% Yield; ^{1}H NMR ($CDCl_3$) δ 1.72–1.80 (m, 1H), 1.88–2.08 (m, 3H), 2.12 (s, 3H), 2.76–2.82 (m, 2H), 3.83 (t, J=6.8 Hz, 1H), 6.97–6.99 (m, 1H), 7.06–7.21 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 20.8, 26.2, 27.7, 29.2, 53.7, 125.9, 126.8, 129.2, 129.5, 133.6, 137.4, 210.6.

3.2.11. 1,2,3,3a,8a-Pentahydrocyclopenta[*a*]inden-8-one (8k).[19] 75% Yield; ^{1}H NMR ($CDCl_3$) δ 1.10–1.13 (m, 1H), 1.55–1.58 (m, 1H), 1.81–1.88 (m, 2H), 1.96–2.00 (m, 2H), 3.01–3.05 (m, 1H), 3.73 (t, J=7.8 Hz, 1H), 7.31 (t, J=7.5 Hz, 1H), 7.44 (dd, J=8.0, 1.0 Hz, 1H), 7.55–7.59 (m, 1H), 7.94 (d, J=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.8, 30.8, 33.1, 43.9, 52.3, 123.1, 125.9, 127.3, 135.1, 137.4, 158.7, 210.2.

3.3. Preparation of starting materials

1,1-Diphenyl-1,5-hexadiene (**1a**),[20] 1,1-diphenyl-1,6-heptadiene (**1b**),[20] *t*-butyldimethyl(1-phenylhexa-1,5-dienyloxy)-silane (**1h**),[21] and *t*-butyldimethyl(1-phenylhepta-1,6-dienyloxy)silane (**1i**),[21] were prepared according to the literature procedures.

3.3.1. 7-Phenyl-1,6-octadiene (1c). Potassium *t*-butoxide (1.0 g, 8.9 mmol) was added to hexenyl triphenylphosphonium bromide[22] (3.8 g, 8.9 mmol) in THF (50 mL). After stirring for 1.5 h at rt, a THF solution (6 mL) of acetophenone (713 mg, 5.94 mmol) was added. After 2 h, the reaction mixture was filtered on a short silica-gel column with ether, and the filtrate was concentrated in vacuo. The crude product was distilled under 1.5 mmHg in Kugelrohr apparatus to give **1c** (1.06 g, 96%) as an oil. *E*, *Z* mixture. Bp 110–120 °C/1.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.44–1.56 (m, 2H), 1.97 (s, 3H), 2.02–2.20 (m, 4H), 4.85–4.99 (m, 2H), 5.69–5.83 (m, 2H), 7.12–7.34 (m, 5H),

3.3.2. 6-Phenyl-1,5-heptadiene (1d). Potassium *t*-butoxide (1.40 g, 12.5 mmol) was added to pentenyl triphenylphosphonium bromide[23] (5.13 g, 12.5 mmol) in THF (80 mL). After stirring for 1.5 h at rt, a THF solution (10 mL) of acetophenone (1.00 g, 8.33 mmol) was added. After 2 h, the reaction mixture was filtered on a short silica-gel column with ether, and the filtrate was concentrated in vacuo. The crude product was distilled under 1.5 mmHg in Kugelrohr apparatus to give **1d** (1.36 g, 95%) as an oil. *E*, *Z* mixture. Bp 110–120/1.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 2.07–2.10 (m, 4H), 4.91–4.99 (m, 2H), 5.45–5.48 (m, 1H), 5.72–5.80 (m, 1H), 7.17–7.19 (m, 2H), 7.21–7.25 (m, 1H), 7.31–7.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.5, 28.4, 34.1, 114.5, 126.4, 126.8, 127.9, 128.0, 136.5, 138.3, 142.0.

3.3.3. 5-(4-Phenylcyclohexylidene)-1-pentene (1e). Potassium *t*-butoxide (1.49 g, 13.3 mmol) was added to pentenyltriphenylphosphonium bromide[23] (5.47 g, 13.3 mmol) in THF (80 mL). After stirring for 1.5 h at rt, a THF solution (10 mL) of 4-phenylcyclohexanone (1.54 g, 8.87 mmol) was added. After stirring for 2 h, the reaction mixture was filtered on a short silica-gel column with ether, and the filtrate was concentrated in vacuo. The crude product was distilled under 1.5 mmHg in Kugelrohr apparatus gave **1e** (1.99 g, 99%) as an oil. Bp 130–140 °C/1.0 mmHg; IR (neat) 2920, 2360, 1490, 1440, 910, 760, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40–1.53 (m, 2H), 1.85–1.90 (m, 1H), 1.94–1.96 (m, 2H), 2.11–2.21 (m, 5H), 2.28–2.31 (m, 1H), 2.65–2.73 (m, 2H), 4.97–5.06 (m, 2H),

5.16–5.17 (m, 1H), 5.80–5.89 (m, 1H), 7.17–7.21 (m, 3H), 7.26–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.7, 28.4, 34.3, 35.1, 35.9, 36.8, 44.8, 114.4, 121.3, 125.9, 126.8, 128.3, 138.6, 138.7, 147.1. HRMS calcd for $C_{17}H_{22}$ 226.1721, found 226.1739.

3.3.4. (5*Z*)-6-(1-Naphthyl)-1,5-hexadiene (1f). Potassium *t*-butoxide (1.46 g, 13.0 mmol) was added to pentenyl triphenylphosphonium bromide[23] (5.35 g, 13.0 mmol) in THF (80 mL). After stirring for 1 h at rt, a THF solution (10 mL) of 1-naphthaldehyde (1.35 g, 8.67 mmol) was added. After stirring for 2 h, the reaction mixture was filtered on a short silica-gel column with ether, and the filtrate was concentrated. The crude product was distilled under 1.0 mmHg in Kugelrohr apparatus to give **1f** (1.72 g, 95%) as an oil. Bp 120–130 °C/1.0 mmHg; IR (neat) 3060, 3010, 2920, 2340, 1640, 1510, 910, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.16 (dt, *J*=7.6, 6.6 Hz, 2H), 2.27 (dt, *J*=7.2, 6.6 Hz, 2H), 4.93 (d, *J*=10.2 Hz, 1H), 4.98 (d, *J*=17.2 Hz, 1H), 5.76 (ddt, *J*=17.2, 10.2, 6.6 Hz, 1H), 5.93 (dt, *J*=11.5, 7.2 Hz, 1H), 6.90 (d, *J*=11.5 Hz, 1H), 7.34 (d, *J*=11.5, 7.0 Hz, 1H), 7.43–7.50 (m, 3H), 7.76 (d, *J*=11.5 Hz, 1H), 7.84–7.86 (m, 1H), 7.99 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0, 33.8, 125.0, 125.2, 125.7, 125.8, 126.3, 127.2, 127.4, 128.3, 131.9, 133.4, 133.5, 133.6, 134.7, 138.1; HRMS calcd for $C_{16}H_{16}O$ 208.1252, found 208.1228.

3.3.5. (5*Z*)-8-Phenyl-1,5-octadiene (1g). Potassium *t*-butoxide (1.31 g, 11.7 mmol) was added to pentenyl triphenylphosphonium bromide[23] (4.81 g, 11.7 mmol) in THF (80 mL). After stirring for 1 h at rt, a THF solution (10 mL) of hydrocinnamaldehyde (1.21 g, 9.00 mmol) was added. After stirring for 2 h, the reaction mixture was filtered on a short silica-gel column with ether, and the filtrate was concentrated in vacuo. The crude product was distilled under 1.0 mmHg in Kugelrohr apparatus to give **1 g** (1.68 g, 99%) as an oil. *Z* isomer. Bp 100–110 °C/1.0 mmHg; IR (neat) 3000, 2850, 1640, 1500, 1450, 910, 720, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01–2.10 (m, 4H), 2.34–2.08 (m, 2H), 2.66 (t, *J*=7.8 Hz, 2H), 4.93–5.01 (m, 2H), 5.36–5.47 (m, 2H), 5.73–5.81 (m, 1H), 7.17–7.20 (m, 3H), 7.25–7.29 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.6, 29.2, 33.7, 35.9, 114.6, 125.8, 128.2, 128.5, 129.1, 129.7, 138.3; HRMS calcd for $C_{14}H_{18}$ 186.1409, found 186.1396, 142.1.

3.3.6. [2-(2-Allylphenyl)-1-methylethenyloxy]-*t*-butyldimethylsilane (1j). *p*-Toluenesulfonic acid monohydrate (38.0 mg, 0.20 mmol) and 1,3-propanediol (4.57 g, 60.0 mmol) were added to a solution of 1-(2-bromophenyl)propan-2-one[24] (4.20 g, 19.7 mmol) in benzene (60 mL). After the reaction mixture was refluxed for 10 h, the reaction was quenched with sat. $NaHCO_3$ aq. The organic materials were extracted with EtOAc, and the organic extract was washed with water followed by brine. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica-gel deactivated by Et_3N (6:1 hexane/EtOAc) to give 2-(2-bromobenzyl)-2-methyl-1,3-dioxane. [97% yield; ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 3H), 1.45–1.55 (m, 1H), 1.67–1.77 (m, 1H), 3.14 (s, 2H), 3.86 (dd, *J*=12.5, 8.5 Hz, 4H), 6.92–6.97 (m, 1H), 7.08–7.14 (m, 1H), 7.30–7.33 (m, 1H), 7.40–7.43; ^{13}C NMR ($CDCl_3$) δ 19.9, 25.4, 43.2, 59.8, 99.6, 126.0, 126.9, 127.9, 132.4, 132.6, 136.7.]

To a solution of 2-(2-bromobenzyl)-2-methyl-1,3-dioxane (2.0 g, 7.0 mmol) in THF (12 mL) was added buthyllithium (7.71 mmol) at −78 °C. After stirring for 1 h, allyl bromide (1.01 g, 8.41 mmol) in THF (5 mL) was added to the reaction mixture at −78 °C. After the reaction mixture was warmed to rt, the reaction was quenched with water. From the mixture organic materials were extracted with EtOAc, and the combined organic extracts were washed with water followed by brine. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. To a solution of the crude product in MeOH (10 mL) was added 1 N HCl (0.5 mL). After stirring for 2 h, the reaction mixture was poured into water and extracted with EtOAc. The combined organic extracts were washed with water followed by brine. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica-gel (6:1:1 hexane/EtOAc/benzene) to give 1-(2-allyl-phenyl)propan-2-one [22% yield; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H), 3.73 (s, 2H), 3.34 (d, *J*=11.5 Hz, 2H), 4.94–5.08 (m, 1H), 5.84–5.96 (m, 1H), 7.12–7.34 (m, 4H).]

To a suspension of NaH (52.1 mg, 2.17 mmol) in THF (2 mL) was added a THF (4 mL) solution of 1-(2-allyl-phenyl)propan-2-one (291 mg, 1.67 mmol) at 0 °C. After the mixture was allowed to warm to rt with stirring, a THF (3 mL) solution of *t*-butyldimethylsilyl chloride (327 mg, 2.17 mmol) was added. After stirring for 2 h, the reaction was quenched with sat. $NaHCO_3$ aq. The organic layer was washed twice with brine and dried over Na_2SO_4. After the solvent was removed in vacuo, the residue was roughly purified by column chromatography deactivated by Et_3N (hexane/EtOAc=9/1) to give **1j**, which was further purified by distillation under 1.0 mmHg to give pure **1j** (0.457 g, 95%) as an oil. *E*, *Z* mixture; Bp 150–160 °C/1.0 mmHg; ^{1}H NMR ($CDCl_3$) δ −0.03 (s, 6H), 0.83 (s, 9H), 1.97 (s, 3H), 3.36–3.38 (m, 2H), 4.96–5.05 (m, 2H), 5.51 (s, 1H), 5.90–6.01 (m, 1H), 7.08–7.16 (m, 3H), 7.60–7.63 (m, 1H).

3.3.7. (3-Allyl-3*H*-1-indenyloxy)-*t*-butyldimethylsilane (1k). To a solution of lithium diisopropylamide [prepared by the reaction of buthyllithium (10.7 mmol) and diisopropylamine (1.08 g, 10.7 mmol) in THF (20 mL)] was added a THF (12 mL) solution of 3-(*t*-butyldimethylsilyloxy)indene[25] (2.49 g, 10.1 mmol) at −78 °C. After stirring for 1 h, allyl bromide (1.32 g, 11.0 mmol) in THF (10 mL) was added to the reaction mixture at −78 °C. After the reaction mixture was warmed to rt, the reaction was quenched with water. From the mixture organic materials were extracted with EtOAc, and the combined organic extracts were washed with water followed by brine. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The yellow residue was distilled under 0.1 mmHg to give **1k** (2.20 g, 76%) as a yellow oil. Bp 85–100 °C/0.1 mmHg; ^{1}H NMR ($CDCl_3$) δ −0.02 (s, 1H), 0.83 (s, 1H), 1.97 (s, 3H), 3.37 (d, *J*=6.2 Hz 2H), 4.96–5.05 (m, 2H), 5.90–6.01 (m, 1H), 7.08–7.16 (m, 4H).

Acknowledgements

This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element

Cyclic Molecules' and a Grant-in-Aid for The 21st Century COE Program for Frontiers in Fundamental Chemistry from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and Notes

1. Curran, P. D. *Chem. Rev.* **1991**, *91*, 1237.
2. Mn (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Nishino, H.; Yoshida, T.; Kurosawa, K. *Bull. Chem. Soc. Jpn* **1991**, *64*, 1097. (c) Narasaka, K. *Pure. Appl. Chem.* **1997**, *69*, 601. (d) Iwasawa, N.; Funakoshi, M.; Hayakawa, S.; Ikeno, T.; Narasaka, K. *J. Org. Chem.* **1997**, *62*, 3762. (e) Hirao, V.; Fujii, T.; Ohshiro, Y. *Tetrahedron Lett.* **1994**, *35*, 8005. (f) Clark, A. J.; Dell, C. P.; McDonagh, M. J.; Geden, J.; Mawdsley, P. *Org. Lett.* **2003**, *5*, 2063. (g) Corey, E. J.; Ghosh, A. K. *Chem. Lett.* **1997**, 223. Cu (h) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1997**, *62*, 3762. Fe (i) Sartori, G.; Maggi, R.; Bigi, F.; Arienti, A.; Casnati, G.; Bocelli, G.; Mori, G. *Tetrahedron* **1992**, *48*, 9483. (j) Jahn, U.; Hartmann, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2227. Co (k) Iqbal, J.; Praveen, T. K.; Manogran, S. *Tetrahedron* **1989**, *30*, 4701. (l) Tarakeshwer, P.; Iqbal, J.; Manogran, S. *Tetrahedron* **1991**, *47*, 297. Ce (m) Arai, N.; Narasaka, K. *Chem. Lett.* **1995**, 987. (n) Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn* **1996**, *68*, 322. (o) Nair, V.; Matthew, J.; Radhakrishnan, K. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1487.
3. Morgat, J. L.; Pallaud, R.; Hebd, C. R. *Seances Acad. Sci.* **1965**, *260*, 5579.
4. For reviews see: (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333. (b) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1. (c) Wipf, P. *Synthesis* **1993**, 537. (d) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853.
5. Blackburn, T. F.; Labinger, J. A.; Schwarts, J. *Tetrahedron Lett.* **1975**, 3041.
6. Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.
7. Brokowsky, S. L.; Jordan, R. F.; Hinch, G. D. *Organometallics* **1991**, *10*, 1268.
8. Ishikawa, T.; Ogawa, A.; Hirao, T. J. *Organomet. Chem.* **1999**, *575*, 76.
9. Although addition of bases such as K_2CO_3, $NaHCO_3$, Et_3N, pyridine, and diisopropyl amine was examined to neutralize nitric acid that would form with the progress of the reaction, the yield of cyclization product **3a** was not increased.
10. Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734.
11. Muathen, H. A. *Indian J. Chem., B* **1992**, 522.
12. McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255.
13. Newcomb, M.; Choi, S. Y.; Horner, J. H. *J. Org. Chem.* **1999**, *64*, 1225.
14. Tokunaga, Y.; Sakakura, T.; Tanaka, M. *J. Mol. Cata.* **1989**, *56*, 305.
15. Avasthi, K.; Baba, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 945.
16. Rieke, R. D.; Hanson, M. V.; Brown, J. D.; Niu, Q. *J. Org. Chem.* **1996**, *61*, 2726.
17. Blay, G.; Fernandez, I.; Formentin, P.; Monje, B.; Pedro, J. R.; Ruiz, R. *Tetrahedron* **2001**, *576*, 1075.
18. Mejer, S.; Pacut, R. *Polish J. Chem.* **1978**, *52*, 529.
19. Foehlisch, B.; Schwaiger, G. *Liebigs Ann. Chem.* **1975**, *1*, 1.
20. Eisch, J. J.; Merkley, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1148.
21. Snider, B. B.; Kwon, T. *J. Org. Chem.* **1992**, *57*, 2399.
22. Hauser, C. F.; Brooks, T. W.; Miles, M. L.; Raymond, M. A.; Butler, G. B. *J. Org. Chem.* **1963**, *24*, 372.
23. Taber, D. F.; Rahimizadeh, M.; You, K. K. *J. Org. Chem.* **1995**, *60*, 529.
24. Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163.
25. Boger, D. L.; Mathvink, *J. Org. Chem.* **1992**, *57*, 1429.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1345–1352
Tetrahedron

Zr-promoted 'pair'-selective and regioselective synthesis of penta-substituted benzene derivatives

Yves R. Dumond and Ei-ichi Negishi*

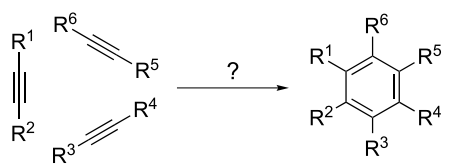
Herbert C. Brown Laboratories of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907-2084, USA

Received 22 August 2003; accepted 2 September 2003

Abstract—Tetra-substituted zirconacyclopentadiene derivatives, obtainable via in situ generation of zirconacyclopropenes and their cyclic carbozirconation with alkynes, can be treated with alkynyllithiums to induce 1,2-migration accompanied by aromatization and protonolysis, leading to the formation of penta-substituted benzene derivatives, in which all five substituted may be different.

1. Introduction

Synthesis of benzenes via cyclotrimerization of three molecules of alkynes is a thermodynamically favorable process reported as early as 1866.[1] Almost a century later, Reppe reported what appears to be the first transition metal-catalyzed cyclooligomerization of alkynes producing benzenes and cyclooctatetraenes.[2] Since then, most, if not all, of the d-block transition metals have been shown to catalyze cyclotrimerization of alkynes.[3] In cases where unsymmetrically substituted alkynes and/or two or three different alkynes are employed, synthetically unattractive mixtures of products are generally obtained. Thus, random cyclotrimerization of three different alkynes can, in principle, produce 10 different products, each of which can exist as two or more regioisomers. These reactions can still be very attractive for the synthesis of compounds of material chemical interest but not of fine chemicals. Development of 'pair'-selective[4] and regioselective synthesis of benzenes from three different unsymmetrically substituted alkenes, as represented by Scheme 1, has indeed been very difficult.



Scheme 1.

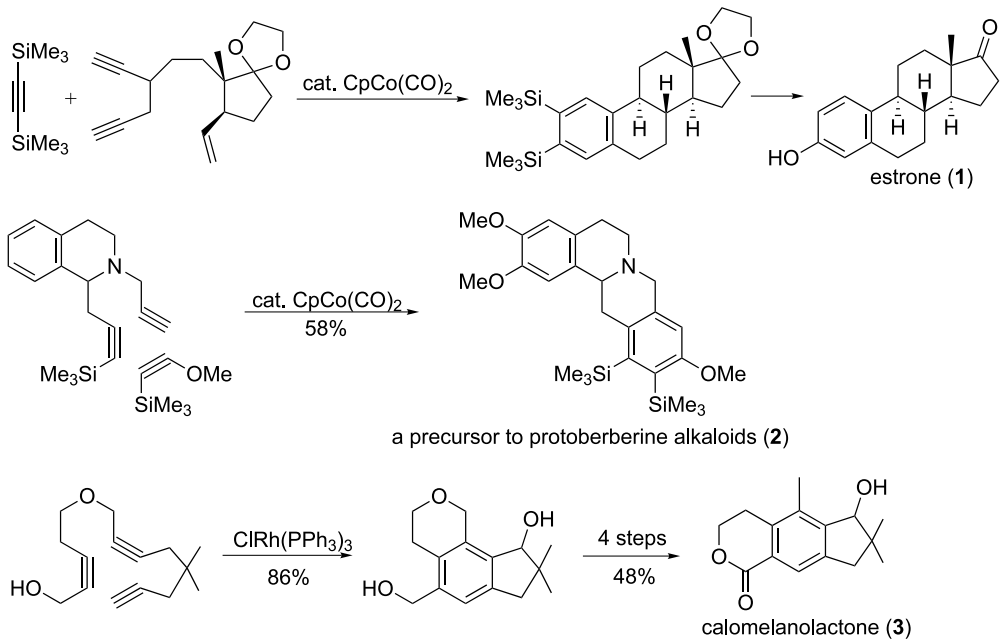
One of the notable earlier investigations of pair-selective and regioselective synthesis of benzene derivatives is the Co-catalyzed alkyne cyclotrimerization developed by Vollhardt,[5] which has been successfully applied to the synthesis of natural products including estrone (**1**) and protoberberine alkaloids (**2**). However, satisfactory results have been obtained mostly with tethered α,ω-diynes and a large excess of symmetrical $Me_3SiC{\equiv}CSiMe_3$ requiring subsequent differentiation of the two Me_3Si groups. The strategy of tethering alkynes has been further extended by the use of tethered triynes, as exemplified by a Rh-catalyzed synthesis of a tricyclic precursor to calomelanolactone (**3**).[6] Although only one alkyne molecule is incorporated into a benzene ring, the Dötz benzannulation[7] via Cr-carbene addition to alkynes is another noteworthy example of transition metal-mediated selective synthesis of arenes.

Although no systematic historical presentation is intended here, various pair-selective and regioselective procedures involving other late transition metals have also been developed. In particular, considerable efforts have been expended in the development of Pd-catalyzed procedures with the use of tethered triynes,[8a] haloenynes[8b] and halodienes[9] by Negishi, haloendiynes also by him[8a] and de Meijere,[10] and haloarenediynes by Grigg.[11] Recent investigations of Pd-catalyzed benzannulation of enynes and diynes by Yamamoto and Gevorgyan are also noteworthy.[12]

Until recently, the use of early transition metals in the alkyne-based selective arene synthesis had been less well-developed. However, conversion of zirconacyclopentadienes to benzene derivatives in a pair-selective manner was reported by Takahashi in 1995[13] and has since been further developed.[14,15] Even so, those procedures that permit regiocontrolled syntheses of benzene derivatives had not been developed at the time of our unexpected

Keywords: Zr-Promoted; 'Pair'-and regioselective synthesis; Penta-substituted benzenes; Zirconacyclopentadienes; Alkynylzirconate migratory insertion.
* Corresponding author. Tel.: +1-765-494-5301; fax: +1-765-494-0239; e-mail address: negishi@purdue.edu

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.102

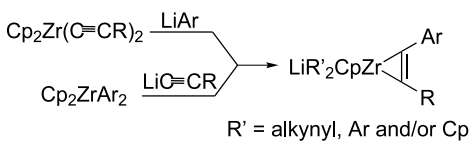


Scheme 2.

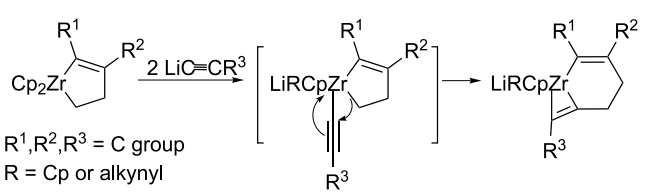
discovery of arene formation by the reaction of zirconacyclopentadienes with alkynyllithiums that has led to the results described below. We report herein a Zr-promoted synthesis of benzene derivatives containing up to five different non-hydrogen groups in the predetermined positions with or without the use of tethering. It may well represent the first demonstration of transition metal-mediated alkyne-based synthesis of such benzene derivatives without two or more of one kind of substituent (Scheme 2).

2. Results and discussion

We have previously discovered a novel migratory insertion reactions of zirconates containing alkynyl and/or aryl groups shown in Scheme 3.[16] During the course of our investigation of related reactions of alkenylzirconates, a similar migratory insertion reaction shown in Scheme 4 was also discovered.[17] In this reaction, an alkyl group rather than an alkenyl group preferentially migrated from Zr to an alkynyl C atom.



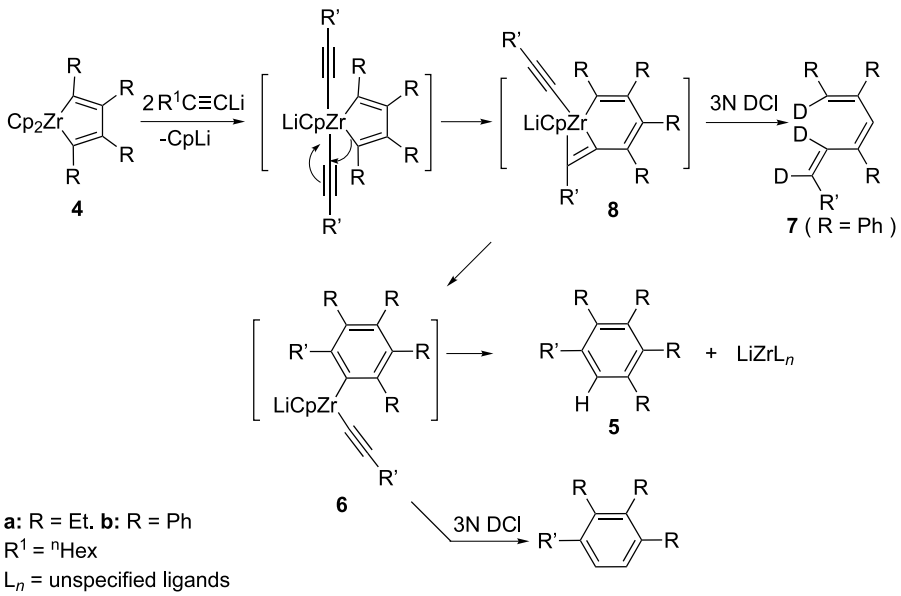
Scheme 3.



Scheme 4.

To further explore the scope of these migratory insertion reactions, a zirconacyclopentadiene (**4a**, generated in situ from $^{n}Bu_2ZrCp_2$ and 2 equiv. of 3-hexyne,[18] was treated with 2 equiv. of 1-octynyllithium in THF at 23 °Cs for 2 h. After quenching the reaction mixture with 3 N HCl, 1-(*n*-hexyl)-2,3,4,5-tetralthylbenzene (**5a**) was produced in 65% NMR yield rather than the expected acyclic, conjugated triene. As a penta-substituted arylzirconium derivative (**6a**) was suspected as the organometallic precursor to the product (**5a**), the reaction mixture was quenched with 3 N DCl. However, the extent of D incorporation at the C-6 position was only 5%. When only 1 equiv. of ^{n}HexC≡CLi was used, the yield of **5a** was 30%. Examination of the reaction mixture before quenching by NMR spectroscopy revealed the following. Firstly, **5a** had already been formed in about 30% yield before quenching, indicating that one H atom was internally supplied and transferred to the product. Secondly, about 50% of the starting **4a** remained unreacted. Addition of the 2 equiv. of ^{n}HexC≡CLi to this mixture consumed essentially all of **4a**, and the yield of **5a** increased to about 60%, thereby establishing the 2:1 stoichiometry between ^{n}HexC≡CLi and **4a**. Thirdly, examination of the 2:1 reaction mixture by ^{1}H NMR spectroscopy revealed the presence of nearly 1 equiv. of LiCp (δ 6.30 ppm).[19] This has provided a plausible explanation for the requirement of 2 equiv. of ^{n}HexC≡CLi.

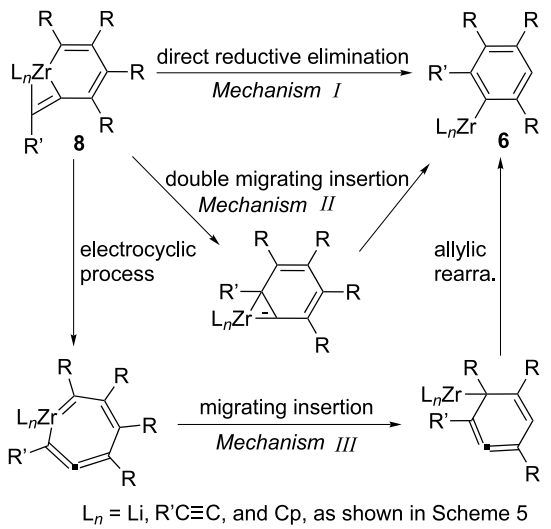
When PhC≡CPh was used in place of EtC≡CEt, the aromatization process must have been significantly slowed down. Upon quenching the reaction mixture with 3 N DCl, examination of the complex product mixture by ^{1}H NMR spectroscopy revealed the formation of the expected benzene derivative (**5a**) and its monodeuterated derivative with an aromatic ring-bound D as well as 1,5,6-trideuterio-1,2,3,4-tetraphenyl-1,3,5-dodecatriene (**7**). The above results have supported our interpretation that the reaction must have proceeded via a bicyclic zirconate (**8**) similar to that identified in the previously reported reaction of



Scheme 5.

zirconacyclopentenes.[17] All of the results presented above may be summarized as shown in Scheme 5.

At this point, the mechanism for the conversion of the bicyclic zirconate (**8**) into **6** still remains to be clarified, although the following three alternatives may be considered as being plausible (Scheme 6). Mechanism I involving direct formation of **6** from **8** via reductive elimination is simple and attractive, and a similar reductive elimination process for the formation of cyclobutenes has been proposed.[20] However, the direct C–C bond formation from diorganylzirconocenes via reductive elimination is essentially unknown, and a more indirect path of lower energy barriers involving active participation of π-bonds and other strained bonds are likely to be operative. With this rationalization in mind, two indirect paths, i.e., Mechanisms II and III, are also proposed for the conversion of **8** into **6**. In Mechanism II, a series of two 1,2-migratory insertion processes are thought to take place to effect an overall reductive elimination, while a six-electron electrocyclic

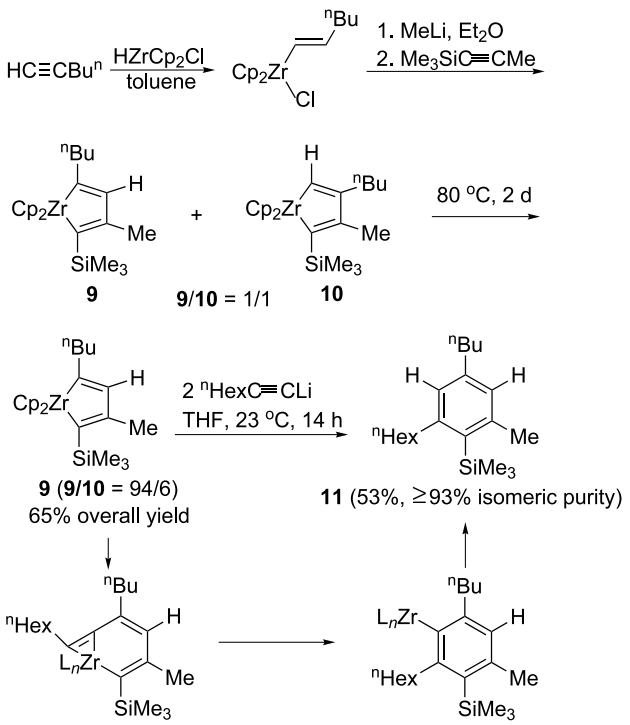


Scheme 6.

process to generate a seven-numbered zirconcycle may then be followed by a migratory insertion and aromatization via allylic rearrangement in Mechanism III. At this moment, it is not possible to choose one over the others, but it would be interesting and important to pursue the question of whether or not direct reductive elimination of diorganylzirconocenes without the involvement of π-bonds is feasible.

One important mechanistic issue that remained to be clarified was the source of H for converting **6** into **5**. As stated earlier, quenching the reaction mixture derived from **4a** and ^{n}HexC≡CLi gave the expected monodeuterated derivative of **5a** only in 5% yield. So, the putative intermediate **6a** either was not actually formed or was indeed formed but converted into **5a** by abstraction of H from one or more compounds present in the reaction mixture before quenching with HCl or DCl. Irrespective of what the correct mechanism might be, the source of the majority of H must be one or more of the compounds in the reaction mixture. Accordingly, some deuterated compounds were used in place of their non-deuterated counterparts. No D incorporation was observed when THF-d_8 was used in place of THF. On the other hand, incorporation of D to the extent of 14% was observed above and beyond 5% from DCl quenching, when cyclopentadiene-d_5 of 96% D was used for the preparation of Cl_2ZrCp_2-d_{10}. Although cleaner D incorporation was never achieved, it was clear that there were more than one source of H and that the organozirconium precursor to **5a**, be it **6a** or not, must have been competively quenched by internal H sources.

It then occurred to us that, if **6** or an alternate precursor to **5** could be either stabilized or competitively protonated by an added protonating agent to give **5** without interfering with the desired process, **5** would be produced in higher yields. Accordingly, various Lewis bases as election pair donors and proton acids as protonating agents were added to the reaction mixture. However, addition of Et_3N, 4-(*N*,*N*-dimethylamino)-pyridine (DMAP), dppp, and dppe had no detectable effect, while that of PMe_3 totally inhibited the reaction.



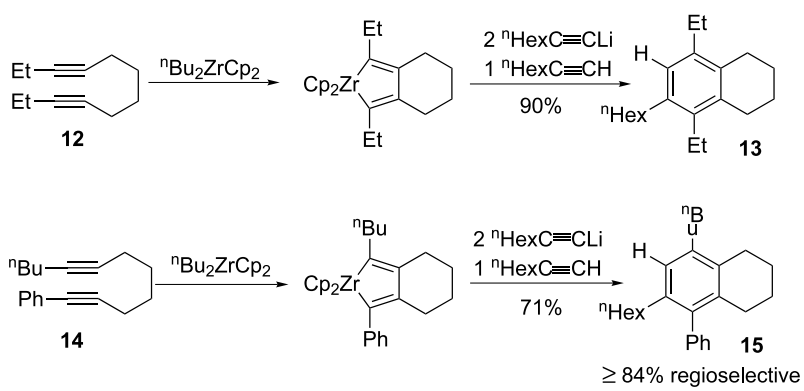
Scheme 7.

Fortunately, addition of proton acids was much more fruitful. The best proton source proved to be the same terminal alkyne as that used for the preparation of the alkynyllithium. Thus, addition of 1 equiv. of 1-octyne to the mixture of the reaction of **4a** with 2 equiv. of ^{n}HexC≡CLi at 23 °C for 3 h led to the formation of **5a** in 90% yield. When ^{n}HexC≡CD was used, D incorporation in the expected position took place to the extent of 86%. These results have not only provided a much superior procedure for the conversion of **4** into **5** but also strongly supported the intermediacy of **6** as the immediate precursor to **5**. Other proton acids were less effective. Methanol was evidently too acidic, as no desired product was formed. Presumably, ^{n}HexC≡CLi was prematurely quenched by MeOH. Indene and *t*-butanol did produce the desired product **5a**, but with no improvement.

As stated earlier, any methods for the synthesis of benzene derivatives that must necessarily incorporate two or more of one kind of substituent are of very limited utility for the synthesis of fine chemicals, even though they may be very useful in the synthesis of oligomers and polymers of material chemical interest. For the former objective, it was essential to be able to synthesize zirconacyclopentadienes containing four different non-hydrogen groups, one or more of which may be replaced with H and/or some other groups, such as $SiMe_3$, that can be differentiated later. Of various methods thus far developed for the synthesis of zirconacyclopentadienes,[21] two of them often referred to as the Erker–Buchwald protocol[22] and the Negishi–Takahashi protocol[23] have been most widely used. A more recently developed method of Rosenthal[24] and its modification by Tilley[25] as well as earlier contributions by Farona[26] and Nugent[27] are also noteworthy. For the purpose of developing pair-selective synthesis of benzene derivatives, modifications of the Negishi–Takahashi protocol through the use of Et_2ZrCp_2 have proved to be useful.[28] At the time of this investigation, however, there was only one reported procedure by Buchwald[29] for the pair-selective and regioselective synthesis of zirconacyclopentadienes with four different groups in the predetermined positions, as exemplified by the process shown in Scheme 7.

Accordingly, we generated **9** in about 65% yield as a 94:6 regiosomeric mixture of **9** with **10**. Under non-optimized conditions, the 94:6 mixture of **9** and **10** was treated with 2 equiv. of ^{n}HexC≡CLi. One regioisomer of >93% regiosomeric purity thus obtained was identified as **11** (Scheme 7). Thus, the conjugated diene moiety containing ^{n}Bu, H, Me, and Me_3Si groups retained its regiochemistry throughout the reaction. Noteworthy is the nearly 100% regioselectivity observed for the incorporation of 1-octyne in the conversion of **9** to **11**. The results indicate that the migratory insertion of 1-octyne took place almost exclusively on the side of ^{n}Bu or away from Me_3Si (Scheme 7). These results were obtained before the development of an improved procedure involving addition of a 1-alkyne, and its application to this case has not yet been performed.

As has been amply demonstrated (vide supra), the use of tethered diynes substantially reduced the level of difficulty in controlling regioselectivity. Some preliminary results along this line are summarized in Scheme 8. In cases where unsymmetrically substituted diynes were used, the reaction proceeded in approximately 85% regioselectivity. When Zr was flanked with ^{n}Bu and Ph, the ^{n}Bu side migrated preferentially. In addition to steric factors, electronic



Scheme 8.

factors, such as the well-documented benzylic, allylic, and propergylic interaction with Zr, appears to be significant. Although only one symmetric tether, i.e., tetramethylene, was used in this study, a variety of unsymmetric tethers including those containing heteroatoms can, in principle, be used in the reaction described herein, and efforts are being made along this line.

All of the reactions discussed above employed Cp_2ZrCl_2, but we also used $(Ind)_2ZrCl_2$, where Ind is indenyl, and Cp_2HfCl_2 for the synthesis of **5a** from 3-hexyne. Without the benefit of added 1-octyne, **5a** was obtained in 60 and 35% yields, respectively. Prior to the experiments described thus far in this paper, we briefly investigated the reaction of dialkynylzirconocoenes with alkenyllithiums. The reaction of $(PhC{\equiv}C)_2ZrCp_2$ with (*E*)-PhC≡CLi gave, upon treatment with I_2, a rather complex mixture containing (*E*)-PhCH=CHC≡CPh and (*E*,*E*)-PhCH=CHCH=CHPh among others. In no case was a clean reaction observed. More recently, Hirao[30] reported the reaction of alkenylzirconocene chlorides with 2 equiv. of alkynyllithiums to give (*E*,*Z*)-conjugated dienes in good yields, thereby further extending the scope of migratory insertion reactions of alkynylzirconates.

3. Conclusions

The migratory insertion reaction of alkynylzirconates, generated in situ by treating zirconacyclopentadienes with 2 equiv. of alkynyllithiums, unexpectedly produced the corresponding benzene derivatives rather than the expected conjugated trienes. Evidently, the expected migratory insertion reaction took place to give bicyclic zirconacycles (**8**), which then underwent reductive C–C bond formation by an as yet unclear mechanism to produce arylzirconates (**6**) Their protonolysis provided benzene derivatives (**5**). Protonolysis can be best achieved in situ by the addition of alkynes corresponding to the alkynyllithium used, since the precursors to **5**, i.e., **6**, are unstable, and they tend to undergo further complex reactions before full consumption of the starting compounds. This novel synthesis of benzene derivatives is, in principle, applicable to pair-selective and regioselective synthesis of benzene derivatives containing up to five different non-hydrogen groups. As such, it appears to represent the first demonstration of transition metal-mediated pair-selective and regioselective synthesis of benzene derivatives from three different and untethered alkynes.

4. Experimental

4.1. General

All manipulations were conducted under an atmosphere of dry argon, unless otherwise noted. Flash chromatographic separations were carried out on 230–400 mesh silica gel 60. Gas chromatography was performed on a HP 6890 Gas Chromatograph using HP-5 capillary column (30 m× 0.32 mm, 0.5 μm film) with mesitylene as an internal standard. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-300 spectrometer. NMR yields were determined using mesitylene as an internal standard. IR spectra were recorded on a Perkin–Elmer Spectrum 2000 FTIR spectrometer. THF was distilled from sodium benzophenone ketyl.

4.2. Preparation of symmetrically tetra-substituted zirconacyclopentadienes

Zirconacyclopentadienes containing four Et groups (**4a**) and four Ph groups (**4b**) were prepared by the reaction of $^nBu_2ZrCp_2$[18] with 2 equiv. of 3-hexyne and diphenylethyne, respectively, according to the previously reported procedure,[18] as described below for the synthesis of **5a**.

4.2.1. Preparation of 1,1-bis(η^5-cyclopentadienyl)-2,3,4,5-tetraethylzirconacyclopentadiene (4a). To a solution of Cl_2ZrCp_2 (584 mg. 2.0 mmol) in THF (6 mL) were added dropwise at −78 °C via syringe ^{n}BuLi (2.5 M in hexane, 1.6 mL, 4.0 mmol) and 3-hexyne (0.33 g, 0.45 mL, 4 mmol). After stirring for 10 min at −78 °C, the reaction mixture was warmed to 23 °C and stirred further for 2 h. After addition of mesitylene (240 mg, 0.28 mL, 2 mmol), clean quantitative formation of 1,1-bis(η^5-cyclopentadienyl)-2,3,4,5-tetraethylzirconacyclopentadiene (**4a**) was observed by GLC and ^1H NMR (C_6D_6, THF) Cp signal at 5.94 ppm.

4.2.2. Preparation of 1,1-bis(η^5-cyclopentadienyl)-2,3,4,5-tetraphenylzirconacyclopentadiene (4b). This compound was prepared as above in 94% NMR yield[31] by using 0.71 g (4 mmol) of diphenylethyne in place of 3-hexyne: ^1H NMR(C_6D_6, THF) Cp signal at 6.22 ppm.

4.3. Reaction of zirconacyclopentadienes (4) with alkynyllithiums

This reaction was carried out as detailed below for the conversion of **4a** into **5a**.

4.3.1. Conversion of 4a into 1-(*n*-hexyl)-2,3,4,5-tetraethylbenzene (5a). Representative procedure. 1-Octynyllithium, prepared in THF at −78 °C from 1-octyne (0.44 g, 0.59 mL, 4 mmol) and ^{n}BuLi (2.5 M in hexane, 1.6 mL, 4 mmol), was added dropwise at −78 °C via cannula to the reaction mixture containing **4a** described in Section 4.2.1, and the resultant mixture was stirred at −78 °C for 1 h, warmed to 23 °C, but the zirconacyclopentadiene **2a** was observed unchanged by ^1H NMR (C_6D_6/THF=6/1) (Cp signal at 5.94 ppm). The reaction mixture was stirred for an additional 1 h to generate the title compound (**5a**) observed in the reaction mixture by ^1H NMR (C_6D_6/THF=6/1) (aromatic proton signal at δ 6.91 ppm, 50% NMR yield). Formation of CpLi (δ 6.30 ppm) up to 100% was also observed. The reaction mixture was quenched with 3 N HCl, extracted with pentane, washed with $NaHCO_3$ dried over $MgSO_4$, and concentrated. GLC and ^1H NMR examination using mesitylene as an internal standard indicated about 65% yields of the title compound over several runs. After filtration on a silica gel pad and evaporation in vacuo, the title compound was isolated in 51% yield (279 mg): ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, *J*=5.7 Hz, 3H), 1.15–1.4 (m, 20H), 2.55–2.7 (m, 10H), 6.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.13, 15.59 (2C), 15.68, 15.92, 21.71, 21.79,

22.03, 22.69, 25.60, 29.83, 31.77, 31.82, 33.10, 127.23, 137.32, 137.40, 138.36, 139.27, 139.77; HRMS (FAB KIPEG) calcd for $C_{20}H_{34}$ (M+1) 275.2739, found 275.2737.

4.3.2. 1-(*n*-Hexyl)-2,3,4,5-tetraphenylbenzene (5b). To the reaction mixture containing **4b** prepared in Section 4.2.2 was added 1-octynyllithium, prepared in THF at −78 °C from 1-octyne (0.44 g, 0.59 mL, 4 mmol) and ^{n}BuLi (2.5 M in hexane, 1.6 mL, 4 mmol), at −78 °C via cannula, and the reaction mixture was stirred at −78 °C for 1 h and warmed to 23 °C. The reaction mixture was further stirred for 3 h, quenched with 3 N HCl, extracted with pentane, washed with $NaHCO_3$ dried over $MgSO_4$, and concentrated. GLC and GC/MS examination showed the formation of the title compound (**5b**) and 1,2,3,4-tetraphenyl-1,3,5-dodecatriene. In case of quenching with 3 N DCl, GLC and GC/MS examination showed the formation of the benzene derivative (**5b**) and **7** containing three deuterium atoms, supporting the proposed structure of **8**.

4.3.3. Preparation of 1,1-bis(η^5-cyclopentadienyl-2-trimethylsilyl-3-methyl-5-(*n*-butyl)zirconacyclopentadiene(9) and its conversion to 1-trimethylsilyl-2-(*n*-hexyl)-4-(*n*-butyl)-6-methylbenzene(11). To $HZrCp_2Cl$ (1.40 g, 5.43 mmol) in 16 mL of toluene was added at 23 °C 1-hexyne (0.45 g, 0.62 mL, 5.43 mmol). After 10 h at 23 °C, MeLi (1.4 M in Et_2O, 3.88 mL, 5.43 mmol) was added at 0 °C. One hour later, 1-trimethylsilyl-1-propyne (0.61 g, 0.80 mL, 5.43 mmol) was added. The reaction mixture was then heated at 80 °C for 2 days to afford regioisomerically 94% pure **9** in 42% yield, only other regiosomer produced being the 3-(*n*-butyl) isomer (6%).

To the mixture containing **9** obtained above was added at −78 °C 1-octynyllithium, prepared in THF from 1-octyne (1.32 g, 1.77 mL, 12.0 mmol) and ^{n}BuLi (2.5 M in hexane, 4.8 mL, 12.0 mmol). After stirring at 23 °C overnight, the standard workup as in Section 4.3.1 afforded **11** in 53% yield based on **9** as a >93% regioisomerically pure substance: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.49 (s, 9H), 1.0–1.1 (m, 6H), 1.4–2.35 (m, 15H), 2.61 (t, J=7.7 Hz, 2H), 2.78 (t, J=8.0 Hz, 2H), 6.92 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 3.82 (3C), 14.10 (2C), 22.62, 22.68, 24.84, 29.56, 31.92, 33.41, 33.82, 35.31, 36.98, 127.40, 128.52, 132.69, 143.30, 144.08, 149.60; HRMS calcd for $C_{20}H_{36}Si$ (M+) 304.2586, found 304.2588.

4.4. Investigation of the proton source

Following the same procedure as in Section 4.3.1 for the preparation of **5a**, the reaction mixture was quenched with 3 N DCl and <5% D incorporation was observed by LRMS. Following the same procedure as above for the preparation of **5a** but using THF-d_8, 0% D incorporation was obtained. By using Cp_2ZrCl_2-d_{10} (>96% D incorporation) for the synthesis of **5a**, 14% D incorporation was recorded by ^{13}C NMR and LRMS.

4.5. Effects of added bases

The reaction of **4a** with 2 equiv. of ^{n}HexC≡CLi was run in the presence of various tertiary amines and phosphines. Addition of 12 equiv. of Et_3N or DMAP, 6 Mequiv. of 2,2′-bipyridyl or dppp, or 1.6 Mequiv. of dppe did not detectably change either the rate of formation or the yield of **5a**, the latter of which ranged 50–70%. Addition of $(MeOCH_2)_2$ or TMEDA (6 equiv.) merely slowed down the reaction, and addition of either PMe_3 (12 equiv.) or 1,10-phenanthroline (6 Mequiv.) inhibited the desired benzene formation. In all cases, ^{1}H NMR examination of the reaction mixture in C_6D_6–THF (6:1) showed the displacement of up to 1 equiv. of CpLi (δ 6.30 pm).

4.6. Reactions of zirconacyclopentadienes with alkynyllithiums in the presence of the corresponding 1-alkynes. An improved synthesis of benzene derivatives

These reactions were run in the same manner as described in Section 4.3.1 except that 1-alkyne (1 equiv. relative to Zr) was added at the beginning of the reaction of zirconacyclopentadienes with 1-alkynyllithium (2 equiv.).

4.6.1. Improved synthesis of 1-(*n*-hexyl)-2,3,4,5-tetraethylbenzene (5a). Improved representative procedure. To the reaction mixture containing **4a** (Section 4.2.1), were added ^{n}HexC≡CLi, prepared from 1-octyne (0.44 g, 0.59 mL, 4.0 mmol) and ^{n}BuLi (2.5 M in hexane, 1.6 mL, 4.0 mmol), and 1-octyne (0.22 g, 2.0 mmol) at −78 °C. After stirring first at −78 °C for 1 h and then at −23 °C for several hours, **5a** was produced in 90% yield by NMR. Its spectral data are presented in Section 4.3.1.

4.6.2. 1-(*n*-Octyl)-6-deuterio-2,3,4,5-tetraethylbenzene. This reaction was carried out as described in Section 4.6.1 except that 1-decyne (0.55 g, 4.0 mmol) was used to prepare ^{n}OctC≡CLi and that 1-deuterio-1-decyne (95% D, 0.28 g, 2.0 mmol) was added as a D source The title compound was obtained in 90% yield with incorporation of D to the extent of 86%: ^{1}H NMR($CDCl_3$, Me_4Si) δ 0.90 (t, J=5.7 Hz, 3H), 1.15–1.4 (m, 24H), 2.55–2.7 (m, 10H), 6.87 (s, 14% of 1H); ^{13}C NMR ($CDCl_3$) δ 13.91, 15.47 (2C), 15.54, 15.79, 21.58, 21.66, 21.90, 22.58, 25.47, 28.89, 29.39, 31.53, 31.73, 32.95, 33.75, no peak at 127 because of D on the benzene ring, 137.07, 137.17, 138.04, 138.98, 139,50; LRMS calcd (M+) 303, found 303 (86%).

4.6.3. Preparation of 3,9-dodecadiyne (12) and its conversion to 5,8-diethyl-6-(*n*-hexyl)-1,2,3,4-tetrahydronaphthalene (13). 3,9-Dodecadiyne (**12**) was prepared in 70% yield by successively treating 1,7-octadiyne (5.3 g, 6.64 mL, 50 mmol) in THF (100 mL) with ^{n}BuLi (2.5 M in hexane, 42 mL, 105 mmol, −78 °C, 1 h) and iodoethane (17.9 g, 9.2 mL, 115 mmol) in DMPU (150 mL): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.11 (t, J=7.5 Hz, 6H), 1.57 (broad t, J=6.5 Hz, 4H), 2.1–2.2 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 12.35 (2C), 14.28 (2C), 18.26 (2C), 28.19 (2C), 79.02 (2C), 81.75 (2C).

3,9-Dodecadiyne (**12**) (0.324 g, 2.0 mmol) prepared above was treated with ^{n}Bu$_2$ZrCp$_2$ generated in THF (6 mL) from Cp_2ZrCl_2 (0.584 g, 2.0 mmol) and ^{n}BuLi (2.5 M in hexane, 1.6 mL, 4.0 mmol) as described in Section 4.2.1. After confirming the formation of a zirconabicycle in nearly quantitative yield by ^{1}H NMR spectroscopy, ^{n}HexC≡CLi generated in situ from 1-octyne (0.44 g, 4.0 mmol) and an

additional 2.0 mmol (0.22 g) of 1-octyne were added at −78 °C, and the reaction mixture was stirred overnight at 23 °C to produce **13** in 90% NMR yield: ^{1}H NMR ($CDCl_3$, Me_4Si) 0.89 (t, J=6.8 Hz, 3H), 1.11 (t, J=6.7 Hz, 3H), 1.19 (t, J=7.6 Hz, 3H), 1.2–1.55 (m, 12H), 1.8–2.8 (m, 10H), 6.85 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.99, 14.23, 14.36, 21.21, 22.91, 23.28, 25.47, 26.46, 26.94, 29.72, 31.57, 31.80, 32.00, 33.03, 126.41, 132.54, 134.87, 137.41, 137.61, 139.29; HRMS calcd for $C_{20}H_{32}$ (M+) 272.2504, found 272.2501.

4.6.4. Preparation of 1-phenyl-1,7-dodecadiyne (14) and its conversion to 5-phenyl-6-(*n*-hexyl)-8-(*n*-butyl)-1,2,3,4-tetrahydronaphthalene (15). 1,7-Octadiyne (10.6 g, 13.3 mL, 100 mmol) was mono-butylated by using ^{n}BuLi (100 mmol), ^{n}BuI (22.1 g, 13.7 mL, 120 mmol), and DMPU (90 mL). After the usual workup, distillation afforded 1,7-dodecadiyne in about 35% yield. Successive treatment of 1,7-dodecadiyne (0.45 g, 2.8 mmol) in THF with ^{n}BuLi (3.36 mmol −78 °C), dry $ZnBr_2$ (4.2 mmol, −78 °C for 1 h and then 23 °C for 0.5 h), iodobenzene (0.86 g, 0.47 mL, 4.2 mmol), and $Pd(PPh_3)_4$ (65 mg, 0.056 mmol, 14 h, 23 °C).[32] The reaction mixture was successively treated with 3 N HCl, pentane, aqueous $NaHCO_3$, and $MgSO_4$ to give **14** in 91% yield: ^{1}H NMR ($CDCl_3Me_4Si$) δ 0.97 (t, J=7 Hz, 3H), 1.45–1.55 (m, 4H), 1.7–1.8 (m, 4H), 2.2–2.3 (m, 4H), 2.49 (t, J=6.8 Hz, 2H), 7.3–7.35 (m, 3H), 7.45–7.5 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.59, 18.30, 18.39, 18.92, 21.90, 27.79, 28.22, 31.18, 79.54, 80.52, 80.74, 89.89, 123.94, 127.43, 128.11 (2C), 131.47 (2C).

1-Phenyl-1,7-dodecadiyne (**14**) (0.476 g, 2.0 mmol) was converted to **15** in 71% NMR yield by its reaction with ^{n}HexC≡CLi (4.0 mmol) and 1-octyne (2.0 mmol) as described in Section 4.6.3. The product (**15**) yielded the following spectral data: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.88 (t, J=6.7 Hz, 6H), 125–1.6 (m, 16H), 1.8–2.75 (m, 8H), 6.93 (s, 1H), 7.1–7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.92 (2C), 22.28, 23.12, 26.37, 26.84, 28.77, 28.87, 29.07, 29.33, 31.71, 31.84, 32.41, 32.61, 126.19, 126.66, 127.99 (2C), 129.55 (2C), 132.06, 134.92, 137.53, 139.00, 139.70, 141.06; HRMS calcd for $C_{26}H_{36}$ (M+) 348.2817, found 348.2816.

4.7. Use of Ind_2ZrCl_2 and Cp_2HfCl_2 in the synthesis of 5a from 3-hexyne and 1-octyne

Following the non-optimized procedure described in Section 4.3.1, the use of Ind_2ZrCl_2 and Cp_2HfCl_2 led to the formation of **5a** in 60 and 35% yields, respectively.

4.8. Reaction of bis(phenylethynyl)zirconocene with (*E*)-2-phenylethenyllithium

Bis(phenylethynyl)-zirconocene was generated by treating Cp_2ZrCl_2 (2.0 mmol) with PhC≡CLi prepared from 4 mmol each of PhC≡CH and ^{n}BuLi in THF (75% NMR yield, Cp signal at δ 6.15 ppm). Its treatment with *(E)*-2-phenylethenyllithium (4 mmol) at 23 °C for 1 d followed by addition of I_2 (2.5 equiv.) let to a complex mixture containing 1,4-diphenyl-1-buten-3-yne and 1,4-diphenyl-1,3-butadiene. This reaction was not further investigated.

Acknowledgements

The authors thank the National Science Foundation (CHE-0309613) and Purdue University for support of this research. Y. R. D. was a Purdue Research Foundation Graduate Fellow (1997–1998). Generous assistance in the procurement of Zr compounds by Boulder Scientific Co. is gratefully acknowledged. We also thank Professor T. Takahashi for sharing unpublished results and Professor V. Gegorgyan for providing us with useful information. Technical assistance provided by Ms Q. Hu is gratefully acknowledged.

References and notes

1. Berthelot, M. C. R. *Acad. Sci.* **1866**, 905.
2. Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Liebigs Ann. Chem.* **1948**, *560*, 1.
3. See, for example Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. Principles and Applications of Organotransition Metal Chemistry; 2nd ed. University Science Books: Mill Valley, CA, 1987; p 989.
4. In place of 'pair'-selective, copuloselective (copulo in Latin= to pair) has been proposed. See Anastasia, A.; Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 311.
5. Vollhardt, K. P. C. *Angew Chem. Int. Ed.* **1984**, *23*, 539, and references therein.
6. Neeson, S. J.; Stevenson, P. J. *Tetrahedron* **1989**, *45*, 6239.
7. For a review, see (a) Wulff, W. D. *Comprehensive Organometallic Chemistry II*, Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, p 469. (b) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187.
8. (a) Negishi, E.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253. (b) Negishi, E.; Ay, M.; Sugihara, T. *Tetrahedron* **1993**, *49*, 5471.
9. Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454.
10. Meyer, F. E.; de Meijere, A. *Synlett* **1999**, 777.
11. Grigg, R.; Rasul, R.; Savic, V. *Tetrahedron Lett.* **1997**, *38*, 1825.
12. (a) Saito, S.; Yamamoto, Y. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; pp 1635–1646 Chapter IV.10.2. (b) Gevorgyan, V.; Yamamato, Y. *J. Organomet. Chem.* **1999**, *576*, 232.
13. Takahashi, T.; Kotora, M.; Xi, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 361.
14. Takahashi, T.; Hara, R.; Nishihara, Y.; Kotora, M. *J. Am. Chem. Soc.* **1996**, *118*, 5154.
15. Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672.
16. Takagi, K.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 1440.
17. Dumond, Y.; Negishi, E. *J. Am. Chem. Soc.* **1999**, *121*, 11223.
18. (a) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829. (b) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.
19. (a) Kondakov, D.; Negishi, E. *Chem. Commun.* **1996**, 963.

(b) See also Razuvaev, G.; Vyshinskaya, L.; Vasil'eva, G.; Malysheva, A. *Dokl. Akad. Nauk. SSSR* **1978**, *243*, 1212.
20. Liu, Y.; Sun, W.; Nakajima, K.; Takahashi, T. *Chem. Commun.* **1998**, 1133.
21. For a review, see Negishi, E.; Takahashi, T. *Houben-Weyl Science of Synthesis*, Imamoto, T., Ed.; Thieme: Stuttgart, 2003; Vol. 2, pp 739–774 Sect. 2.11.5.
22. For a review, see Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047.
23. For a review, see Takahashi, T.; Li, Y. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 50–85 Chapter 2.
24. For a review, see Rosenthal, V.; Burlakov, V. V. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 355–389 Chapter 10.
25. Nitschke, J. R.; Zürcher, S.; Tilley, D. T. *J. Am. Chem. Soc.* **2000**, *122*, 10345.
26. Thanedar, S.; Farona, M. F. *J. Organomet. Chem.* **1982**, *235*, 65.
27. Nugent, W. A.; Thorn, D. L.; Harlow, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 2788.
28. (a) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 687. (b) Xi, Z.; Hara, R.; Takahashi, T. *J. Org. Chem.* **1995**, *60*, 4444.
29. (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544. (b) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870.
30. Ishikawa, T.; Ogawa, A.; Hirao, T. *J. Organomet. Chem.* **1999**, *575*, 76.
31. Ref. 21, p 753.
32. King, A. O.; Negishi, E.; Villani, Jr. F. J.; Silveira, Jr. A. *J. Org. Chem.* **1978**, *43*, 358.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1353–1358
Tetrahedron

Synthesis of an enantiomerically pure 2,2,4-trisubstituted cyclobutanone building block by zirconocene-promoted deoxygenative ring contraction of structurally modified 4-vinylfuranosides

Leo A. Paquette* and Ho-Jung Kang†

Evans Chemical Laboratories, The Ohio State University, Columbus, OH 43210, USA

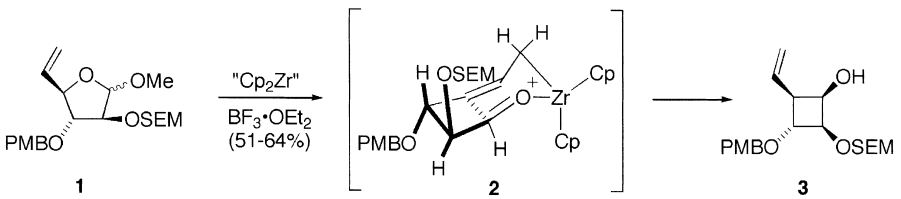
Received 24 January 2003; revised 15 July 2003; accepted 15 July 2003

Abstract—A route to an enantiopure trisubstituted cyclobutanone has been devised. The pursuit of this building block begins with D-glucose and features a zirconocene-promoted ring contraction.

The Taguchi/Hanzawa team[1] and our own group[2] have previously reported several studies dealing with diastereoselectivity control in the zirconocene-mediated ring contraction of 4-vinylfuranosides to enantiopure cyclobutanes. Multiply functionalized four-membered ring products are formed with the absolute configuration at each constituent carbon being fully definable under normal circumstances.[2] The potential importance of this process to natural products synthesis[2] and to the elaboration of useful organic scaffolds[3] has been recognized. The initial work with readily accessible modified carbohydrates has shown that transition state models typified by **2** can play a useful role in the concise rationalization of the stereochemical outcome of the deoxygenative transformations.[2] The predictability is thought to be associated with the interplay of nonbonded steric interactions during intramolecular cyclization within the allylzirconocene–aldehyde complex (Scheme 1).

In the course of another investigation, the need arose to prepare the 2,2,4-trisubstituted cyclobutanone of generic formula **4** having the (2*S*,4*R*) configuration as depicted. This scenario led us to consider the possibility that one or both of the diastereomers **5** and **6** might qualify as a suitable precursor. At least two major concerns surfaced immediately. Despite the fact that no prior attention had yet been accorded to 4,4-disubstituted systems of this type, we speculated that reaction with the zirconocene reagent[4] would materialize, particularly at more elevated temperatures, and lead to an intermediate such as **2**. Less certain was the issue of whether the additional substituent on the nucleophilic carbon would serve to retard formation of the C–C cyclobutane bond and to what degree. Also, in light of available precedent, the lack of substitution at C-3 was likely to present itself as a deterrent to high-level diastereoselectivity (Scheme 2).[2]

Our path to the targeted cyclobutanone commenced with the known D-glucose-derived tosylate **7**.[5,6] In order to facilitate elimination of the sulfonate ester, **7** was stirred in acidic methanol at rt to produce regioselectively the side chain diol,[7] oxidative cleavage of which with sodium periodate proceeded well, giving rise to the aldehyde. When the direct

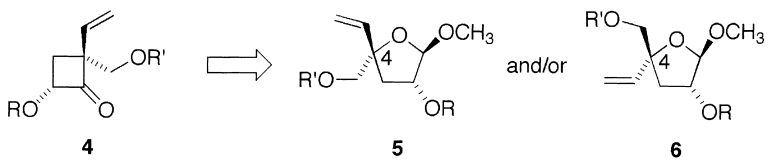


1 2 3

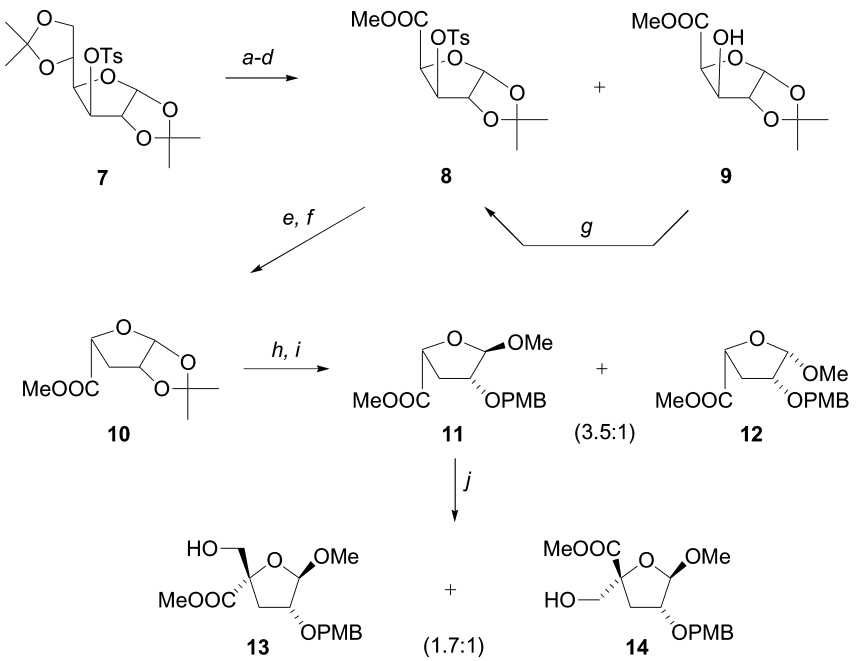
Scheme 1.

Keywords: Zirconocene; Cyclobutanes; Diastereoselectivity; D-Glucose; Ring contraction.
* Corresponding author. Tel.: +1-614-292-2520; fax: +1-614-292-1685; e-mail address: paquette.1@osu.edu
† Permanent address: Department of Chemistry, Kyung Hee University, 1 Hoe Ki-Dong, Dong Dae Moon-Gu, Seoul 130-701, Korea.

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.07.012



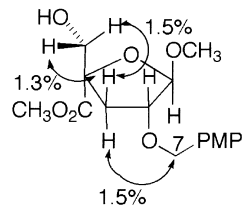
Scheme 2.



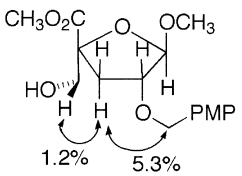
Scheme 3. (a) H^+, MeOH, rt, (b) $NaIO_4$, H_2O, THF, (c) $NaClO_2$, H_2O, CH_3CN, rt, (d) CH_2N_2, ether, (e) DBU, CH_2Cl_2, (f) H_2, 10% Pd/C, EtOH (90% for 6 steps), (g) TsCl, DMAP, Et_3N, CH_2Cl_2, rt, (h) H^+, MeOH, reflux, (i) PMB imidate, CSA, CH_2Cl_2, rt (88% for 2 steps), (j) LDA, THF, −78°C; CH_2O (93%).

oxidation of this intermediate to ester **8** with bromine in methanol[8] met with failure, recourse was made to sequential treatment with sodium chlorite[9] and diazomethane. Although these conditions were met with partial detosylation, it proved a simple matter to return from **9** to **8** (Scheme 3). At this stage, the intended E_2 elimination occurred smoothly in the presence of DBU, making possible a stereocontrolled catalytic hydrogenation to generate **10**. The six-step conversion of **7** is not demanding of chromatographic purification in its intermediary stages and delivers the saturated ester **10** in 92% overall yield.

The latter was subjected to acidic methanol at the reflux temperature to effect removal of the remaining acetonide unit and allow for protection of the C-2 hydroxyl as its *p*-methoxybenzyl ether via the trichloroacetimidate option.[10] As expected on steric grounds, methyl glycoside **11** predominated over **12** by a factor of 3.5:1 (88% yield). The major anomer was readily separated by means of silica gel chromatography and its enolate anion was condensed with formaldehyde in ether.[11] The implementation of this reaction resulted in the formation of **13** and **14**. The diastereomeric ratio of 1.7:1 indicated that π-facial discrimination for electrophilic capture by the conjugate base of **11** was not pronounced. The distinctive structural features of the aldol isomers were apparent following 1D NMR analysis and NOE studies as summarized in **A** and **B**.

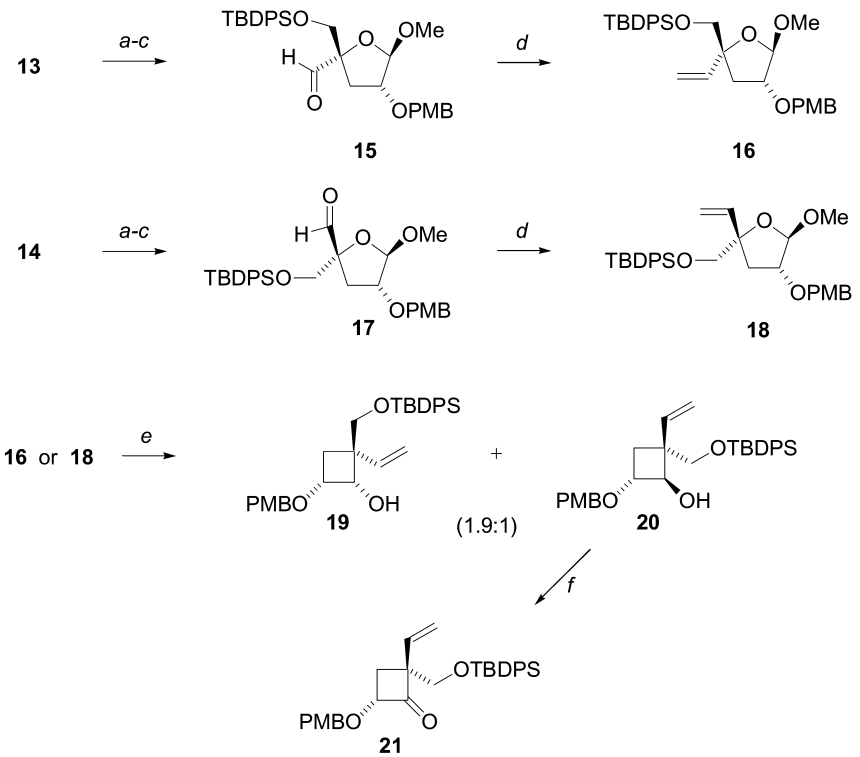


A



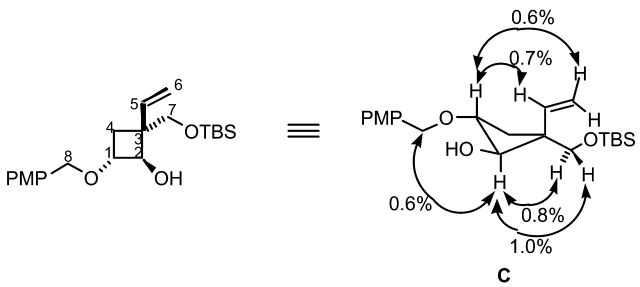
B

With these successes as a platform, the focus was next placed on chemical modification of the carbomethoxy substituent in both series. For this purpose, the primary carbinol was masked with *tert*-butyldiphenylsilyl chloride in advance of diisobutylaluminum hydride reduction to the aldehyde level and Wittig olefination (Scheme 4). It will be appreciated that the conversion of **13** to **16** and of **14** to **18** by this means is not accompanied by any concern regarding epimerization. The reactivity of both 4-vinylfuranosides toward the zirconocene reagent was independently probed and found to deliver the cyclobutanols **19** and **20** in an identical 1.9:1 ratio. The co-addition of boron trifluoride etherate as promoter gave rise to lower yields, messier reaction mixtures, and inverted product ratios. Magnesium bromide was also tested, with similar consequences. We

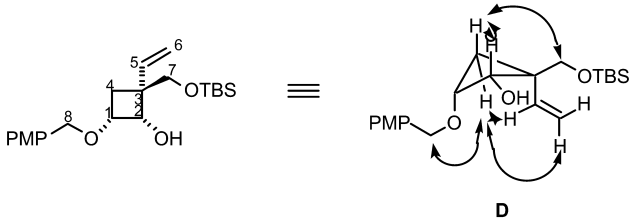


Scheme 4. (a) TBDPSCl, imid, DMF, rt (94%), (b) Dibal-H, CH_2Cl_2, −20°C, (c) Swern, (d) $Ph_3P{=}CH_2$, THF, −30°C→rt (68% for 4 steps), (e) 'Cp_2Zr', THF, 65°C (56–70%), (f) IBX, DMSO, rt (92%).[12]

offer no explanation of these effects at this time. The relative and absolute configurations of **19** and **20** were deduced by detailed NOE measurements. In particular, the observed proximity of H-2 to H-8 in **20** requires that the C-2 hydroxyl be β-oriented as shown in **C**. The α-projection of C-7 follows from the integral enhancement noted between both of its attached methylene protons and H-2. Further confirmation was derived from the interaction of H-1 with H-5 and H-6.



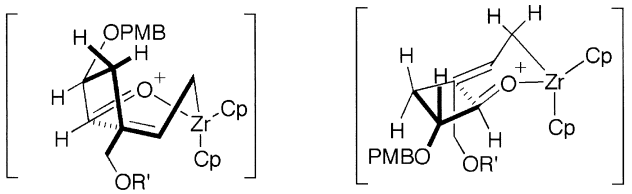
C



D

In the case of **19**, the effect observed between H-8 and H-4α in a NOESY experiment was used to differentiate the methylene pair. Following that assignment, it was possible to define the C-2 hydroxyl as α on the strength of the H-2↔H-4β interaction. The β-orientation of C-7 was similarly deciphered. The readily recognized proximity of H-4α to H-5 and H-6 provided additional compelling confirmatory evidence.

These results bring into focus several mechanistic facets of this fascinating ring contraction. The stereochemical predisposition of the OPMB substituent at C-2 in either reactant has a low-level impact on the distribution of cyclobutanols **19** and **20** as foreshadowed by less substituted congeners. The possibility that the product ratio may depend on the steric bulk of the oxygen protecting group at C-2 was not examined. Significantly, however, the π-facial selectivity of attack by the zirconocene reagent on the vinyl double bond has no major product-determining consequences. This phenomenon may be the result of a substantive kinetic bias for the subsequent ring opening that leads to the *E*-configured allylzirconocene intermediate. The possible operation of a $Z \rightleftarrows E$ isomerization cannot be ruled out, but the *cis* arrangement of the vinyl and hydroxyl groups in **19** and **20** is almost certain to stem from transition states **22** and **23**. Finally, the combined yield of **19** and **20** (56–70%) under purely thermal conditions indicates that the added $CH_2OTBDPS$ substituent is not a deterrent to four-membered ring closure, although kinetic retardation was evident relative to the ring-contracting reactions performed with similar but less crowded examples.



19 20

1. Experimental[13]

1.1. General

1.1.1. Conversion of tosylate 7 to ester 10. A solution of **7**[5,6] (67.0 g, 162 mmol) in methanol (1650 mL) was treated with sulfuric acid (84 mL of 2.5 M), stirred at rt for 16 h, neutralized with concentrated sodium hydroxide, and freed of solvent. The residue was slurried with CH_2Cl_2 (1 L) and the organic phase was dried and evaporated to provide the diol. The latter was directly dissolved in THF (500 mL), cooled to 0 °C, and treated with a solution of sodium periodate (52 g, 243 mmol) in water (700 mL). The reaction mixture was stirred overnight, the THF was removed under reduced pressure, and ethyl acetate (500 mL) was introduced. The separated organic phase was washed with water (200 mL) and brine (200 mL), the aqueous layers were combined and extracted with ethyl acetate (3×200 mL), and the unified organic phases were dried and evaporated to furnish the aldehyde that was directly submitted to oxidation.

The above material dissolved in acetonitrile (440 mL) was treated sequentially with a solution of sodium dihydrogen phosphate (33.7 g, 244 mmol) in water (120 mL) and 30% hydrogen peroxide (25 mL). This mixture was cooled to 0 °C prior to the introduction of sodium chlorite (22.1 g, 244 mmol) dissolved in water (120 mL). The reaction mixture was allowed to warm to rt, stirred overnight, and freed of acetonitrile under reduced pressure. The resulting aqueous solution was extracted with ethyl acetate (2×200 mL). The aqueous layer was acidified with citric acid to pH 1–2 and extracted with ethyl acetate (2×200 mL). The combined organic phases were washed with brine (300 mL), dried, concentrated to a volume of 300 mL, and treated with an excess of diazomethane until N_2 effervescence stopped. The solvent was evaporated and the residual ester was dissolved in CH_2Cl_2 (200 mL). To this solution was added 4-(dimethylamino)pyridine (2.0 g, 16 mmol), triethylamine (3.5 mL, 25 mmol), and tosyl chloride (5.0 g, 26 mmol), and the resulting mixture was stirred overnight at rt prior to dilution with ether (500 mL), filtration, and sequential washing with saturated calcium sulfate, sodium bicarbonate, and sodium chloride solutions (200 mL of each). The organic layer was dried and evaporated to give ester **8**. The latter was directly dissolved in CH_2Cl_2 (400 mL), treated with DBU (25.2 g, 166 mmol), stirred at rt for 5 h, concentrated to a volume of 100 mL, and diluted with ethyl acetate (200 mL) prior to filtration through a pad of silica gel. Solvent evaporation furnished the unsaturated ester, which was taken up in ethanol (100 mL), and hydrogenated over 5% Pd/C (1.3 g) under an atmosphere of H_2 (40 psi). After 1 h, the reaction mixture was filtered through Celite, concentrated, and subjected to chromatography on silica gel. Elution with 3:2 hexanes/ethyl acetate afforded pure **10** as a colorless oil (29.4 g, 90% over six steps); IR (neat, cm^{-1}) 1757, 1734; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, J=3.4 Hz, 1H), 4.63 (t, J=4.2 Hz, 1H), 4.55 (dd, J=0.9, 9.2 Hz, 1H), 3.69 (s, 3H), 2.59 (dd, J=0.5, 14.1 Hz, 1H), 2.23 (ddd, J=4.8, 9.2, 14.1 Hz, 1H), 1.38 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 112.4, 106.8, 79.3, 76.9, 51.8, 34.8, 25.5 (2C); ES HRMS m/z $(M+Na)^+$ calcd 225.0733, obsd 225.0740; $[\alpha]_D^{20}=-63.3$ (c 1.03, $CHCl_3$).

Anal. calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.28; H, 7.03.

1.1.2. Transformation of 10 into esters 11 and 12. A solution of **10** (5.00 g, 24.7 mmol) in methanol (100 mL) was treated with concentrated HCl (1.3 mL), refluxed for 1 h, neutralized with solid $NaHCO_3$ (5 g), and freed of methanol under reduced pressure. The residue was taken up in CH_2Cl_2 (300 mL), dried, and evaporated to leave a mixture of hydroxy methyl glycosides. This material was dissolved in CH_2Cl_2 (100 mL), treated with *p*-methoxybenzyl trichloroacetimidate (9.21 g, 32.6 mmol), and cooled to 0 °C. Camphorsulfonic acid (380 mg, 1.63 mmol) was introduced and the reaction mixture was stirred for 24 h at 0 °C and 2 days at rt, quenched with saturated $NaHCO_3$ solution, diluted with CH_2Cl_2 (300 mL), and worked up in the predescribed manner. Medium-pressure liquid chromatography on silica gel (elution with 7:3 hexanes/ethyl acetate) afforded **11** (3.88 g) and **12** (1.10 g) in 88% overall yield for 2 steps. The minor product remained contaminated with minor impurities and was not fully characterized.

For **11**: colorless oil; IR (neat, cm^{-1}) 1759, 1731, 1613; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 2H), 6.86 (m, 2H), 5.10 (s, 1H), 4.63 (dd, J=4.5, 9.0 Hz, 1H), 4.43 (s, 2H), 3.93 (dd, J=2.1, 5.5 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.37 (s, 3H), 2.46 (ddd, J=5.5, 9.0, 13.5 Hz, 1H), 2.27 (ddd, J=2.1, 4.5, 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 159.3, 129.7, 129.2, 113.8, 108.0, 81.1, 75.9, 70.8, 55.2, 55.0, 52.2, 34.0; ES HRMS m/z $(M+Na)^+$ calcd 319.1152, obsd 319.1161; $[\alpha]_D^{20}=-27.4$ (c 1.96, $CHCl_3$).

Anal. calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 61.00; H, 6.77.

1.1.3. Hydroxymethylation of 11. *n*-Butyllithium (36.4 mL of 1.5 M in hexanes, 54.6 mmol) was added to a cold (−30 °C) solution of diisopropylamine (10.2 mL, 72.8 mmol) in dry THF (80 mL). The reaction mixture was stirred for 20 min at this temperature, then cooled to −78 °C in advance of the introduction of a solution of **11** (10.8 g, 36.4 mmol) in THF (30 mL). After 1 h of stirring, a solution of excess formaldehyde dissolved in THF was added until the color of the reaction mixture turned light brown. Subsequent

warming to −10 °C was followed by a quench with saturated NH_4Cl solution (50 mL) and subsequent dilution with ethyl acetate (500 mL) and water (200 mL). The resulting organic phase was dried and concentrated to leave a residue that was chromatograhed on silica gel. Elution with 2:3 hexanes/ethyl acetate gave **13** (7.03 g, 59%) and **14** (4.08 g, 34%).

For **13**: colorless oil; IR (neat, cm^{-1}) 3480, 1733, 1613; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 2H), 6.82 (m, 2H), 5.05 (s, 1H), 4.38 (ABq, J=11.4 Hz, $\Delta\nu$=14.2 Hz, 2H), 3.91 (d, J=4.3 Hz, 1H), 3.80 (d, J=11.4 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.61 (d, J=11.4 Hz, 1H), 3.36 (s, 3H), 2.52 (br s, 1H), 2.43 (d, J=13.8 Hz, 1H), 2.21 (dd, J=4.9, 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 159.1, 129.4, 129.0, 113.6, 108.4, 88.3, 81.4, 70.4, 67.0, 55.2, 55.0, 52.4, 34.8; ES HRMS m/z $(M+Na)^+$ calcd 349.1258, obsd, 349.1249; $[\alpha]_D^{20}$=−39.1 (c 1.71, $CHCl_3$).

For **14**: colorless oil; IR (neat, cm^{-1}) 3490, 1737, 1613; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 2H), 6.86 (m, 2H), 5.01 (s, 1H), 4.44 (ABq, J=11.3 Hz, $\Delta\nu$=15.5 Hz, 2H), 3.96 (d, J=5.0 Hz, 1H), 3.80 (ABq, J=11.3 Hz, $\Delta\nu$=19.9 Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.39 (s, 3H), 2.63 (br s, 1H), 2.50 (dd, J=5.6, 14.3 Hz, 1H), 2.18 (d, J=14.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 159.4, 129.3, 129.2, 113.9, 107.9, 87.3, 81.7, 70.9, 67.0, 55.2, 54.8, 52.3, 35.1; ES HRMS m/z $(M+Na)^+$ calcd 349.1258, obsd 349.1235.

1.1.4. Conversion of 13 to 16. To a solution of **13** (810 mg, 2.48 mmol) and imidazole (835 mg, 12.2 mmol) in DMF (10 mL) was added *tert*-butyldiphenylsilyl chloride (823 mg, 3.0 mmol). The reaction mixture was stirred at rt for 3 h before being quenched with water (30 mL) and diluted with ethyl acetate (200 mL). The separated organic layer was washed with brine, dried, and evaporated to leave a residue, chromatography of which on silica gel (elution with 7:1 hexanes/ethyl acetate) provided pure silyl ether (1.30 g, 94%) as a colorless oil; IR (neat, cm^{-1}) 1730, 1514, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.65 (m, 4H), 7.41 (m, 6H), 7.22 (m, 2H), 6.86 (m, 2H), 5.15 (s, 1H), 4.43 (s, 2H), 3.98 (d, J=10.1 Hz, 1H), 3.90 (d, J=4.1 Hz, 1H), 3.80 (s, 3H), 3.74 (d, J=10.1 Hz, 1H), 3.73 (s, 3H), 3.33 (s, 3H), 2.55 (d, J=13.7 Hz, 1H), 2.06 (dd, J=4.7, 13.7 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 159.2, 135.6 (2C), 133.1, 133.0, 129.8, 129.7, 129.1, 127.7, 127.6, 113.7, 108.0, 88.6, 81.1, 70.3, 69.5, 55.2, 54.8, 52.3, 35.6, 26.6, 19.2; ES HRMS m/z $(M+Na)^+$ calcd 587.2436, obsd 587.2410; $[\alpha]_D^{20}$=−13.8 (c 2.68, $CHCl_3$).

A cold (−78 °C) solution of the above ester (1.21 g, 2.14 mmol) in CH_2Cl_2 (15 mL) was treated with diisobutylaluminum hydride (6.3 mL of 1.0 M in hexanes, 6.3 mmol). The reaction mixture was warmed to −20 °C, stirred for 1 h, and quenched with sodium potassium tartrate solution (20%, 20 mL). Stirring was maintained until a clear phase separation had been achieved. The aqueous phase was extracted with CH_2Cl_2 (2×100 mL) and the combined organic phases were washed with brine (100 mL) prior to drying and evaporation. The resulting alcohol was used directly.

To CH_2Cl_2 (20 mL) containing 1.0 mL of DMSO was added oxalyl chloride (280 μL) at −78 °C. After 20 min of stirring, the alcohol from above was introduced as a solution in CH_2Cl_2 (7 mL). The reaction mixture was stirred for 1 h at −78 °C, quenched with triethylamine (3 mL), and warmed to rt before being treated with saturated $NaHCO_3$ solution (20 mL) and diluted with CH_2Cl_2 (100 mL). The separated organic phase was dried and evaporated to furnish the aldehyde that was carried forward without delay.

To a solution of methyltriphenylphosphonium bromide (1.53 g, 4.28 mmol) in THF (15 mL) was added *n*-butyllithium (2.3 mL of 1.5 M in hexanes, 3.45 mmol) at −30 °C and this mixture was stirred for 20 min before the aldehyde was introduced as a solution in THF (8 mL) and for 3 h at rt before being quenched with saturated $NaHCO_3$ solution (5 mL), diluted with ethyl acetate (300 mL) and washed with brine (100 mL). The organic phase was dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with 15:1 hexanes/ethyl acetate gave **16** as a colorless oil (847 mg, 74% over three steps); IR (neat, cm^{-1}) 1613, 1588, 1514; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.40 (m, 6H), 7.24 (m, 2H), 6.87 (m, 2H), 6.10 (dd, J=10.8, 17.4 Hz, 1H), 6.34 (dd, J=1.6, 17.4 Hz, 1H), 6.13 (dd, J=1.6, 10.8 Hz, 1H), 5.01 (s, 1H), 4.44 (s, 2H), 3.97 (ddd, J=1.0, 2.6, 6.1 Hz, 1H), 3.80 (s, 3H), 3.62 (s, 2H), 3.28 (s, 3H), 2.35 (dd, J=6.1, 13.5 Hz, 1H), 2.01 (dd, J=2.6, 13.5 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 141.0, 135.7, 133.5, 130.1, 129.6, 129.2, 127.6, 113.8, 113.3, 108.2, 87.0, 83.2, 70.8, 69.8, 55.3, 54.7, 37.2, 26.8, 19.3; ES HRMS m/z $(M+Na)^+$ calcd 555.2537, obsd 555.2537; $[\alpha]_D^{20}$=−14.8 (c 2.04, $CHCl_3$).

Anal. calcd for $C_{32}H_{40}O_5Si$: C, 72.14; H, 7.57. Found: C, 71.90; H, 7.59.

1.1.5. Conversion of 14 to 18. A 763 mg (2.34 mmol) sample of **14** was reacted with *tert*-butyldiphenylsilyl chloride (820 mg, 3.00 mmol) and imidazole (820 mg, 12.0 mmol) in DMF (10 mL) as described above to give 1.21 g (92%) of the silyl ether as a colorless oil; IR (neat, cm^{-1}) 1738, 1614, 1586; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.37 (m, 6H), 7.13 (m, 2H), 6.82 (m, 2H), 4.96 (s, 1H), 4.37 (s, 2H), 4.03 (d, J=9.5 Hz, 1H), 3.96 (dd, J=1.4, 6.0 Hz, 1H), 3.88 (d, J=9.5 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.36 (s, 3H), 2.72 (dd, J=6.0, 14.2 Hz, 1H), 2.11 (dd, J=1.4, 14.2 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 159.2, 135.7, 135.6, 133.4, 133.2, 129.8, 129.6, 129.1, 127.6 (2C), 113.8, 108.0, 87.2, 82.3, 70.9, 68.9, 55.3, 54.7, 52.1, 35.4, 26.7, 19.3; ES HRMS m/z $(M+Na)^+$ calcd 587.2436, obsd 587.2477; $[\alpha]_D^{20}$=−31.7 (c 3.29, $CHCl_3$).

Reduction of the above ester (1.21 g, 2.14 mmol) with diisobutylaluminum hydride (6.3 mL of 1.0 M in hexanes, 6.3 mmol) at −78 to −20 °C in the predescribed manner provided the primary alcohol that was directly oxidized by the Swern method detailed above. The resulting unpurified aldehyde **17** was treated with the ylide prepared from *n*-butyllithium (2.3 mL of 1.5 M in hexanes, 3.45 mmol) and methyltriphenylphosphonium bromide (1.53 g, 4.28 mmol). There was isolated 847 mg (74% over three steps) of **18** as a colorless oil; IR (neat, cm^{-1}) 1613, 1514, 1470; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.34 (m, 6H), 7.18 (m, 2H), 6.84 (m, 2H), 6.12 (dd, J=10.8, 17.4 Hz,

1H), 5.33 (dd, J=1.6, 17.4 Hz, 1H), 5.11 (dd, J=1.6, 10.8 Hz, 1H), 4.95 (d, J=1.1 Hz, 1H), 4.42 (s, 2H), 3.99 (ddd, J=1.1, 3.3, 6.1 Hz, 1H), 3.81 (s, 3H), 3.77 (d, J=9.5 Hz, 1H), 3.64 (d, J=9.5 Hz, 1H), 3.38 (s, 3H), 2.40 (dd, J=3.3, 13.5 Hz, 1H), 2.10 (dd, J=6.1, 13.5 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 141.6, 135.7 (2C), 133.6 (2C), 130.1, 129.5 (2C), 129.1, 127.5, 113.8, 113.2, 108.4, 87.0, 83.1, 71.0, 69.3, 55.3, 55.1, 36.5, 26.9, 19.4; ES HRMS m/z $(M+Na)^+$ calcd 555.2537, obsd 255.2537; $[\alpha]_D^{20}=-51.8$ (c 1.70, $CHCl_3$).

Anal. calcd for $C_{32}H_{40}O_5Si$: C, 72.14; H, 7.57. Found: C, 72.02; H, 7.56.

1.1.6. Ring contraction of 16. To a THF solution (4 mL) of zirconocene dichloride (82.4 mg, 0.282 mmol) was added n-butyllithium (0.38 mL of 1.5 M, 0.57 mmol) at −78 °C and the reaction mixture was stirred for 1 h prior to the introduction of **16** (100 mg, 0.188 mmol) dissolved in THF (3 mL) and warming to rt. After 9 h, the reaction temperature was raised to 55 °C and stirring was maintained overnight prior to quenching with 1N HCl (1 mL) and extraction with ethyl acetate (3×50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL), dried, and evaporated. The residue was chromatographed on silica gel (elution with 5:1 hexanes/ethyl acetate) to deliver **19** (29 mg) and **20** (21 mg) in 70% combined yield based on 25% recovered starting material.

For **19**: colorless oil; IR (neat, cm^{-1}) 3544, 1612, 1514; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.41 (m, 6H), 7.27 (m, 2H), 6.89 (m, 2H), 5.95 (dd, J=10.9, 17.6 Hz, 1H), 5.26 (dd, J=1.3, 10.9 Hz, 1H), 5.09 (dd, J=1.3, 17.6 Hz, 1H), 4.46 (s, 2H), 4.41(m, 1H), 4.17 (m, 1H), 3.81 (s, 3H), 3.64 (d, J=10.1 Hz, 1H), 3.46 (d, J=10.1 Hz, 1H), 2.57 (br s, 1H), 2.27 (ddd, J=2.3, 6.8, 12.7 Hz, 1H), 2.10 (dd, J=4.9, 12.7 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 137.6, 135.6, 133.3, 133.2, 129.9, 129.7, 129.5, 127.7, 116.5, 113.8, 71.6, 71.3, 70.8, 67.9, 55.2, 49.9, 31.1, 26.8, 19.3; ES HRMS m/z $(M+Na)^+$ calcd 525.2432, obsd 525.2429; $[\alpha]_D^{20}=-25.6$ (c 1.28, $CHCl_3$).

For **20**: colorless oil; IR (neat, cm^{-1}) 3440, 1613, 1587; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.40 (m, 6H), 7.29 (m, 2H), 6.88 (m, 2H), 5.89 (dd, J=11.0, 17.7 Hz, 1H), 5.30 (dd, J=1.1, 11.0 Hz, 1H), 5.19 (dd, J=1.1, 17.7 Hz, 1H), 4.49 (s, 2H), 4.22 (d, J=6.4 Hz, 1H), 3.81 (s, 3H), 3.77 (dt, J=6.4, 8.4 Hz, 1H), 3.65 (d, J=10.2 Hz, 1H), 3.50 (d, J=10.2 Hz, 1H), 2.13 (dd, J=8.4, 11.2 Hz, 1H), 1.79 (dd, J=8.4, 11.2 Hz, 1H), 1.72 (br s, 1H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 137.0, 135.6, 133.4, 130.4, 129.7, 129.4, 127.7, 117.1, 113.7, 78.0, 75.1, 70.5, 67.3, 55.2, 45.4, 27.7, 26.9, 19.4; ES HRMS m/z $(M+Na)^+$ calcd 525.2432, obsd 525.2423; $[\alpha]_D^{20}=+10.2$ (c 0.66, $CHCl_3$).

The entirely comparable treatment of **17** with the zirconocene reagent prepared from the same quantity of reagents resulted in the isolation of 24 mg of **19** and 18 mg of **20** (56% yield based on 19% recovered starting material).

1.1.7. Oxidation of 20 to 21. To a DMSO solution (2 mL) of **20** (241 mg, 0.479 mmol) was added 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX, 364 mg, 1.30 mmol) dissolved in DMSO (2 mL) and the reaction mixture was stirred overnight at rt prior to the introduction of ethyl acetate (4 mL) and water (4 mL), and filtration through a cotton plug. The organic phase was washed with brine, dried, and concentrated to leave a residue that was chromatographed on silica gel. Elution with 10:1 hexanes/ethyl acetate provided 220 mg (92%) of **21** as a colorless oil; IR (neat, cm^{-1}) 1782, 1613, 1514; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 7.30 (m, 2H), 6.89 (m, 2H), 5.73 (dd, J=10.4, 17.3 Hz, 1H), 5.16 (d, J=17.3 Hz, 1H), 5.12 (d, J=10.4 Hz, 1H), 4.79 (dd, J=8.3, 9.9 Hz, 1H), 4.74 (d, J=11.3 Hz, 1H), 4.58 (d, J=11.3 Hz, 1H), 3.96 (d, J=10.3 Hz, 1H), 3.82 (s, 3H), 3.52 (d, J=10.3 Hz, 1H), 2.62 (dd, J=8.3, 11.3 Hz, 1H), 2.40 (dd, J=9.9, 11.3 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 159.4, 135.7, 135.6, 134.6, 133.3, 132.9, 129.7 (2C), 129.6 (2C), 127.7, 116.4, 113.8, 84.0, 71.6, 66.3, 64.8, 55.2, 27.6, 26.7, 19.3; ES HRMS m/z $(M+Na)^+$ calcd 523.2275, obsd 523.2242; $[\alpha]_D^{20}=-2.9$ (c 1.2, $CHCl_3$).

Acknowledgements

We thank the Yamanouchi USA Foundation and the National Science Foundation for their support of our research program.

References and notes

1. Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835. Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299.
2. Paquette, L. A.; Cuniére, N. *Org. Lett.* **2002**, *4*, 1927.
3. Paquette, L. A.; Kim, I. H.; Cuniére, N. *Org. Lett.* **2003**, *5*.
4. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
5. Schmidt, O. Th. *Methods Carbohydr. Chem.* **1963**, *2*, 318.
6. Hwang, C. K.; Li, W. S.; Nicolaou, K. C. *Tetrahedron Lett.* **1984**, *25*, 2295.
7. Just, G.; Luthe, C. *Can. J. Chem.* **1980**, *58*, 2286.
8. Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29*, 5087.
9. Hase, T.; Wähälä, K. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 7, pp 4533–4534.
10. Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218, and references cited therein. Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481.
11. Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.
12. Boeckman, Jr. R. K.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141.
13. For a prior listing of general experimental conditions, consult Paquette, L.; Arbit, R.; Funel, J.-A.; Bolshakov, S. *Synthesis* **2002**, 2105.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1359–1364
Tetrahedron

A study of the 1,2-addition of group IV metallacycles derived from 1-alkynylphosphonates to conjugated enones

Ofir Baum, Abed Al Aziz Quntar, Valery M. Dembitsky and Morris Srebnik*

Department of Medicinal Chemistry and Natural Products†*, School of Pharmacy, Hebrew University Jerusalem, POB 12065, Jerusalem 91120, Israel*

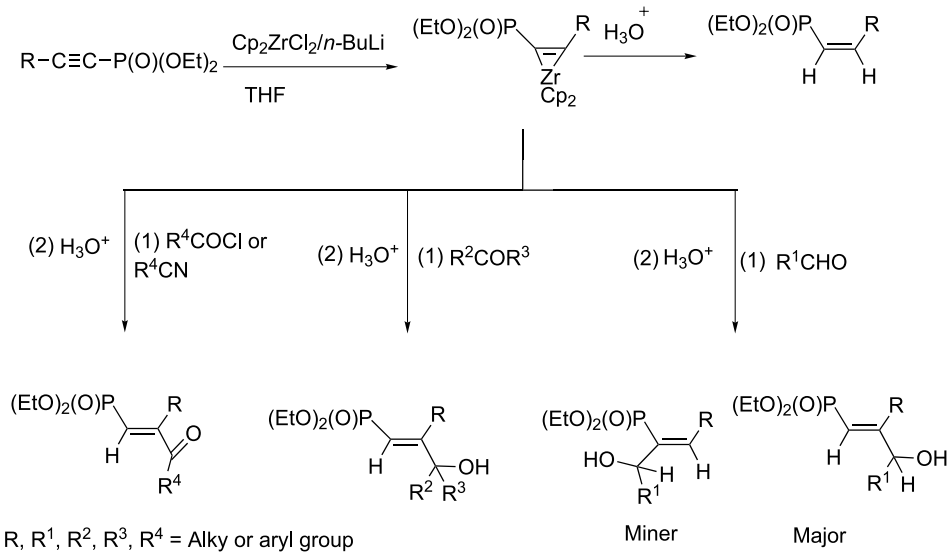
Received 1 August 2003; accepted 1 September 2003

Abstract—Addition of group IV cyclopropenemetallocycles to conjugated enones indicates that the reaction course is mostly dependent on the metallocyle and the enone moiety. The zirconacycle affords the unrearranged products **3**. On the other hand, some rearranged products, 1,3-butadienylphosphonates, are obtained when titanacycles are used.

1. Introduction

Stereodefined vinylphosphonates are an important class of compounds that have interesting biological activity,[1] and are useful intermediates in further organic transformations.[2] Recently, we have prepared various types of stereodefined vinylphosphonates including *cis*-vinylphosphonates, 1,3-butadienylphosphonates,[3] 1-(hydroxymethyl)vinylphosphonates, 2-(hydroxymethyl)vinylphosphonates,[4] 3-oxo-vinylphosphonates,[5] 3-aminovinylphosphonates,[6] and various other di- and tri-substituted vinylphosphonates, (Scheme 1).[7]

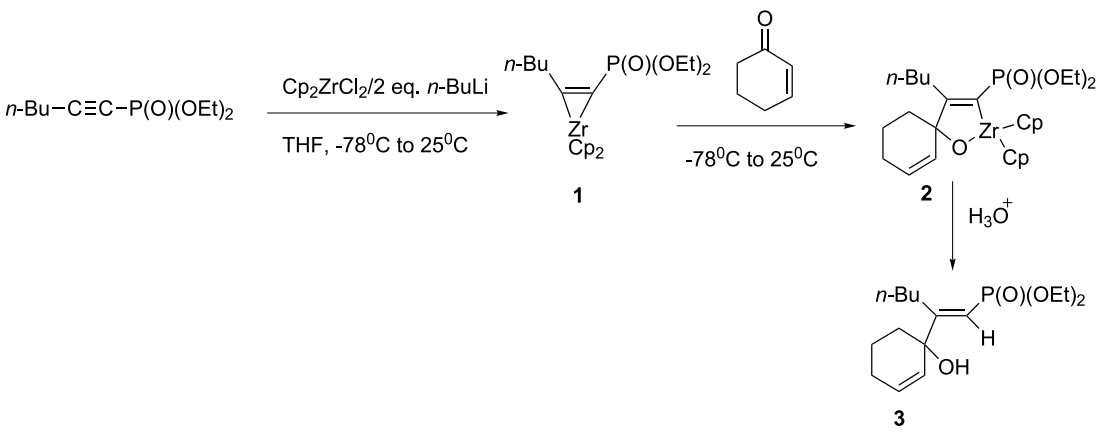
As part of our ongoing program to synthesize stereodefined vinylphosphonates from group IV metals, we were interested in studying the addition of metallocyclopropenes to structurally diverse enones. The 1,2-addition has not been reported and could provide several interesting types of stereo defined vinylphosphonates. In this paper we report our initial results.



Scheme 1.

Keywords: Metallocycle; Zirconacycle; Titanacycle; 1,3-Butadienylphosphonates; Enones; Allylic rearrangement.
* Corresponding author. Tel.: +972-2-675-7301; fax: +972-2-675-8201; e-mail address: msrebni@md2.huji.ac.il
† Affiliated with the David R. Bloom Center for Pharmaceutics at the Hebrew University in Jerusalem.

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.103



Scheme 2.

Table 1. Preparation and selectivity of **3** and **4**

Entry	Enone	Reactions with Ti		Reactions with Zr	
		Rearranged **4** (%)	Un-rearranged **3** (%)	Rearranged **4** (%)	Un-rearranged **3** (%)
a	Cyclohexenone	100	0	0	100
b	Cycloheptenone	100	0	0	100
c	4,4-Dimethylcyclohexenone	0	100	0	100
d	Methyl vinyl ketone	0	100	0	100

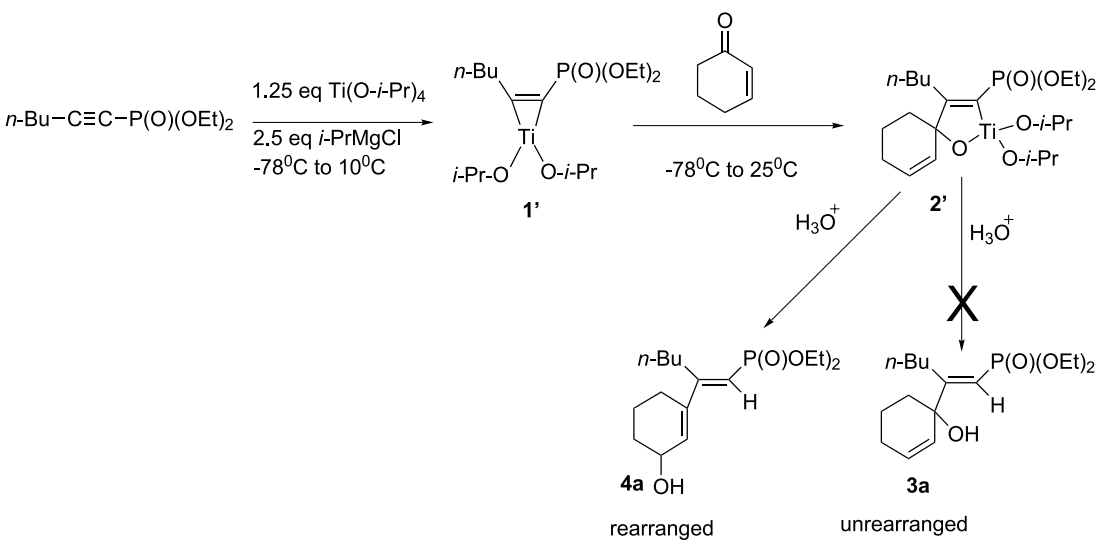
2. Results and discussion

When diethyl 1-hexynylphosphonate was treated with Cp_2ZrCl_2/2 *n*-BuLi, zirconacyclopropene **1** were produced.[8] When **1** was treated with 2-cyclohexen-1-one, the five membered ring zirconacylces **2**, were obtained, which upon workup, compounds **3a** was afforded, (Scheme 2).

The structure of **3** was determined by NMR, LCMS, and UV spectroscopy. These diallylic alcohols are new types of vinylphosphonates which have not been reported before. The results are listed in Table 1.

The regio- and stereochemistry of compounds **3** were determined by NMR analysis and phosphorous carbon coupling constants. The presence of doublet in the ^{1}H NMR, due to the phosphorous splitting of the vinylic hydrogen in the region (4.9–5.8 ppm) in ^{1}H NMR is indicative that the enone coupling was on C2 to phosphorous. In addition, the large $^3J_{PC}$ of the alcoholic carbon (22.0–22.7 Hz) of the inserted enone moiety, compared to the small $^3J_{PC}$ of the allylic carbon of *n*-Bu (~7 Hz) is consistent with *cis* configuration of *n*-Bu group with respect to phosphorous, whereas the inserted enone moieties are in *trans* position to phosphorous (Table 3).

Diallylic alcohol compounds are of increasing interests. Besides possessing significant biological activity,[9] they are



Scheme 3.

Table 2. UV data of selected **3** and **4**

Compound	λ_{max} (nm)	ε	Conc. (M) in methanol
3c	252 (sh)	869	6.9×10^{-4}
3d	250	1469	1.4×10^{-4}
4a	251	8614	7.1×10^{-4}
4b	251	8642	1.8×10^{-4}

important intermediates in organic transformation. They are transformed to epoxy alcohols,[10] to bicyclic allylic alcohols and ethers.[11] Moreover, they are interesting intermediates in the asymmetric synthesis of polyhydroxylated celastracease sesquiterpene core.[10]

In contrast to the results obtained with the zirconacyclopropenes, reaction of diethyl 1-hexynylphosphonate with Ti(O-*i*Pr)$_4$/2 *i*PrMgCl, followed by cyclohexenone gave after workup the rearranged products,[12] butadienylphosphonate **4**, which was isolated as the sole product (Scheme 3).

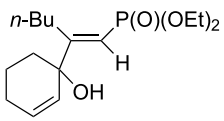
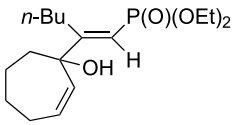
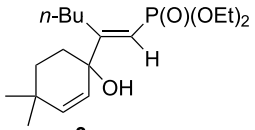
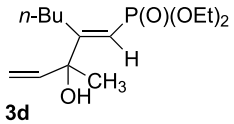
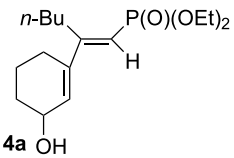
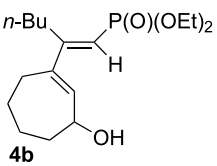
Initially, compounds **3**, were expected to be obtained after the acidic workup, but the allylic rearranged products **4** were obtained in two examples (Table 1). However, under the same acidic workup, 4,4-dimethylcyclohexenone and methyl vinyl ketone gave unrearranged products **3**. The results are listed in Table 1, and selected UV data are listed in Table 2.

The regio- and the stereochemistry of compounds **4** were determined from the NMR data and the coupling constants. The small $^3J_{PC}$ values of *n*-Bu (~7 Hz) compared to the larger $^3J_{PC}$ values of the vinylic carbon ~20 Hz is indicative *cis* position of *n*-Bu to the phosphorous and *trans* position of the enone moiety (Table 3).

The UV data (Table 2) are consistent with the NMR analysis. The diallylic alcohols **3c** and **3d** have relatively a small ε, while ε of the rearranged compounds **4a** and **4b** are >8000.

No rearranged products **4** were detected in the zirconacycle reactions, whereas rearrangement occurred on two occasions with the titanacycles. Since all reactions were

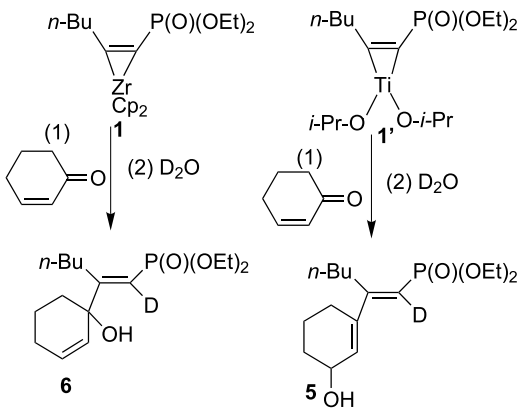
Table 3. Structure and selected NMR data for **3** and **4**

Entry	Structure of **3** and **4**	$^2J_{PH}$ (Hz)	$^3J_{PC}$ (Hz) of enone moiety	$^3J_{PC}$ (Hz) of (*n*-Bu)	δ ^{31}P NMR
3a	 **3a**	17.1	22.7	7.1	19.31
3b	 **3b**	17.4	22.6	7.0	20.48
3c	 **3c**	17.4	22.6	6.9	20.17
3d	 **3d**	16.8	22.0	6.9	20.32
4a	 **4a**	17.1	23.8	7.0	20.31
4b	 **4b**	15.5	23.8	6.9	20.08

purified on silica gel chromatography, silica gel is ruled out as cause of the rearrangement.[10]

To get insight into the rearrangement and the mechanism, the reaction mixture with the Ti reagent was also worked up under neutral and basic conditions. Rearrangement product **4a** was obtained in all cases. In addition, when **3a** was subjected to Lewis acid catalysis, complex reaction mixtures were obtained with no detection of product **4a**.

All this seems to indicate that rearrangement takes place on the titanacycle, possibly by ring expansion of the titanacycle. At any rate, the C–Ti bond is intact prior to work up as indicated by deuterium labeling (attempts to monitor the reaction by NMR were unsuccessful). When the reaction mixture was quenched with D_2O and D_2SO_4, GCMS analysis of the deuterium quenched rearranged and un-rearranged products **5**, **6** indicated only one stable atom of deuterium is incorporated on C1 to the phosphorous (Scheme 4).



Scheme 4.

Dienylphosphonates are of considerable synthetic interest. They undergo a variety of reactions including 1,3-dipolar additions,[13] cycloaddition with CH_2N_2,[14] and [2+2] cycloadditions.[15] In addition, these compounds possess biological activities by themselves.[16] Synthesis of these compounds are few in number. In the literature there is no general method for their preparation. They have been prepared by isomerization of 1-alkynylphosphonates in the presence of palladium salts,[17] by Knoevenagel reaction,[15] by reaction of unsaturated cyanophosphonates with *N*-tosylsulfonylimines.[18]

3. Conclusions

In this study, various stereodefined vinylphosphonates were prepared by addition of group IV metallacycles to enones. When the enones were added to the zirconacyclopropenes, the unrearranged products, 3-hydroxy allylic vinylphosphonates, **3** were obtained. On the other hand, the reaction course of the enones with the titanacyclopropenes was dependent on the enone moiety, in which, in certain cases, the rearranged 1,3-butadienylphosphonates products **4** were obtained. The use of different workup media, i.e., acidic, neutral, and basic, has no influence on the rearrangement.

4. Experimental

4.1. General comments

All reactions were carried out under dry nitrogen atmosphere using pre heated dry glassware. All the solvents that were used were dried and distilled from sodium–benzophenone mixture prior to use. Starting materials were used as purchased from commercial suppliers without further purification. ^1H (300 MHz), ^{13}C (75.4 MHz) and ^{31}P (121 MHz) NMR spectra were recorded in $CDCl_3$. ESMS analysis was performed on a LCMS. UV was used to determine the maximum absorbance.

General procedure for **4** (*reactions of enones with titanacycles*). To a 50 ml round bottom flask containing a solution of 0.355 g of $Ti(O\text{-}iPr)_4$ (1.25 mmol) dissolved in 10 ml of dry diethyl ether, 1.25 ml of iPrMgCl 2 M in ether (2.5 mmol) were introduced at −78 °C followed by the addition of 0.218 g of diethyl-1-hexynylphosphonate (1 mmol). The reaction mixture was allowed to warm gradually, over a period of 4 h to 5 °C. Then the reaction was cooled again to −78 °C and 1.1 mmol of the enone was added. The reaction was allowed to warm gradually to 25 °C overnight. After acidic workup the product was extracted by dietyl ether (2×20), dried over magnesium sulphate, and was purified on silica gel, using petroleum ether–ethyl acetate.

General procedure for **3** (*reactions of enones with zirconacycles*). To a 50 ml round bottom flask charged with 0.292 g of Cp_2ZrCl_2 (1.25 mmol) dissolved in 6 ml of dry THF, 1 ml of 2 M solution of *n*-BuLi was introduced at −78 °C. After 4 h of stirring in the range −50 to −30 °C, 0.26 g (0.9 mmol) of 1-hexynylphosphonate was added, the reaction mixture was allowed to warm gradually to 25 °C and left stirring over night. Then the reaction was cooled again to −78 °C and 1.1 mmol of the enone was added. The reaction was allowed to warm gradually to 25 °C over night followed by acidic work-up with diluted hydrochloric acid (1 M). The product was extracted in diethyl ether, and dried over magnesium sulphate, and was isolated on silica gel column chromatography, using petroleum ether–ethyl acetate.

General procedure for **5** *and* **6**. The same procedure for **3** and **4** except the D_2O workup instead of H_3O^+.

4.2. Spectroscopic data

4.2.1. Compound 3a. 50% isolated yield; (30% petroleum ether: 70% ethyl acetate); R_f=0.42; ^1H NMR (300 MHz: δ 0.84 (t, 3H, J_{HH}=7.5 Hz), 1.27 (t, 6H, J_{HH}=6.6 Hz), 1.29–1.99 (overlap, 10H), 2.42 (m, 2H), 2.50 (broad s, 1H), 3.90–4.01 (m, 4H), 5.47–5.51 (d, 1H, J_{HH}=9.9 Hz), 5.69–5.74 (d, 1H, $^2J_{PH}$=17.1 Hz), 5.88 (m, 1H); ^{31}P NMR (121 MHz): δ 19.31; ^{13}C NMR (75.4 MHz): δ 13.7, 16.2 (d, $^3J_{PC}$=6.5 Hz), 18.5, 23.4, 24.7, 30.1 (d, $^3J_{PC}$=7.1 Hz, *cis*), 33.2, 35.5, 61.1 (d, $^2J_{PC}$=5.7 Hz), 74.3 (d, $^3J_{PC}$=22.7 Hz, trans), 111.0 (d, $^1J_{PC}$=189.4 Hz), 130.5, 131.3, 170.96 (d, $^2J_{PC}$=6.6 Hz); ESMS (MH^+, *m/z*, 317.4). Anal. calcd for $C_{16}H_{29}O_4P$: C, 60.74; H, 9.24; P, 9.79. Found: C, 60.64; H, 9.36; P, 9.70%.

4.2.2. Compound 3b. 54% isolated yield; (30% petroleum ether: 70% ethyl acetate); R_f=0.44; ^{1}H NMR (300 MHz): δ 0.91 (t, 3H, J_{HH}=7.5 Hz), 1.23–1.51 (m, 8H), 1.51–2.01 (m, 6H), 2.15–2.21 (m, 2H), 2.36–2.46 (m, 2H), 2.54–2.63 (m, 2H), 3.37 (s, broad, 1H), 4.00–4.12 (m, 4H), 5.50 (d, 1H, J_{HH}=11.8 Hz) 5.78 (d, 1H, $^2J_{PH}$=17.4 Hz), 5.80–5.89 (m, 1H); ^{31}P NMR (121 MHz): δ 20.48; ^{13}C NMR (75.4 Hz): δ 13.9, 16.39 (d, $^3J_{PC}$=6.6 Hz), 22.9, 23.7, 26.7, 27.1, 30.1 (d, $^3J_{PC}$=7.0 Hz, *cis*), 33.5, 37.6, 61.3 (d, 2C, $^2J_{PC}$=5.8 Hz), 80.6 (d, $^3J_{PC}$=22.6 Hz), 111.2 (d, $^1J_{PC}$=188 Hz), 132.1, 136.0, 170.9 (d, $^2J_{PC}$=6.9 Hz); ESMS (MH^+, *m/z*, 331.2). Anal. calcd for $C_{17}H_{31}O_4P$: C, 61.80; H, 9.46; P, 9.37. Found: C, 61.66; H,9.40; P, 9.31%.

4.2.3. Compound 3c. 55% isolated yield; (30% petroleum ether: 70% ethyl acetate); R_f=0.53; ^{1}H NMR (300 MHz): δ 0.72–0.90 (m, 3H), 0.96 (s, 3H), 1.00 (s, 3H), 1.29 (m, 6H), 1.32–1.87 (overlap, 8H), 2.41 (m, 2H), 4.02 (m, 4H), 5.35 (d, 1H, J_{HH}=9.9 Hz), 5.61 (d, 1H, J_{HH}=10.2 Hz), 5.73 (d, 1H, $^2J_{PH}$=17.4 Hz); ^{31}P NMR (121 Hz): d 20.17; ^{13}C NMR (75.4 MHz): δ 14.0, 16.5, 16.6, 23.7, 27.7, 29.9, 30.3 (d, $^3J_{PC}$=6.9 Hz, *cis*), 31.9, 32.9, 33.3, 33.5 (d, $^3J_{PC}$=2.3 Hz), 61.4, 61.4, 74.7 (d, $^3J_{PC}$=22.6 Hz), 111.2 (d, $^1J_{PC}$= 188.9 Hz), 128.2, 141.5, 171.0 (d, $^2J_{PC}$=6.9 Hz); UV: 252 nm/869; ESMS (MH^+, *m/z*, 345.3). Anal. calcd for $C_{18}H_{33}O_4P$: C, 62.77; H, 9.66; P, 8.99. Found: C, 62.59; H,9.70; P, 8.81%.

4.2.4. Compound 3d. 50% isolated yield; (50% petroleum ether: 50% ethyl acetate); R_f=0.36; ^{1}H NMR (300 MHz): δ 0.75 (t, 3H, J_{HH}=6.9 Hz), 1.18 (t, 6H, J_{HH}=7.2 Hz), 1.29 (s, 3H), 1.22–1.39 (overlap, 4H), 2.29 (t, 2H, J_{HH}=8.4 Hz), 3.55 (s, broad, 1H), 3.90 (m, 4H), 4.96 (d, 1H, J_{HH}=10.8 Hz), 5.13 (d, 1H, $^2J_{PH}$=16.8 Hz), 5.69–5.82 (m, 2H); ^{31}P NMR (121 MHz); δ 20.32; ^{13}C NMR (75.4 MHz): δ 14.2, 16.6, 16.6, 23.2, 26.4, 30.1 (d, $^3J_{PC}$=6.9 MHz, *cis*), 32.8, 60.9 (d, $^2J_{PC}$=5.7 Hz), 76.4 (d, $^3J_{PC}$= 22.0 Hz) 109.8 (d, $^1J_{PC}$=189.8 Hz), 113.1, 142.7, 170.0 (d, $^2J_{PC}$=7.2 MHz); UV: 266 nm/2439; ESMS (MH^+, *m/z*, 291.1). Anal. calcd for $C_{14}H_{27}O_4P$: C, 57.92; H, 9.37; P, 10.67. Found: C, 57.78; H, 9.40; P, 10.52%.

4.2.5. Compound 4a. 50% isolated yield; (30% petroleum ether: 70% ethyl acetate); R_f=0.11; ^{1}H NMR (300 MHz): δ 0.75 (t, 3H, J_{HH}=6.9 Hz), 1.07–1.47 (overlap,12H), 1.66–2.03 (overlap, 5H), 2.45–2.58 (m, 2H), 3.86–3.99 (m, 4H), 4.17 (s, 1H, broad), 5.36 (d, 1H, $^2J_{PH}$=17.1 Hz), 5.96 (s, 1H); ^{31}P NMR (121 MHz) δ 20.31; ^{13}C NMR (75.4 Hz): δ 14.0, 14.2, 16.4, 16.4, 19.8, 23.1, 26.3, 31.5 (d, $^3J_{PC}$= 7.0 Hz, *cis*), 32.1, 60.5, 61.5, 66.3, 110.5 (d, $^1J_{PC}$=191.1 Hz), 131.9, 138.4 (d, $^3J_{PC}$=23.8 Hz), 163.6 (d, $^2J_{PC}$=8.3 Hz); UV: 251 nm/8614; ESMS (MH^+, *m/z*, 317.4). Anal. calcd for $C_{16}H_{29}O_4P$: C, 60.74; H, 9.24; P, 9.79. Found: C, 60.70; H, 9.33; P, 9.70%.

4.2.6. Compound 4b. 50% isolated yield; (30% petroleum ether: 70% ethyl acetate); R_f=0.11; ^{1}H NMR (300 MHz): δ 0.86 (m, 3H, J_{HH}=7.2 Hz), 1.27 (t, 6H, J_{HH}=2.1 Hz), 1.31–2.38 (overlap, 13H), 2.63 (m, 2H), 4.06 (m, 4H), 4.47 (m, 1H), 4.94 (d, 1H, $^2J_{PH}$=15.0 Hz), 5.97 (s, 1H); ^{31}P NMR (121 MHz): δ 20.08; ^{13}C NMR (75.4 Hz): δ 14.2, 16.6, 16.6 (d, $^3J_{PC}$=6.9 Hz), 19.7, 23.3, 26.4, 30.8 (d, $^3J_{PC}$=6.9 Hz, *cis*), 31.7, 32.2, 61.6 (d, $^2J_{PC}$=5.4 Hz), 66.7,111.5 (d, $^1J_{PC}$=190 Hz), 138.1, 142.4 (d, $^3J_{PC}$=23.8 Hz), 166.1 (d, $^2J_{PC}$=8.1 Hz); UV: 251 nm/8642; ESMS (MH^+, *m/z*, 331.2). Anal. calcd for $C_{17}H_{31}O_4P$: C, 61.80; H, 9.46; P, 9.37. Found: C, 61.66; H, 9.40; P, 9.23%.

4.2.7. Compound 5. 45% isolated yield; (30% petroleum ether: 70% ethyl acetate); R_f=0.10; ^{1}H NMR (300 MHz): δ 0.75 (t, 3H, J_{HH}=6.9 Hz), 1.07–1.47 (overlap,12H), 1.66–2.03 (overlap, 5H), 2.45–2.58 (m, 2H), 3.86–3.99 (m, 4H), 4.17 (s, 1H, broad), 5.96 (s, 1H); ^{31}P NMR (121 MHz) δ 20.31; ^{13}C NMR (75.4 Hz): δ 14.0, 14.2, 16.4, 16.4, 19.8, 23.1, 26.3, 31.5 (d, $^3J_{PC}$=7.0 Hz, *cis*), 32.1, 60.5, 61.5, 66.3, 110.5 (d, $^1J_{PC}$=191.1 Hz), 131.9, 138.4 (d, $^3J_{PC}$=23.8 Hz), 163.6 (d, $^2J_{PC}$=8.3 Hz); ESMS (MH^+, *m/z*, 318.4).

4.2.8. Compound 6. 48% isolated yield; (30% petroleum ether: 70% ethyl acetate); R_f=0.40; ^{1}H NMR (300 MHz: δ 0.84 (t, 3H, J_{HH}=7.5 Hz), 1.27 (t, 6H, J_{HH}=6.6 Hz), 1.29–1.99 (overlap, 10H), 2.42 (m, 2H), 2.50 (broad s, 1H), 3.90–4.01 (m, 4H), 5.47–5.51 (d, 1H, J_{HH}=9.9 Hz), 5.88 (m, 1H); ^{31}P NMR (300 MHz): δ 19.31; ^{13}C NMR (75.4 MHz): δ 13.7, 16.2 (d, $^3J_{PC}$=6.5 Hz), 18.5, 23.4, 24.7, 30.1 (d, $^3J_{PC}$=7.1 Hz, *cis*), 33.2, 35.5, 61.1 (d, $^2J_{PC}$=5.7 Hz), 74.3 (d, $^3J_{PC}$=22.7 Hz, trans), 111.0 (d, $^1J_{PC}$=189.4 Hz), 130.5, 131.3, 170.96 (d, $^2J_{PC}$=6.6 Hz); ESMS (MH^+, *m/z*, 318.4).

Acknowledgements

The authors thank the Israeli Science Foundation and MECC for support of this work.

References and notes

1. Biology, (a) Harnden, R.; Parkin, A.; Parratt, J.; Perkin, R. *J. Med. Chem.* **1993**, *36*, 1343. (b) Smeyers, Y.; Sanchez, F.; Laguna, A.; Ibanez, N.; Ruano, E.; Perez, S. *J. Pharm. Sci.* **1987**, *76*, 753. (c) Megati, S.; Phadtare, S.; Zemlicka, J. *J. Org. Chem.* **1992**, *57*, 2320. (d) Lazrek, H.; Rochdi, A.; Khaider, H.; Barascut, J.; Imbach, J.; Balzarini, J.; Witvrouw, M.; Pannecouque, C.; De Clerq, E. *Tetrahedron* **1998**, *54*, 3807. (e) Smith, P.; Chamiec, A.; Chung, G.; Cobley, K.; Duncan, K.; Howes, P.; Whittington, A.; Wood, M. J. *J. Antibiot.* **1995**, *48*, 73. (f) Holstein, S.; Cermak, D.; Wiemer, D.; Lewis, K.; Hohl, R. *Bioorg. Med. Chem.* **1998**, *6*, 687. (g) Chance, L.; Moreau, J. US Patent 3,910,886, 1975..
2. For a review: (a) Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333. (b) Thomas, A.; Sharpless, K. *J. Org. Chem.* **1999**, *64*, 8379. (c) Lee, S.; Lee, B.; Lee, C.; Oh, D. *Synth. Commun.* **1999**, *29*, 3621. (d) Telan, L.; Poon, C.; Evans, S. *J. Org. Chem.* **1996**, *61*, 7455. (e) Zhao, Y.; Pei, C.; Wong, Z.; Xi, S. *Phosphor Sulfur Silicon* **1992**, *66*, 115. (f) Kim, D.; Rhie, D. *Tetrahedron* **1997**, *53*, 13603. (g) Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 6428. (h) Defacqz, N.; Touillaux, R.; Marchand-Brynaert, J. *J. Chem. Res.* **1998**, 512.
3. Quntar, A.; Srebnik, M. *Org. Lett.* **2001**, *3*, 1379.
4. (a) Quntar, A.; Srebnik, M. *J. Org. Chem.* **2001**, *66*, 6650–6653. (b) Quntar, A.; Srebnik, M. *Synlett* **2002**, *1*, 61.
5. Quntar, A.; Srebnik, M.; Milman, A. *J. Org. Chem.* **2002**, *67*, 3769.

6. Quntar, A.; Dembitsky, V.; Srebnik, M. *Org. Lett.* **2003**, *5*, 357.
7. Quntar, A.; Srebnik, M. *Chem. Commun.* **2003**, *59*, 58.
8. (a) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. (b) Negishi, E.; Takahashi, T. *Synthesis* **1988**, *1*, 1. (c) Thander, S.; Farona, M. *J. Organometal.* **1982**, *235*, 65. (d) Negishi, E.; Cederbaum, F.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
9. (a) White, J.; Shin, H.; Kim, T.; Cutshall, N. *J. Am. Chem. Soc.* **1997**, 119. (b) Zheng, Y.; Xu, Y.; Lin, J. *Acta Pharm. Sin.* **1989**, *24*, 568. (c) Beroza, M.; Bottger, G. *J. Econ. Entomol.* **1954**, *47*, 188. (d) Kubo, I.; Kim, M.; De Boer, G. *J. Chromatogr.* **1987**, *402*, 354.
10. Spivey, A.; Woodhead, S.; Wesr, M.; Andrews, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 769.
11. Lautens, M.; Hughes, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 129.
12. (a) Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2000**, *343*, 759. (b) Sviridov, O.; Vasilevskii, S.; Pritytskaya, T. *Zh. Org. Khim.* **1989**, *25*, 2244. (c) Kulinkovitch, O.; Sviridov, S.; Vasilevskii, D. *Synthesis* **1991**, 234. (d) Klinkovitch, O.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (e) Sato, F.; Urabe, H.; Okamoto, S. *Synlett.* **2000**, 753. (f) Kulinkovich, O.; Savchgenko, A.; Sviridov, S.; Vasilevskii, D. *Mendeleev Commun.* **1993**, 192.
13. Martin, S.; Garrison, P. *Synthesis* **1982**, 394.
14. Minami, T.; Tokomasu, S.; Mimasu, R.; Hirao, I. *Chem. Lett.* **1985**, 1099.
15. Okauchi, T.; Kakiuchi, T.; Kitamura, N.; Utsunomiya, T.; Ichikawa, J.; Minami, T. *J. Org. Chem.* **1997**, *62*, 8419.
16. Combridge, D. Phosphorus 2000, Chemistry, Biochemistry and Technology; Elsevier: Amsterdam, 2000; p 1285.
17. Ma, C.; Lu, X.; Ma, Y. *Main Group Metal Chem.* **1995**, *18*, 39.
18. Shen, Y.; Jiang, G.; Sun, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3495.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1365–1373
Tetrahedron

Cationic zirconocene- or hafnocene-based Lewis acids in organic synthesis: glycoside–flavonoid analogy

Ken Ohmori, Keisuke Hatakeyama, Hiroki Ohrui and Keisuke Suzuki*

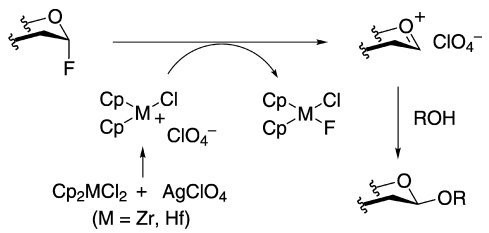
Department of Chemistry, Tokyo Institute of Technology, and CREST, Japan Science and Technology (JST) Corporation, O-okayama, Meguro-ku, Tokyo 152-8551, Japan

Received 23 July 2003; accepted 7 August 2003

Abstract—Cationic metallocene species, generated from Cp_2MCl_2 and $AgClO_4$ (M=Zr, Hf), were used for the glycosylation of catechin derivative **2**, enabling a concise synthesis of a glycosyl flavonoid, astilbin (**1**). Further study revealed the efficiency of this Lewis acidic species for S_N1-type activation of the C(4) position of catechin derivative **11**, enabling selective substitution with various nucleophiles.

1. Introduction

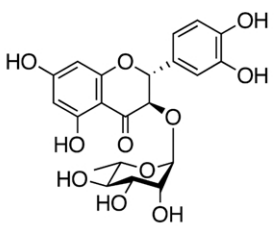
Lewis acidic activation of various functionalities is one of the current focuses in organic synthesis,[1] and has experienced considerable advance[2] during the last two decades. In the case of our study in carbohydrate synthesis, we found that the metallocene-based promoters,[3] Cp_2MCl_2–AgX (M=Ti, Zr, Hf; X^-=ClO_4^-, OTf^-), serve as efficient activator of glycosyl fluorides[3a,b] or acetates.[3c] These reagents have found various applications in the synthesis of complex oligosaccharides.[4]



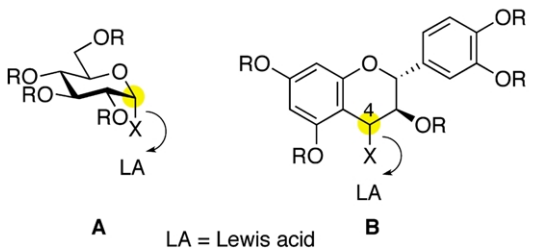
The high reactivity is ascribed to the cationic metallocene species of high electrophilicity, which could be further reinforced by generating the corresponding dicationic species (Eq. 1).[5]

$$Cp_2MCl_2 + 2\ AgClO_4 \longrightarrow Cp_2M^{2+} \cdot 2\ ClO_4^- + 2\ AgCl \quad (M = Zr, Hf) \qquad (1)$$

We wished to develop a novel application of these metallocene-based Lewis acids, that is, the extension of this methodology to the functionalization of flavonoids. In particular, we endeavored to utilize this approach to an implement of our recently reported synthesis of astilbin (**1**), a glycosyl flavonoid isolated from Chinese folk medicine.[6,7] Described in the following report are (1) the synthetic route of **1**, including glycosidation study, and (2) the implication of unsuccessful glycosylation within the context of polyphenol synthesis. The latter aspect can be summarized as the controlled S_N1-type activation of the C(4) position of catechin derivatives **B**, which represents an interesting analogy to the glycosidic activation **A**.



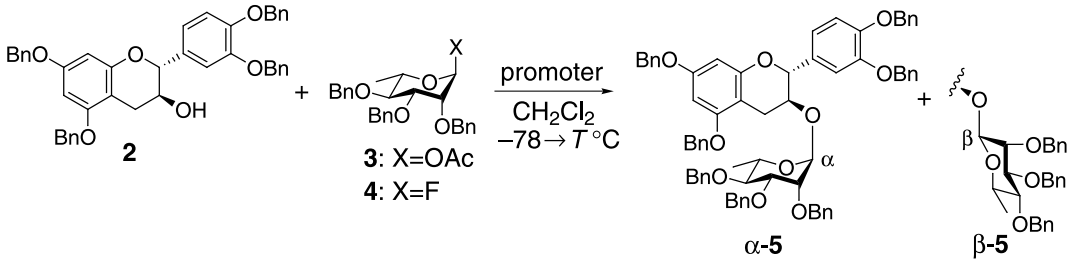
astilbin (**1**)



Keywords: Zirconocene; Hafnocene; Astilbin; Flavonoid; Catechin.
* Corresponding author. Tel.: +81-3-5734-2228; fax: +81-3-5734-2788; e-mail address: ksuzuki@chem.titech.ac.jp

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.08.076

Table 1. Lewis acid-promoted glycosylation of **2**



Run	X	Promoter	T (°C)[a]	**5** (yield, %)	Recovery of **2** (%)
1	OAc	Cp_2ZrCl_2,[b] $AgClO_4$[c]	−35	α (74)	8
2	OAc	Cp_2HfCl_2,[b] $AgClO_4$[c]	−35	α (82)	7
3	OAc	$BF_3{\cdot}OEt_2$[d]	25	α (38)	16
4	OAc	TMSOTf[b]	−30	α (55), β (16)	16
5	OAc	$SnCl_4$[e]	−30	α (10), β (20)	18
6	F	Cp_2HfCl_2,[b] $AgClO_4$[c]	−55	α (57), β (31)	10
7	F	Cp_2HfCl_2,[b] AgOTf[c]	−72	α (47), β (36)	10

[a] The reaction mixture was gradually warmed to the temperature over 60 min.
[b] 1.1 mol equiv.
[c] 2.2 mol equiv.
[d] 2.0 mol equiv.
[e] 1.0 mol equiv.

2. Results and discussion

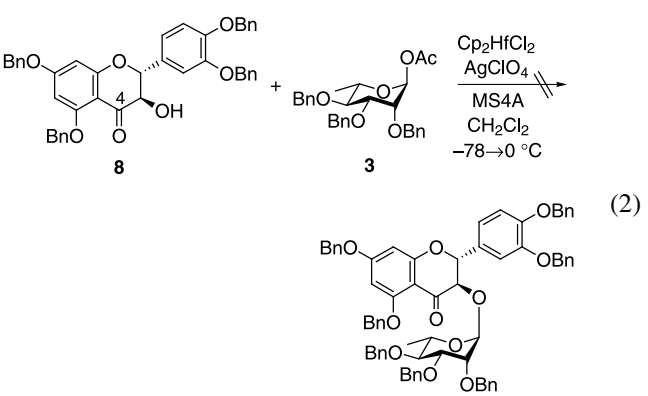
2.1. Successful route to astilbin (1)

Our synthetic route to **1** consisted of two stages, (1) glycosylation of the catechin derivative **2**,[8] and (2) oxidation of the C(4) position of the flavan skeleton. The first stage, that is, the glycosylation required considerable optimization as summarized in Table 1. The optimum conditions were the use of Cp_2ZrCl_2 or Cp_2HfCl_2 coupled with $AgClO_4$ as the activator for L-rhamnosyl acetate **3**,[9] and the reaction in CH_2Cl_2 (−78→−35 °C) afforded good yield of the desired α-glycoside **5** (runs 1 and 2). In contrast, other promoters gave only unsatisfactory results (runs 3–5). $BF_3{\cdot}OEt_2$ required higher temperature for the activation of acetate **3**, giving poor yield of α-**5** (run 3). The reactions smoothly proceeded with TMSOTf at low temperature, giving the glycoside α-**5**, which, however, was accompanied by a considerable amount of the β-anomer (run 4). $SnCl_4$ was even more β-selective, although the yield was poor. These results were amazing that rhamnosidation is generally α-selective, which is favored under both kinetic as well as thermodynamic conditions. The factor relevant to this α/β selectivity seemed quite delicate, since it was found that the stereoselectivity diminished by replacing the acetate donor **3** by the corresponding fluoride donor **4**[10] under the hafnocene-promoted conditions (runs 6 and 7, cf. run 2).

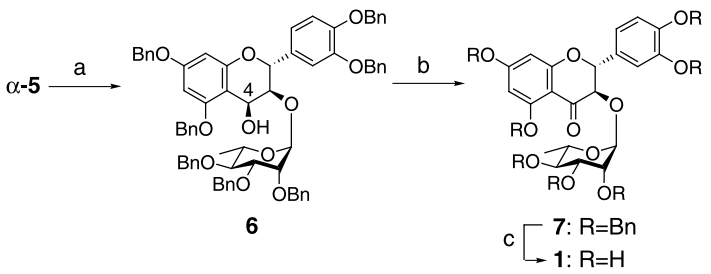
Having the desired glycoside α-**5** in hand, the stage was set for its conversion to the final target (**1**) (Scheme 1). Thus, oxidation of the C(4) position of the flavan skeleton of α-**5** was easily effected by the following two steps; upon treatment of α-**5** with DDQ (H_2O, CH_2Cl_2, 25 °C, 5 h), alcohol **6** was obtained in 66% yield as a single diastereomer, which was then treated with PDC (CH_2Cl_2, 25 °C, 19 h) to give ketone **7** in 85% yield. It is interesting to note that the C(4)-hydroxylation occurred from the β-side, which is a general tendency of reactions at this position (vide infra, Tables 2 and 3). Final removal of the seven benzyl protecting groups in **7** was effected by employing Pd–black as the catalyst, and the target **1** was obtained in 91% yield. All the physical data of **1** (^1H and ^{13}C NMR, IR, $[\alpha]_D$, mp) were fully identical with those of the authentic specimen by direct comparison, $[\alpha]_D^{18}$ −11 (*c* 0.52, EtOH), [lit. $[\alpha]_D^{25}$ −13.6 (*c* 0.52, EtOH)],[6d] mp 179–182 °C, [lit. mp 179–180 °C].[6b]

2.2. Implication from unsuccessful glycosidation attempts

At the preliminary stage of this synthetic study, we attempted also the glycosylation of the flavanols, **8** and **9**, with higher oxidation levels at C(4).[7] Upon attempted glycosylation of keto alcohol **8** by using Cp_2HfCl_2 and $AgClO_4$ as the promoter in CH_2Cl_2 at −78 °C followed by warming to 0 °C, no glycosylated product was obtained, although acetate **3** was completely consumed (Eq. 2). This failure was in line with the general difficulty in glycosylation of a hydrogen-bonded hydroxy group. Furthermore, poor recovery of the glycosyl acceptor **8** (40%) suggested its instability under glycosylation conditions.

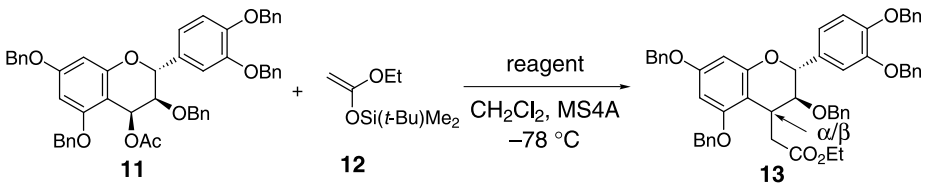


(2)



Scheme 1. *Reagents and conditions*: (a) DDQ, H_2O, CH_2Cl_2, 25 °C, 5 h (66%); (b) PDC, CH_2Cl_2, 25 °C, 40 h (85%); (c) H_2, Pd–black, MeOH, 25 °C, 50 h (91%).

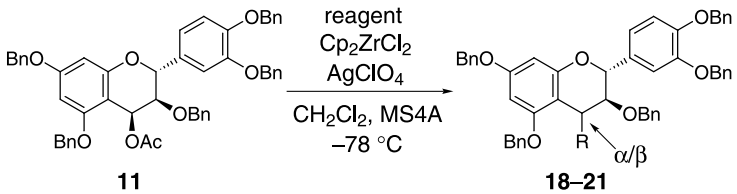
Table 2. Activation of **11** by using various Lewis acids

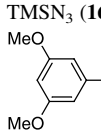
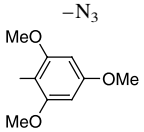


Run	Reagent (mol equiv.)	Time (min)	Yield (%)	α/β
1	Cp_2ZrCl_2 (1.2), $AgClO_4$(2.4)	<10	80	16:84
2	Cp_2ZrCl_2 (0.1), $AgClO_4$(0.2)	15	85	16:84
3	Cp_2ZrCl_2 (0.1), AgOTf(0.2)	240[a]	98	15:85
4	Cp_2ZrCl_2 (0.1)	15	n.r.[b]	—
5	$AgClO_4$ (0.2)	15	n.r.[b]	—
6	$BF_3{\cdot}OEt_2$ (1.2)	60	95	13:87
7	$BF_3{\cdot}OEt_2$ (0.1)	15	n.r.[b]	—
8	TMSOTf (1.2)	60	95	13:87
9	TMSOTf (0.1)	15	n.r.[b]	—

[a] At −78→0 °C.
[b] n.r., no reaction.

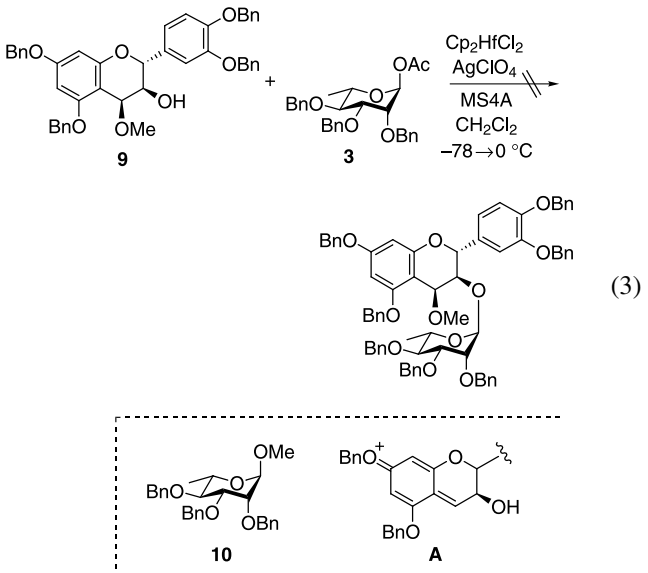
Table 3. Stoichiometric reaction of **11**[a]



Run	Reagent	Product	R	Time (min)	Yield (%)	α/β
1	 (**14**)	**18**	$-C(Me)_2CO_2i$-Pr	10	92	<1/>99
2	PhSH (**15**)	**19**	−SPh	10	83	5/95
3	$TMSN_3$ (**16**)	**20**	$-N_3$	10	52	6/94
4	 (**17**)	**21**		10	80	84/16

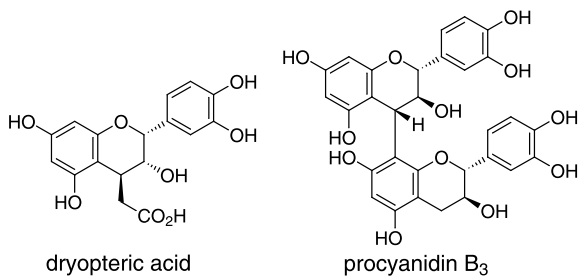
[a] Reagent (3 mol equiv.), Cp_2ZrCl_2 (1.2 mol equiv.), $AgClO_4$ (2.4 mol equiv.).

The glycosylation was also unsuccessful for the acceptor **9**, however, for a different reason. Decomposition of **9** was the main event observed, as rationalized by the Lewis acid-induced departure of the C(4)-methoxy group to generate a quinonemethide **A**, which undergoes various side reactions. Convincing evidence was the formation of the methyl glycoside **10**, albeit in 12% yield, suggesting that the methanol liberated from **9** was glycosylated.

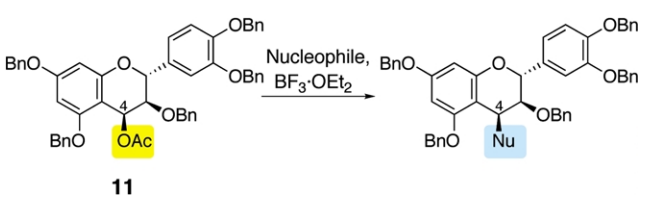


(3)

This result, though unfortunate for the total synthesis, gave us an interesting hint in flavonoid synthesis. Namely, the potential reactivity of the C(4)-position of flavan is similar to that of the anomeric position of a sugar. Activation by a Lewis acid could generate a resonance stabilized cationic species as **A**, providing opportunity for bond formation at this particular position. Given the case, this potential reactivity must be relevant to the enormous structure diversity of natural flavonoids, as exemplified by two natural products shown below.[11]



Through preliminary experiments along these lines, it soon became clear that stereoselective substitution was possible for acetate **11** in the presence of a common Lewis acid, for example, $BF_3{\cdot}OEt_2$, giving substitution products in good yield (Eq. 4).[12]



(4)

In further pursuit of the more effective protocols, we were delighted to find that the cationic metallocene species serve as effective catalyst for this reaction.

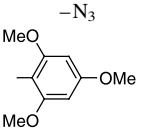
As a model reaction to compare various Lewis acids, the reaction of acetate **11** with ketene silyl acetal **12** (3 mol equiv.) was employed (Table 2). Upon treatment of **11** and **12** with Cp_2ZrCl_2 (1.2 mol equiv.) and $AgClO_4$ (2.4 mol equiv.), the reaction completed almost instantaneously at −78 °C, giving the substitution product **13** in 80% yield (run 1). The activation level offered by this protocol seemed to be too high, judging from the substantial formation of oligomeric products derived from self-condensation of **11** (ca. 15%). We were pleased to find that this side reaction could be effectively suppressed by employing catalytic conditions (run 2): In the presence of Cp_2ZrCl_2 (0.1 mol equiv.) and $AgClO_4$ (0.2 mol equiv.), the reaction smoothly proceeded at −78 °C within 15 min, giving the product **13** in a higher yield than that of the stoichiometric case. Change in the counter anion from ClO_4^- to TfO^- led to much slower reaction, which, however, led to a cleaner formation of **13** in almost quantitative yield (run 3).

It should be noted that the combination of Cp_2ZrCl_2 and a Ag(I) salt was essential for this catalytic reaction. Thus, independent use of these did not work as a promoter (runs 4 and 5). The catalytic activity is quite high, because other promoters, such as $BF_3{\cdot}OEt_2$ and TMSOTf, were only effective when they were used in a stoichiometric amount (runs 6 and 8, cf. runs 7 and 9).

Table 3 shows the reactions of **11** with various other nucleophiles **14**–**17** by using stoichiometric amount of Cp_2ZrCl_2 (1.2 mol equiv.) and $AgClO_4$ (2.4 mol equiv.).[12] Under these conditions, a sterically demanding ketene silyl acetal **14** took part in the reaction at −78 °C within 15 min, and gave the substitution product in excellent yield. An electron-rich aromatic **15** was also smoothly introduced, giving the arylated product in high yield. A sulfur nucleophile, PhSH, and a nitrogen nucleophile, $TMSN_3$, cleanly took part in the reaction. Notably, in all cases, the reactions again proceeded faster than $BF_3{\cdot}OEt_2$ promoted conditions described in our previous report.[12]

Table 4 shows the efficacy of the cationic zirconocene species, which was further highlighted by the catalytic conditions. The reactions listed in Table 3 were just repeated in the presence of Cp_2ZrCl_2 (0.1 mol equiv.) and

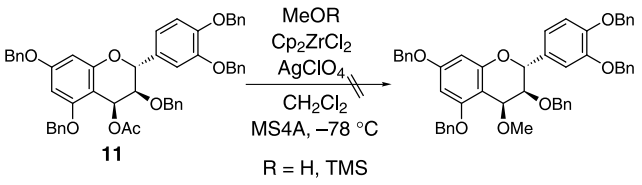
Table 4. Catalytic reaction of **11**[a]

Run	Reagent	Product	R	Time	Yield (%)	α/β
1	**14**	**18**	$-C(Me)_2CO_2i$-Pr	3 h	94	<1/>99
2	**15**	**19**	−SPh	15 min	88	4/96
3	**16**	**20**	$-N_3$	15 min	81	2/98
4	**17**	**21**		21 h	96	94/6

[a] Reagent (3 mol equiv.), Cp_2ZrCl_2 (10 mol%), $AgClO_4$ (20 mol%).

$AgClO_4$ (0.2 mol equiv.), which gave good to excellent yields of products, albeit longer reaction periods were required. It is noted that the reaction rate with hetero nucleophiles, azide and sulfide, remained rather rapid (runs 2 and 3), while the reactions with carbon nucleophiles became considerably slower, although still synthetically acceptable (runs 1 and 4).

In contrast to these positive results, introduction of oxygen nucleophiles has been so far unsuccessful. For example, MeOH or its TMS ether (TMSOMe) failed to react under the stoichiometric conditions. Formation of considerable amount of oligomeric products by self-condensation of **11** was observed, which could be rationalized by the lability of C(4)-methoxylated product. Even if formed, it would undergo reactivation under Lewis acidic conditions to cause oligomerization.



3. Conclusion

Through the synthetic study of a biologically active glycosyl flavonoid, we uncovered the high reactivity of cationic metallocene-based Lewis acids, not only as a glycosylation agent, but also as a catalyst for the S_N1-type reaction of flavan acetate **11** with various nucleophiles. Further study of these reactions is under way in our laboratory.

4. Experimental

4.1. General

All experiments dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. Dichloromethane was distilled successively from P_2O_5 and CaH_2 and stored over 4 Å molecular sieves. For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) were used. For silica gel preparative TLC (PTLC) was performed on Merck silica gel 60 PF_{254} (Art 7747). Melting point (mp) determinations were performed by using a Yanako MP-S3 instrument and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL lambda300 spectrometer or Bruker DRX500. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer. High resolution mass spectra (HRMS) were obtained with a JEOL JMS AX505HA spectrometer. Optical rotations ($[\alpha]_D$) were measured on a DIP-1000 polarimeter.

4.2. Glycosylation of 2

The promoter was prepared in situ by stirring the mixture of Cp_2HfCl_2 (83.0 mg, 0.218 mmol) and $AgClO_4$ (90.8 mg, 0.439 mmol) in the presence of powdered molecular sieves 4 Å (214 mg) in CH_2Cl_2 (1.5 mL) for 10 min at room temperature. To this suspension was added a solution of alcohol **2** (127 mg, 0.195 mmol) in CH_2Cl_2 and glycosyl acetate **3** (93.7 mg, 0.197 mmol) in CH_2Cl_2 (3.0 mL) at −78 °C. The reaction mixture was gradually warmed to −35 °C during 1 h, and the stirring was continued for 1 h. The reaction was stopped by the addition of saturated aqueous $NaHCO_3$. The mixture was filtered through a Celite pad, and extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 98:2) to afford α-glycoside **5** (70.1 mg, 82%) as white solid.

4.2.1. Glycoside 5α. $[\alpha]_D^{22}$ +26.2 (*c* 1.05, $CHCl_3$); mp 36–38 °C; IR (KBr) 3030, 2910, 2865, 1950, 1875, 1810, 1750, 1620, 1590, 1515, 1500, 1455, 1430, 1375, 1310, 1260, 1215, 1145, 1120, 1095, 910, 840, 810, 735, 695, 615 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (d, 3H, *J*=6.3 Hz), 2.66 (dd, 1H, *J*=16.5, 9.0 Hz), 3.06 (dd, 1H, *J*=16.5, 6.0 Hz), 3.36 (dd, 1H, *J*=3.0, 1.5 Hz), 3.52 (dd, 1H, *J*=9.5, 9.5 Hz), 3.75 (dd, 1H, *J*=9.5, 3.0 Hz), 3.79 (dq, 1H, *J*=9.5, 6.5 Hz), 3.95 (ddd, 1H, *J*=9.0, 9.0, 6.0 Hz), 4.20 (d, 1H, *J*=12.5 Hz), 4.259 (d, 1H, *J*=12.5 Hz), 4.263 (d, 1H, *J*=1.5 Hz), 4.47 (d, 1H, *J*=11.5 Hz), 4.54 (d, 1H, *J*=11.5 Hz), 4.58 (d, 1H, *J*=11.0 Hz), 4.60 (d, 1H, *J*=9.0 Hz), 4.89 (d, 1H, *J*=11.0 Hz), 4.98 (s, 2H), 5.03 (d, 1H, *J*=12.0 Hz), 5.05 (d, 1H, *J*=12.0 Hz), 5.09 (s, 2H), 5.12 (s, 2H), 6.18 (d, 1H, *J*=2.5 Hz), 6.24 (d, 1H, *J*=2.5 Hz), 6.88–6.94 (m, 2H), 7.06 (d, 1H, *J*=1.5 Hz), 7.19–7.21 (m, 5H), 7.25–7.43 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 27.9, 68.5, 70.0, 70.1, 71.3, 71.4, 71.9, 72.4, 74.2, 75.4, 75.5, 79.7, 80.1, 80.4, 93.9, 94.4, 98.1, 102.5, 114.0, 114.7, 120.8, 127.12, 127.14, 127.39, 127.41, 127.50, 127.54, 127.7, 127.80, 127.84, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.475, 128.483, 128.5, 128.6, 131.9, 136.9, 136.96, 137.00, 137.1, 138.2, 138.5, 138.7, 149.1, 149.2, 155.3, 157.6, 158.8. Anal. Calcd for $C_{70}H_{66}O_{10}$: C, 78.78; H, 6.23. Found C, 78.82, H, 6.36.

4.2.2. Glycoside 5β. $[\alpha]_D^{21}$ +46.3 (*c* 1.04, $CHCl_3$); mp 96–98 °C; IR (KBr) 3030, 2860, 1950, 1870, 1620, 1590, 1515, 1500, 1455, 1430, 1375, 1315, 1260, 1215, 1140, 1120, 1075, 1025, 910, 855, 805, 735, 695, 620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, 3H, *J*=6.5 Hz), 2.57 (dd, 1H, *J*=16.5, 4.0 Hz), 2.74 (dd, 1H, *J*=16.5, 5.0 Hz), 3.28 (dq, 1H, *J*=9.5, 6.5 Hz), 3.40 (dd, 1H, *J*=9.5, 3.0, 6.0 Hz), 3.58 (dd, 1H, *J*=9.0, 9.0 Hz), 3.74 (d, 1H, *J*=3.0 Hz), 4.33 (d, 1H, *J*=12.0 Hz), 4.39 (ddd, 1H, *J*=5.0, 5.0, 4.0 Hz), 4.42 (d, 1H, *J*=12.0 Hz), 4.51 (s, 1H), 4.61 (d, 1H, *J*=11.0 Hz), 4.63 (d, 1H, *J*=12.5 Hz), 4.71 (d, 1H, *J*=12.5 Hz), 4.94 (d, 1H, *J*=11.0 Hz), 4.99 (d, 1H, *J*=12.0 Hz), 5.00 (d, 1H, *J*=12.0 Hz), 5.02 (d, 2H, *J*=12.0 Hz), 5.07 (s, 2H), 5.10 (s, 2H), 5.26 (d, 1H, J=5.0 Hz), 6.27 (d, 1H, *J*=2.0 Hz), 6.29 (d, 1H, *J*=2.0 Hz), 6.85 (d, 2H, *J*=1.0 Hz), 6.97 (s, 1H), 7.16–7.45 (m, 35H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 21.1, 70.0, 70.1, 71.07, 71.13, 71.2, 71.3, 72.1, 73.1, 73.4, 75.4, 79.6, 80.0, 93.5, 94.5, 98.5, 101.1, 113.5, 114.9, 119.6, 127.18, 127.19, 127.3, 127.46, 124.47, 127.5, 127.6, 127.7, 127.9, 127.97, 128.04, 128.26, 128.32, 128.39, 128.44, 128.54, 128.57, 128.63, 132.4, 136.9, 137.0, 137.2, 137.3, 138.2, 138.5, 138.6, 148.6, 148.8, 155.2, 157.7, 158.9. Anal. Calcd for $C_{70}H_{66}O_{10}$: C, 78.78; H, 6.23. Found C, 78.56, H, 6.05.

4.2.3. Synthesis of alcohol 6. To a solution of **5**α (28.5 mg, 0.0267 mmol) in CH_2Cl_2 (2.7 mL) was added water (0.14 mL) and DDQ (12.6 mg, 0.0555 mmol) at 25 °C, and the mixture was stirred for 5 h. After cooling to 0 °C, the mixture was diluted with water and Et_2O. The mixture was extracted with Et_2O (×3). The combined organic extracts were successively washed with saturated aqueous $NaHCO_3$, brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 95:5) to afford **6** (19.1 mg, 66%) as white solid.

Compound **6**. $[\alpha]_D^{23}$ +36.7 (*c* 1.04, $CHCl_3$); mp 40–42 °C; IR (KBr) 3435, 3030, 2915, 1615, 1595, 1515, 1495, 1455, 1430, 1375, 1265, 1210, 1150, 1120, 1050, 1030, 905, 810, 735, 695, 624 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, 3H, *J*=6.0 Hz), 2.46 (br s, 1H, OH), 3.36 (dd, 1H, *J*=3.0, 1.5 Hz), 3.51 (dd, 1H, *J*=9.5, 9.5 Hz), 3.73 (dd, 1H, *J*=9.5, 3.0 Hz), 3.83 (dq, 1H, *J*=9.5, 6.0 Hz), 3.95 (dd, 1H, *J*=10.0, 3.0 Hz), 4.09 (d, 1H, *J*=12.5 Hz), 4.18 (d, 1H, *J*=12.5 Hz), 4.20 (d, 1H, *J*=1.5 Hz), 4.45 (d, 1H, *J*=12.0 Hz), 4.53 (d, 1H, *J*=12.0 Hz), 4.58 (d, 1H, *J*=11.0 Hz), 4.88 (d, 1H, *J*=11.0 Hz), 4.97 (d, 1H, *J*=13.0 Hz), 4.99 (d, 1H, *J*=13.0 Hz), 5.06–5.11 (m, 5H), 5.12–5.15 (m, 3H), 6.15 (d, 1H, *J*=2.0 Hz), 6.25 (d, 1H, *J*=2.0 Hz), 6.95 (d, 1H, *J*=8.0 Hz), 7.01 (dd, 1H, *J*=8.0, 2.0 Hz), 7.14 (d, 1H, *J*=2.0 Hz), 7.16–7.42 (m, 35H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 61.9, 69.0, 70.1, 70.3, 71.2, 71.4, 72.0, 74.7, 75.31, 75.34, 77.1, 79.5, 80.1, 94.3, 94.4, 98.5, 104.7, 114.5, 114.6, 121.1, 127.1, 127.37, 127.41, 127.45, 127.48, 127.5, 127.6, 127.7, 127.8, 127.88, 127.93, 128.0, 128.1, 128.2, 128.3, 128.4, 128.47, 128.49, 128.59, 128.61, 131.3, 136.6, 136.7, 136.9, 137.0, 138.0, 138.4, 138.5, 149.1, 149.4, 155.9, 158.6, 160.9. Anal. Calcd for $C_{70}H_{66}O_{11}$: C, 77.61; H, 6.14. Found C, 77.42, H, 6.44.

4.2.4. Synthesis of ketone 7. To a solution of alcohol **6** (35.7 mg, 0.0330 mmol) in CH_2Cl_2 (3 mL) was added pyridinium dichromate (24.9 mg, 0.0662 mmol) at 0 °C. After stirring for 21 h at room temperature, second portion of pyridinium dichromate (24.9 mg, 0.0662 mmol) was added. After stirring for 19 h, the reaction was cooled to 0 °C, and diluted with Et_2O. The mixture was filtered through the Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 95:5) to give ketone **7** (30.2 mg, 85%) as while solid.

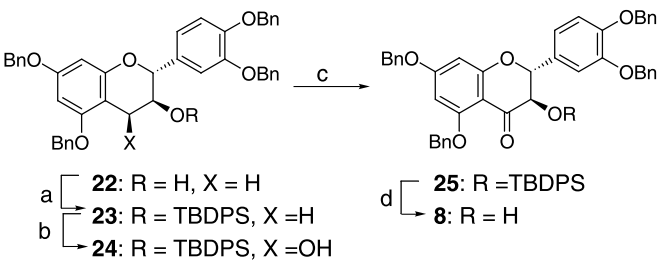
Compound **7**. $[\alpha]_D^{24}$ +25.7 (*c* 1.03, $CHCl_3$); mp 47–49 °C; IR (KBr) 3030, 2930, 1955, 1695, 1610, 1575, 1515, 1455, 1430, 1380, 1265, 1235, 1215, 1165, 1115, 1030, 820, 750, 695, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, 3H, *J*=6.0 Hz), 3.47 (dd, 1H, *J*=3.3, 1.5 Hz), 3.52 (dd, 1H, *J*=9.5, 9.5 Hz), 3.91 (dd, 1H, *J*=9.5, 3.3 Hz), 4.179 (d, 1H, *J*=1.5 Hz), 4.180 (d, 1H, *J*=12.5 Hz), 4.23 (d, 1H, *J*=12.5 Hz), 4.33 (dq, 1H, *J*=9.5, 6.0 Hz), 4.44 (d, 1H, *J*=11.0 Hz), 4.49 (d, 1H, *J*=11.5 Hz), 4.61 (d, 2H, *J*=11.5 Hz), 4.90 (d, 1H, *J*=11.5 Hz), 5.01 (s, 2H), 5.08 (s, 2H), 5.12 (d, 1H, *J*=11.0 Hz), 5.13 (s, 2H), 5.19 (s, 2H), 6.16 (d, 1H, *J*=2.2 Hz), 6.21 (d, 1H, *J*=2.2 Hz), 6.94 (d, 1H, *J*=8.0 Hz), 6.98 (dd, 1H, *J*=8.0, 2.0 Hz), 7.12 (d, 1H, *J*=2.0 Hz), 7.18–7.43 (m, 33H), 7.52 (d, 2H, *J*=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 68.8, 70.3, 70.5, 71.2, 71.4, 72.2, 72.4, 74.9, 76.0, 78.2, 79.7, 80.4, 82.3, 94.7, 95.6, 98.0, 105.5, 114.0, 114.5, 126.5, 127.1, 127.3, 127.29, 127.33, 127.38, 127.39, 127.50, 127.52, 127.6, 127.8, 127.86, 127.93, 128.1, 128.2, 128.4, 128.50, 128.52, 128.6, 128.7, 129.6, 135.7, 136.4, 136.8, 136.9, 138.3, 138.9, 139.0, 149.2, 149.8, 161.2, 163.9, 164.8, 186.7. Anal. Calcd for $C_{70}H_{64}O_{11}$: C, 77.76; H, 5.97. Found C, 77.54, H, 6.27.

4.2.5. Synthesis of astilbin (1). To a solution of **7** (39.5 mg, 0.0365 mmol) in MeOH (5.0 mL) was added Pd–black (6.0 mg) at 25 °C. After stirring under H_2 atmosphere for 50 h, the mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo. The residue was purified by LH-20 column chlomatography (MeOH) to give **1** (14.9 mg, 91%) as white solid.

Compound **1**. $[\alpha]_D^{18}$ −11 (*c* 0.52, EtOH); mp 178.5–181.5 °C; IR (KBr) 3380, 1645, 1520, 1455, 1260, 1160, 1085, 1035, 809 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.18 (d, 3H, *J*=6.0 Hz), 3.30 (dd, 1H, *J*=9.5, 9.5 Hz, overlapped with MeOH), 3.54 (dd, 1H, *J*=3.3, 1.3 Hz), 3.65 (dd, 1H, *J*=9.5, 3.3 Hz), 4.05 (d, 1H, *J*=1.3 Hz), 4.23 (dq, 1H, *J*=9.5, 6.0 Hz), 4.56 (d, 1H, *J*=10.5 Hz), 5.06 (d, 1H, *J*=10.5 Hz), 5.89 (d, 1H, *J*=2.0 Hz), 5.91 (d, 1H, *J*=2.0 Hz), 6.80 (d, 1H, *J*=8.3 Hz), 6.83 (dd, 1H, *J*=8.3, 1,8 Hz), 6.95 (d, 1H, *J*=1.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 18.6, 71.3, 72.6, 73.0, 74.6, 79.4, 84.7, 97.1, 98.2, 102.9, 103.3, 116.3, 117.1, 121.3, 130.0, 147.3, 148.2, 164.9, 166.3, 169.5, 196.7. Anal. Calcd for $C_{21}H_{22}O_{11}$: C, 56.00; H, 4.92. Found C, 56.00, H, 5.22; HRFAB-MS (*m*-nitrobenzyl alcohol, added NaI) exact mass calcd for $C_{21}H_{22}O_{11}$+Na requires *m*/*z* 473.1059. Found *m*/*z* 473.1053.

4.3. Preparation of the glycosyl acceptors, 8 and 9

Acceptor **8** was prepared from tetrabenzyl catechin (**22**) by the following sequence (Scheme 2).



Scheme 2. (a) *tert*-$BuPh_2SiCl$, imidazole, DMF (90%). (b) DDQ, H_2O, CH_2Cl_2 (76%). (c) *n*-Pr_4NRuO_4, NMO, CH_2Cl_2 (32%). (d) PPTS, EtOH (60%).

4.3.1. Silyl ether 23. To a solution of alcohol **22** (1.014 g, 1.56 mmol) in DMF (3.3 mL) was added imizazole (321 mg, 4.71 mmol) and TBDMSCl (352 mg, 2.34 mmol) at 25 °C. After stirring for 12 h at this temperature, the reaction was stopped by adding aqueous pH 7 phosphate buffer. The mixture was extracted with Et_2O (×3). The combined organic extracts were washed with brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 95:5) to give **23** (1.07 mg, 90%) as colorless oil.

Compound **23**. $[\alpha]_D^{20}$ +21.9 (*c* 1.00, $CHCl_3$); IR (neat) 3030, 2855, 1620, 1595, 1500, 1455, 1430, 1375, 1260, 1215, 1150, 1125, 1050, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.48 (s, 3H), −0.18 (s, 3H), 0.72 (s, 9H), 2.62 (dd, 1H, *J*=16.4, 9.5 Hz), 3.10 (dd, 1H, *J*=16.4, 5.8 Hz), 3.89 (ddd, 1H, *J*=9.5, 9.0, 5.8 Hz), 4.56 (d, 1H, *J*=9.0 Hz), 4.95 (d, 1H, *J*=11.7 Hz), 4.99 (d, 1H, *J*=11.7 Hz), 5.04 (d, 1H, *J*=11.7 Hz), 5.08 (d, 1H, *J*=11.9 Hz), 5.12 (d, 1H, *J*=11.9 Hz), 5.159 (d, 1H, *J*=10.3 Hz), 5.162 (d, 1H, *J*=11.9 Hz), 5.19 (d, 1H, *J*=10.3 Hz), 6.20 (d, 1H, *J*=2.2 Hz), 6.23 (d, 1H, *J*=2.2 Hz), 6.92 (s, 2H), 7.05 (s, 1H), 7.27–7.48 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.9, 17.8, 25.6, 30.3, 69.4, 69.9, 70.1, 71.2, 71.4, 82.1, 93.8, 94.3, 102.9, 114.2, 115.1, 121.1, 126.8, 127.3, 127.5, 127.72, 127.76, 127.8, 127.9, 128.42, 128.46, 128.50, 128.6, 132.7, 136.9, 137.16, 137.26, 137.29, 147.7, 149.0, 155.6, 157.5, 158.7. Anal. Calcd for $C_{49}H_{52}O_6Si$: C, 76.93; H, 6.85. Found C, 76.92, H, 7.08.

4.3.2. Alcohol 24. To a solution of **23** (35.8 mg, 0.0478 mmol) in CH_2Cl_2 (9.0 mL) was added DDQ (80.9 mg, 0.356 mmol) and H_2O (0.45 mL, 25.0 mmol) at 25 °C. After stirring for 1.5 h at this temperature, the reaction was stopped by adding water. The mixture was extracted with Et_2O (×3). The combined organic extracts were successively washed with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 95:5) to give **24** (106 mg, 76%) as white solid.

Compound **24**. $[\alpha]_D^{21}$ +31.4 (*c* 1.02, $CHCl_3$); IR (neat) 3540, 3060, 3030, 2940, 2855, 1620, 1590, 1515, 1455, 1430, 1375, 1310, 1265, 1200, 1150, 1120, 1090, 1060, 1030, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.56 (s, 3H), −0.14 (s, 3H), 0.76 (s, 9H), 2.91 (s, 1H), 3.86 (dd, 1H, *J*=9.8, 3.4 Hz), 4.93–5.00 (m, 4H), 5.09–5.21 (m, 6H), 6.16 (d, 1H, *J*=2.0 Hz), 6.24 (d, 1H, *J*=2.0 Hz), 6.94 (s, 2H), 7.08 (s, 1H), 7.29–7.48 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.7, −5.1, 17.9, 25.7, 62.3, 70.0, 71.1, 71.3, 72.7, 75.8, 94.3, 94.3, 94.4, 104.3, 114.3, 115.0, 121.4, 126.7, 127.2, 127.5, 127.6, 127.7, 127.8, 128.0, 128.4, 128.5, 129.2, 131.9, 136.5, 137.0, 137.1, 137.2, 148.8, 149.0, 156.1, 158.8, 160.7. Anal. Calcd for $C_{49}H_{52}O_7Si$: C, 73.35; H, 6.71. Found C, 75.18, H, 6.96.

4.3.3. Ketone 25. To a solution of **24** (39.8 mg, 0.0510 mmol) in CH_2Cl_2 (1.0 mL) was added *N*-methyl morpholine *N*-oxide (6.5 mg 0.081 mmol) and TPAP (1.6 mg, 0.0046 mmol) at 25 °C. After stirring for 10 h, an additional portion of TPAP (1.6 mg, 0.0046 mmol) was added, and stirred for 4.5 h. The mixture was diluted with CH_2Cl_2, filtered through the Celite pad. The filtrate was concentrated in vacuo, and extracted with Et_2O (×3), and the combined organic extracts were successively washed with saturated aqueous $NaHCO_3$, brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 98:2) to give **25** (12.6 mg, 32%) as white solid.

Compound **25**. $[\alpha]_D^{20}$ +19.7 (*c* 1.02, $CHCl_3$); IR (KBr) 3065, 3030, 2925, 2855, 1695, 1610, 1575, 1515, 1455, 1430, 1375, 130.5, 1260, 1210. 1160, 1115, 1025, 875, 840, 780, 735, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.31 (s, 3H), 0.13 (s, 3H), 0.63 (s, 9H), 4.30 (d, 1H, *J*=11.2 Hz), 4.99 (s, 2H), 5.03 (d, 1H, *J*=11.2 Hz), 5.14 (d, 1H, *J*=12.0 Hz), 5.19 (s, 2H), 5.20 (d, 1H, *J*=12.0 Hz), 5.21 (s, 2H), 6.16 (d, 1H, *J*=2.0 Hz), 6.19 (d, 1H, *J*=2.0 Hz), 6.94 (d, 1H, *J*=8.3 Hz), 6.99 (dd, 1H, *J*=8.3, 2.0 Hz), 7.11 (d, 1H, *J*=2.0 Hz), 7.28–7.53 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −6.1, −4.2, 18.3, 25.5, 70.2, 70.4, 71.3, 76.0, 76.6, 83.7, 94.6, 95.7, 105.0, 114.1, 115.0, 121.2, 126.4, 127.2. 127.3, 127.5, 127.8,128.3, 128.5, 128.7, 130.9, 135.7, 136.6, 137.10, 137.13, 149.0, 149.3, 160.9, 164.1, 164.6, 189.6. Anal. Calcd for $C_{49}H_{50}O_7Si$: C, 75.55; H, 6.47. Found C, 75.26, H, 6.71.

4.3.4. Alcohol 8. To a solution of **25** (8.6 mg, 0.011 mmol) in EtOH (0.5 mL) was added PPTS (5 mg) at 25 °C. After stirring for 66 h, the reaction was stopped by adding water. The mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 95:5) to give **8** (4.5 mg, 60%) as white solid.

$[\alpha]_D^{21}$ −9.0 (*c* 0.46, $CHCl_3$); mp 193.5–194.2 °C; IR (KBr) 3465, 3035, 2925, 1675, 1610, 1580, 1515, 1440, 1375, 1310, 1260, 1215, 1170, 1135, 1120, 1010, 810, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.06 (br s, 1H), 4.42 (d, 1H, *J*=12.2 Hz), 4.95 (d, 1H, *J*=12.2 Hz), 5.05 (s, 2H), 5.10–5.25 (m, 6H), 6.19 (d, 1H, *J*=2.2 Hz), 6.26 (d, 1H, *J*=2.2 Hz), 7.00 (d, 1H, *J*=8.3 Hz), 7.09 (dd, 1H, *J*=8.3, 1.9 Hz), 7.18 (d, 1H, *J*=1.9 Hz), 7.27–7.58 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.4, 70.5, 71.2, 71.4, 72.7, 83.1, 94.8, 95.2, 103.4, 114.1, 114.7, 121.0, 126.6, 127.2, 127.5, 127.6, 127.8, 127.85, 127.92, 128.48, 128.51, 128.7, 128.8, 129.6, 135.5, 136.0, 137.1, 137.2, 149.1, 149.8, 160.9, 164.8, 165.9, 190.6. Anal. Calcd for $C_{43}H_{36}O_7$: C, 77.69; H, 5.46. Found C, 77.41; H, 5.73.

4.3.5. Preparation of alcohol 9. To a solution of **22** (56 mg, 0.086 mmol) in $CHCl_3$ (10 mL) was added MeOH (0.5 mL) and DDQ (39 mg, 0.017 mmol) at 25 °C. After stirring for 4 h, the mixture was diluted with water and Et_2O, and the products were extracted with Et_2O (×4). The combined organic extracts were successively washed with saturated aqueous $NaHCO_3$, brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 95:5) to give **9** (45 mg, 79%) as white solid.

Compound **9**. $[\alpha]_D^{21}$ −53.1 (*c* 1.02, $CHCl_3$); mp 142–144 °C; IR (KBr) 3415, 3030, 2910, 1620, 1590, 1515, 1500, 1430, 1380, 1260, 1220, 1165, 1120, 1070, 1030, 815, 735, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (d, 1H, *J*=9.0 Hz), 3.50 (s, 6H), 3.89 (ddd, 1H, *J*=10.3, 9.0, 3.7 Hz), 4.73 (d, 1H, *J*=3.7 Hz), 4.94 (d, 1H, *J*=10.3 Hz), 4.99 (s, 2H), 5.01 (d, 1H, *J*=11.2 Hz), 5.07 (d, 1H, *J*=11.2 Hz), 5.16 (s,

4H), 6.17 (d, 1H, *J*=2.1 Hz), 6.27 (d, 1H, *J*=2.1 Hz), 6.96 (d, 1H, *J*=8.3 Hz), 7.01 (dd, 1H, *J*=8.3, 1.5 Hz), 7.08 (d, 1H, *J*=1.5 Hz), 7.27–7.64 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.4, 69.8, 70.1, 70.6, 71.2, 71.3, 93.3, 94.2, 103.0, 114.3, 114.7, 121.2, 127.2, 127.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.5, 128.6, 131.4, 136.4, 136.5, 137.2, 137.3, 149.0, 149.3, 156.2, 158.7, 160.9. Anal. Calcd for $C_{44}H_{40}O_7$: C, 77.63; H, 5.92. Found C, 77.35, H, 6.12.

4.4. Cp_2ZrCl_2–$AgClO_4$-Mediated substitution reaction of 11 with ketene silyl acetal 12 under the stoichiometric conditions

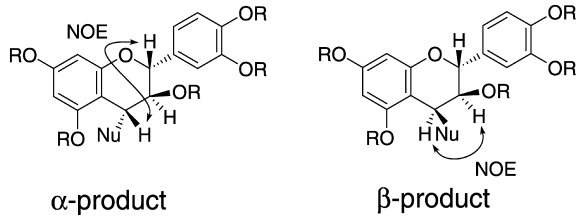
The promoter was prepared in situ by stirring the mixture of Cp_2ZrCl_2 (22 mg, 0.075 mmol) and $AgClO_4$ (31 mg, 0.15 mmol) in the presence of powdered molecular sieves 4 Å (63 mg) in CH_2Cl_2 (0.5 mL) for 5 min at room temperature. To this suspension was added a mixture of **11** (50 mg, 0.063 mmol) and **12** (38 mg, 0.19 mmol) in CH_2Cl_2 (0.75 mL) at −78 °C. The reaction mixture was stirred for 10 min at −78 °C. The reaction was stopped by adding saturated aqueous $NaHCO_3$. The mixture was filtered through a Celite pad, and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc, 3:1) to afford **13** (42 mg, 80%) as amorphous solid.

4.5. Cp_2ZrCl_2–$AgClO_4$-Mediated substitution reaction of 11 with ketene silyl acetal 12 under the catalytic conditions

The promoter was prepared in situ by stirring the mixture of Cp_2ZrCl_2 (3.7 mg, 0.013 mmol) and $AgClO_4$ (5.2 mg, 0.025 mmol) in the presence of powdered molecular sieves 4 Å (125 mg) in CH_2Cl_2 (1.0 mL) for 5 min at room temperature. To this suspension was added a mixture of **11** (100 mg, 0.125 mmol) and **12** (76 mg, 0.38 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C. The reaction mixture was stirred for 15 min at −78 °C. The reaction was stopped by adding saturated aqueous $NaHCO_3$. The mixture was filtered through a Celite pad, and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc, 3:1) to afford **13** (88 mg, 85%) as amorphous solid.

4.5.1. Ethyl ester 13. The title compound is a mixture of two diastereomers, α/β, 16:84. IR (neat) 3064, 3031, 2903 (br), 1732, 1616, 1592, 1514, 1498, 1455, 1439, 1376, 1264, 1216, 1152, 1028, 811, 736, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, conspicuous signal of minor isomer was marked with an asterisk) δ 1.06* (t, 3H, *J*=7.1 Hz), 1.07 (t, 3H, *J*=7.1 Hz), 2.24* (dd, 1H, *J*=15.8, 8.5 Hz), 2.61* (dd, 1H, *J*=15.8, 3.2 Hz), 2.64–2.71 (m, 2H), 3.44–3.48* (m, 1H), 3.71 (dd, 1H, *J*=9.9, 5.9 Hz), 3.77 (dq, 1H, *J*=10.8, 7.1 Hz), 3.85 (d, 1H, *J*=11.4 Hz), 3.88 (dq, 1H, *J*=10.8, 7.1 Hz), 3.96* (dd, 1H, *J*=6.5, 5.9 Hz), 3.99* (d, 1H, *J*=11.5 Hz), 4.17–4.21 (m, 1H), 4.29 (d, 1H, *J*=11.4 Hz), 4.77 (d, 1H, *J*=9.9 Hz), 4.84* (d, 2H, *J*=6.6 Hz), 4.95 (d, 1H, *J*=11.8 Hz), 4.97 (d, 1H, *J*=11.8 Hz), 5.01 (d, 1H, *J*=12.1 Hz), 5.08 (s, 2H), 5.09 (d, 1H, *J*=12.1 Hz), 5.10* (s, 2H), 5.17* (s, 2H), 5.20 (s, 2H), 6.16 (d, 1H, *J*=2.3 Hz), 6.26* (d, 1H, *J*=2.4 Hz), 6.27 (d, 1H, *J*=2.3 Hz), 6.27* (d, 1H, *J*=2.4 Hz), 6.81–6.84 (m, 2H), 6.84* (d, 1H, *J*=2.0 Hz), 6.86* (d, 1H, *J*=1.8 Hz), 6.92–6.99 (m, 3H), 7.10–7.15 (m, 3H), 7.27–7.47 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 30.7, 36.6, 60.0, 69.8, 70.0, 70.9, 71.3, 72.2, 75.9, 77.2, 93.8, 94.1, 105.5, 113.9, 114.7, 121.2, 126.7, 127.2, 127.3, 127.5, 127.70, 127.74, 127.8, 128.0, 128.2, 128.42, 128.44, 128.46, 128.6, 132.0, 136.7, 137.2, 137.3, 137.7, 148.8, 155.0, 157.5, 159.2, 172.4. Anal. Calcd for $C_{54}H_{50}O_8$: C, 78.43; H, 6.09. Found C, 78.21, H, 6.30.

The stereochemical assignment and the ratio of the isomers were determined by NMR. Although the α- and β- were generally inseparable, the spectra were resolved enough to assess the selectivity, and both stereoisomers showed diagnostic NOE as shown below.



4.5.2. Isopropyl ester 18. IR (neat) 3064, 3031, 2979, 2934 (br), 1715, 1615, 1590, 1514, 1498, 1454, 1374, 1261, 1218, 1144, 1106, 1028, 910, 817, 734, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.11 (d, 3H, *J*=6.2 Hz), 1.15 (s, 3H), 1.15 (d, 3H, *J*=5.1 Hz), 3.92 (s, 1H), 4.03 (d, 1H, *J*=11.2 Hz), 4.15 (d, 1H, *J*=8.1 Hz), 4.36 (d, 1H, *J*=8.1 Hz), 4.50 (d, 1H, *J*=11.2 Hz), 4.91–4.97 (m, 1H), 4.96 (d, 1H, *J*=11.9 Hz), 4.98 (d, 1H, *J*=11.9 Hz), 5.04 (s, 2H), 5.12 (s, 2H), 5.18 (s, 2H), 6.31 (d, 1H, *J*=1.1 Hz), 6.36 (d, 1H, *J*=1.1 Hz), 6.93 (d, 1H, *J*=8.2 Hz), 7.01 (d, 1H, *J*=8.2 Hz), 7.13–7.16 (m, 3H), 7.19–7.24 (m, 3H), 7.27–7.48 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 25.6, 25.7, 44.3, 47.9, 68.0, 70.0, 70.1, 71.0, 71.1, 71.2, 84.2, 84.5, 95.4, 96.3, 108.1, 113.3, 115.0, 119.7, 126.9, 127.2, 127.3, 127.59, 127.64, 127.70, 127.72, 128.0, 128.2, 128.41, 128.44, 128.6, 133.8, 136.7, 137.0, 137.2, 137.3, 138.3, 148.5, 148.9, 158.6, 158.9, 159.9, 177.0. Anal. Calcd for $C_{57}H_{56}O_8$: C, 78.78; H, 6.49. Found C, 78.86, H, 6.68.

4.5.3. Sulfide 19. The title compound is a mixture of two diastereomers, α/β, 5:95. IR (neat) 3063, 3031, 2925, 2868, 1615, 1591, 1513, 1498, 1454, 1438, 1377, 1310, 1263, 1217, 1182, 1151, 1118, 1027, 812, 741, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, conspicuous signal of minor isomer was marked with an asterisk) δ 3.60 (d, 1H, *J*=11.7 Hz), 3.67 (d, 1H, *J*=11.7 Hz), 3.80 (dd, 1H, *J*=9.5, 3.9 Hz), 3.90* (d, 1H, *J*=11.5 Hz), 4.02* (dd, 1H, *J*=10.0, 7.4 Hz), 4.33* (d, 1H, *J*=11.5 Hz), 4.54* (d, 1H, *J*=3.9 Hz), 4.82 (d, 1H, *J*=3.9 Hz), 4.97 (s, 2H), 5.03 (d, 1H, *J*=11.9 Hz), 5.04 (d, 1H, *J*=11.2 Hz), 5.09 (d, 1H, *J*=11.2 Hz), 5.11 (d, 1H, *J*=11.9 Hz), 5.21 (s, 2H), 5.35 (d, 1H, *J*=9.5 Hz), 6.14 (d, 1H, *J*=2.0 Hz), 6.23* (d, 1H, *J*=2.2 Hz), 6.26 (d, 1H, *J*=2.0 Hz), 6.30* (d, 1H, *J*=2.2 Hz), 6.48 (d, 2H, *J*=8.3 Hz), 6.93–7.52 (m, 31H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.7, 70.0, 70.6, 70.9, 71.3, 71.4, 77.7, 93.7, 93.9, 102.6, 114.2, 114.7, 121.3, 126.9,

127.2, 127.3, 127.5, 127.7, 127.8, 128.0, 128.2, 128.26, 128.32, 128.40, 128.45, 128.6, 131.9, 133.6, 136.4, 136.6, 136.8, 137.2, 137.3, 137.4, 148.77, 148.81, 155.1, 157.5, 160.2. Anal. Calcd for $C_{56}H_{48}O_6S$: C, 79.22; H, 5.70; S, 3.78. Found C, 78.95, H, 5.85; S, 3.89.

4.5.4. Azide 20. IR (neat) 3031, 2872, 2099, 1618, 1593, 1513, 1498, 1454, 1377, 1315, 1263, 1216, 1190, 1152, 1123, 1090, 1028, 911, 814, 736, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.73* (dd, 1H, J=8.5, 6.2 Hz), 3.68 (dd, 1H, J=10.1, 3.9 Hz), 3.95* (d, 1H, J=11.0 Hz), 4.08 (d, 1H, J=11.9 Hz), 4.21 (d, 1H, J=11.9 Hz), 4.34* (d, 1H, J=11.0 Hz), 4.76* (d, 1H, J=8.5 Hz), 4.77* (d, 1H, J=6.2 Hz), 4.97 (s, 2H), 5.00 (d, 1H, J=10.1 Hz), 5.03 (d, 1H, J=11.8 Hz), 5.05 (d, 1H, J=3.9 Hz), 5.06 (d, 1H, J=12.2 Hz), 5.10 (d, 1H, J=11.8 Hz), 5.12 (d, 1H, J=12.2 Hz), 5.22 (s, 2H), 6.14 (d, 1H, J=2.2 Hz), 6.26 (d, 1H, J=2.2 Hz), 6.92–6.94 (m, 2H), 6.95–7.03 (m, 3H), 7.15–7.19 (m, 3H), 7.27–7.44 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.0, 70.2, 70.5, 71.1, 71.4, 72.1, 75.9, 76.7, 93.8, 94.4, 101.0, 114.2, 115.0, 121.1, 127.3, 127.4, 127.53, 127.57, 127.78, 127.84, 128.0, 128.1, 128.2, 128.3, 128.49, 128.51, 128.65, 131.3, 136.4, 136.5, 137.16, 137.20, 137.28, 148.9, 149.1, 155.8, 158.4, 161.2. Anal. Calcd for $C_{50}H_{43}N_3O_6$: C, 76.81; H, 5.54; N, 5.37. Found C, 76.90, H, 5.81; N, 5.34.

4.5.5. Trimethyl ether 21. The title compound is a mixture of two diastereomers, α/β, 84:16. IR (neat) 3030, 2935, 1606, 1591, 1512, 1496, 1454, 1377, 1263, 1215, 1149, 1119 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$, conspicuous signal of minor isomer was marked with an asterisk) δ *3.28 (s, 3H), 3.39 (s, 6H), 3.51 (d, 1H, J=10.8 Hz), *3.56 (s, 3H), 3.66 (d, 1H, J=10.8 Hz), 3.79 (s, 3H), 3.98 (dd, 1H, J=8.2, 9.7 Hz), *4.07 (d, 1H, J=11.8 Hz), *4.34 (d, 1H, J=11.8 Hz), 4.55 (d, 1H, J=11.4 Hz), 4.59 (d, 1H, J=9.7 Hz), 4.76 (d, 1H, J=11.4 Hz), 4.77 (d, 1H, J=8.2 Hz), 4.95 (s, 2H), 5.09 (d, 1H, J=12.5 Hz), 5.15 (d, 1H, J=12.5 Hz), 5.19 (s, 2H), 5.88–5.95 (br s, 1H), 6.00–6.07 (br s, 1H), *6.11 (d, 1H, J=2.1 Hz), 6.12 (d, 1H, J=2.4 Hz), *6.17 (d, 1H, J=2.1 Hz), 6.23 (d, 1H, J=2.4 Hz), 6.59–6.63 (m, 2H), 6.73–7.46 (m, 26H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3, 55.2, 56.0, 69.9, 70.0, 71.1, 71.4, 73.8, 81.3, 81.5, 91.2, 92.1, 94.4, 94.5, 109.5, 114.2, 114.5, 115.1, 120.9, 127.1, 127.3, 127.37, 127.39, 127.5, 127.7, 127.8, 127.9, 128.0, 128.2, 128.37, 128.40, 128.43, 133.0, 136.9, 137.1, 137.26, 137.32, 138.0, 148.7, 148.8, 157.1, 157.65, 157.74, 158.6, 159.3; Anal. calcd for $C_{59}H_{54}O_9$: C, 78.12; H, 6.00. Found: C, 78.39; H, 6.27.

Acknowledgements

Partial financial supports from 21st Century COE Program (Chemistry) and that Suntory Corporation are gratefully acknowledged.

References and notes

1. (a) In *Lewis Acid Reagents*. Yamamoto, H., Ed.; Oxford University Press: New York, 1999. (b) *Lewis acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vols. 1 and 2.
2. Suzuki, K.; Hintermann, L.; Yamanoi, S. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 282–318.
3. (a) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567–3570. (b) Suzuki, K.; Maeta, H.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3571–3574. (c) Matsumoto, T.; Hosoya, T.; Suzuki, K. *Tetrahedron. Lett.* **1990**, *31*, 4629–4632.
4. For selected examples, see; (a) Matsuzaki, Y.; Ito, Y.; Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1993**, *34*, 1061–1064. (b) Nicolaou, K. C.; Caulfield, T. J.; Kataoka, H.; Stylianides, N. A. *J. Am. Chem. Soc.* **1990**, *112*, 3693–3695.
5. Suzuki, K.; Maeta, H.; Matsumoto, T. *Tetrahedron Lett.* **1989**, *30*, 4853–4856.
6. For isolation, see: (a) Hayashi, K.; Ouchi, K. *Shigenkagaku Kenkyusyo Iho* **1950**, *17–18*, 19–24. (b) Shimada, H.; Sawada, T.; Fukuda, S. *Yakugaku Zasshi* **1952**, *72*, 578–580. For bioactivity, see: (c) Han, L.-K.; Ninomiya, H.; Taniguchi, M.; Baba, K.; Kimura, Y.; Okuda, H. *J. Nat. Prod.* **1998**, *61*, 1006–1011. (d) Britto, J. D.; Manichckam, V. S.; Gopalakrishinam, S.; Ushioda, T.; Tanaka, N. *Chem. Pharm. Bull.* **1995**, *43*, 338–339. (e) Hiraguchi, H.; Ohmi, I.; Fukuda, A.; Tamura, Y.; Mizutani, K.; Tanaka, O.; Chou, W.-H. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 651–654.
7. Ohmori, K.; Ohrui, H.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 5537–5541.
8. (a) Kawamoto, H.; Nakatsubo, F.; Murakami, K. *Mokuzai Gakkaishi* **1991**, *37*, 488–493. (b) Kawamoto, H.; Nakatsubo, F.; Murakami, K. *Synth. Commun.* **1996**, *36*, 531–534.
9. (a) Fügedi, P. *J. Carbohydr. Chem.* **1987**, *6*, 377–398. (b) Paulsen, H.; Kutschker, W.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3233–3241.
10. Hosoya, T.; Takashiro, E.; Yamamoto, Y.; Matsumoto, T.; Suzuki, K. *Heterocycles* **1996**, *42*, 397–414, and references therein.
11. (a) *The Handbook of Natural Flavonoids*; Harborne, J. B., Baxter, H., Eds.; Wiley: Chichester, 1999; Vol. 2, p 499. (b) Hwang, T.-H.; Kashiwada, Y.; Nonaka, G.; Nishioka, I. *Phytochemistry* **1990**, *29*, 279–282. For isolation of related compounds: see: (c) Karl, C.; Pedersen, A. P.; Müller, G. *Z. Naturforsch* **1981**, *36C*, 607–610. (d) Tanaka, N.; Orii, R.; Ogasa, K.; Wada, H.; Murakami, T.; Saiki, Y.; Chen, C.-M. *Chem. Pharm. Bull.* **1991**, *39*, 55–59. (e) Baek, N.-I.; Kennelly, E. J.; Kardono, L. B. S.; Tsauri, S.; Padmawinata, K.; Soejarto, D. D.; Kinghorn, A. D. *Phytochemistry* **1994**, *36*, 513–518.
12. Ohmori, K.; Ushimaru, N.; Suzuki, K. *Tetrahedron Lett.* **2002**, *43*, 7753–7756.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1375–1383
Tetrahedron

Pentadienyl transfer reagents based on zirconium: preparation and reactions with carbonyl compounds

Philippe Bertus, Ludovic Drouin, Christophe Laroche and Jan Szymoniak*

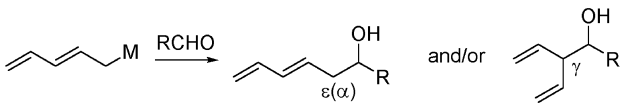
Réactions Sélectives et Applications (UMR 6519), CNRS and Université de Reims, 51687 Reims Cedex 2, France

Received 26 June 2003; revised 28 August 2003; accepted 31 August 2003

Abstract—A variety of 2,4-pentadienylzirconiums were generated by reacting pentadienyl ethers with zirconocene 'Cp_2Zr'. These complexes underwent a highly γ-regioselective and *anti*-stereoselective in situ addition with carbonyl compounds to afford bis(homoallylic) alcohols in good yields. The reversal of *anti* vs *syn* selectivity was simply achieved with BF_3, thus expanding the synthetic potential of the reaction.

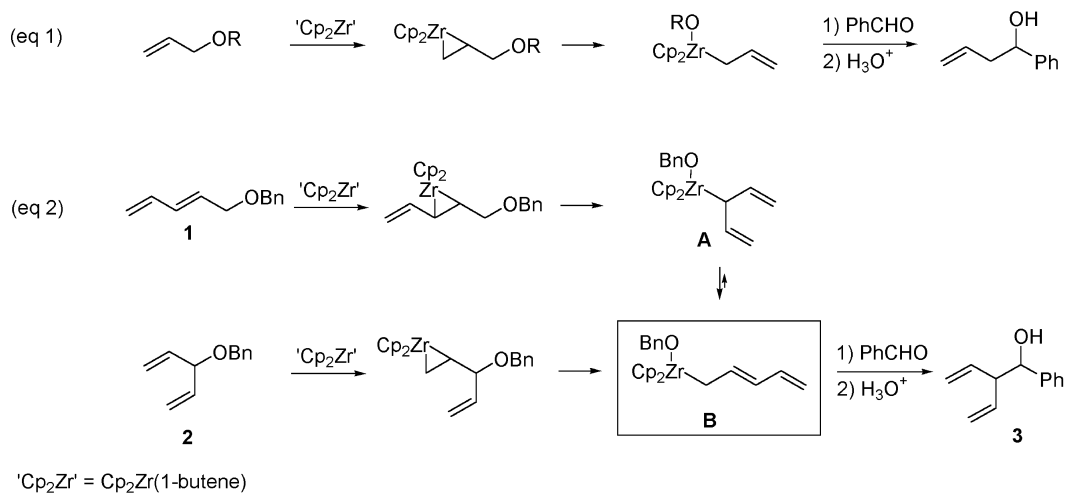
1. Introduction

Allylmetals are important reagents for the stereoselective carbon–carbon bond-forming reactions.[1] Particularly, they react with carbonyl compounds to produce homoallylic alcohols, which are useful synthetic intermediates. In contrast, the analogous 2,4-pentadienylmetals employing reactions have been much less investigated.[2] The regiochemical outcome of the pentadienylation reactions is shown in Scheme 1.



Scheme 1.

When the reaction occurs at the ε (or α)-carbon in the complex, a linear alcohol is formed, whereas at the γ-carbon a branched alcohol is obtained. The regioselectivity of these reactions has been demonstrated to vary with the metal.[2] Whereas lithium, potassium and magnesium generally give poor regioselectivity, the addition at the γ-position preferentially occurs with indium, titanium, boron, zinc or chromium, and at the ε-position with silicon and tin. Furthermore, the stereoselectivity of the pentadienylation reactions have not been studied systematically. Both *anti*



Scheme 2.

Keywords: Homoallylic alcohols; Pentadienylation reaction; Stereocontrol; Zirconium.
* Corresponding author. Fax: +33-326-913-166; e-mail address: jan.szymoniak@univ-reims.fr

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.08.065

and/or *syn* diastereoselectivity have been observed depending on the metal.

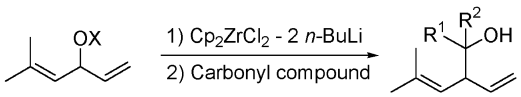
Pentadienylmetals are typically prepared by transmetalation from lithium or potassium pentadienyl precursors or by Barbier-type reactions from the corresponding pentadienyl bromides. The synthetic potential of pentadienylmetals would be considerably enhanced if these complexes could be prepared from chemically more stable and readily available starting materials.[3] With this aim in view we have reported a preliminary work on a simple and practical way of preparing pentadienylzirconocenes from dienyl ethers.[4] These complexes proved to react with aldehydes in the γ-selective manner. We disclose herein a full account on the reactions involving pentadienylzirconium reagents.

2. Results and discussion

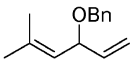
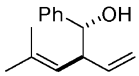
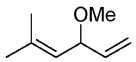
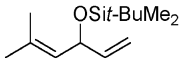
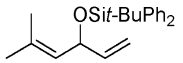
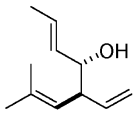
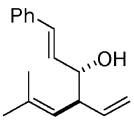
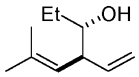
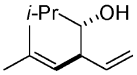
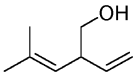
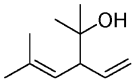
It is known that allylic ethers react with (1-butene)zirconocene[5] to afford allylzirconium derivatives.[6] The reaction occurs through ligand exchange, formation of a zirconacyclopropane and the successive β-elimination of the alkoxy group (Scheme 2, Eq. (1)).

We have demonstrated that, analogously, pentadienylzirconium compounds could be generated from dienyl ethers (Scheme 2, Eq. (2)).[7] It is noteworthy that the same complex **B** was solely obtained from both the linear ether **1** and the ramified ether **2**. We assumed the zirconium fragment (Cp_2ZrOBn) would migrate in **A** to a less hindered site of the allyl moiety, leading to the thermodynamically more favorable complex **B**.[8] Accordingly, both linear and

Table 1. Zr-mediated pentadienylation of carbonyl compounds



4a-d **5a-g**

Entry	Ether	Carbonyl compound	*T* (°C)	Product[a]	Yield (%)[b] (*anti*/*syn*)[c]
1	**4a** 	PhCHO	20	**5a** 	96 (86:14)
2	**4b** 	PhCHO	20	**5a**	55 (84:16)
3	**4c** 	PhCHO	20	**5a**	94 (87:13)
4	**4d** 	PhCHO	20	**5a**	93 (94:6)
5	**4a**	PhCHO	−78	**5a**	78 (92:8)
6	**4a**	MeCH=CHCHO	−78	**5b** 	83 (93:7)
7	**4a**	PhCH=CHCHO	−78	**5c** 	93 (92:8)
8	**4a**	EtCHO	−78	**5d** 	57 (>95:5)
9	**4a**	*i*-PrCHO	−78	**5e** 	64 (>95:5)
10	**4a**	$(HCHO)_n$[d]	−78	**5f** 	81 (−)
11	**4a**	Me_2CO	−78	**5g** 	70 (−)

[a] Only the major stereoisomer is shown.
[b] Isolated yield.
[c] *anti*/*syn* Ratio determinated by ^1H NMR.
[d] Paraformaldehyde was used.

ramified pentadienyl ethers can be employed as starting materials to form the unique penta-2,4-dienylzirconium species.

The pentadienylzirconocenes were typically formed from the pentadienyl ether, Cp_2ZrCl_2 and 2*n*-BuLi by applying the Taguchi protocol for the formation of allylzirconocenes[6d] or better by a modified procedure.[4,9] The zirconium species thus generated were further used for the pentadienylation reactions. In the first experiment, the preformed complex **B** was reacted with benzaldehyde to produce the alcohol **3** regioselectively, in 60–70% yield (Scheme 2).[4] To investigate both the regio- and the stereoselectivity of the reaction we next used the pentadienyl ethers **4a–d** and various carbonyl compounds as substrates. The results are summarized in Table 1.

2.1. Temperature and structure effects on stereoselectivity

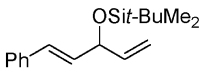
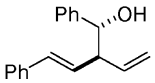
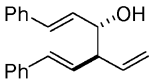
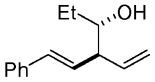
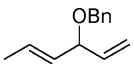
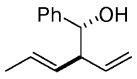
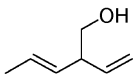
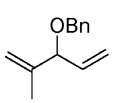
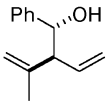
In all cases the reaction occurred regioselectively at the γ-carbon of the complex to afford the branched alcohols **5a–g** solely. Furthermore, the pentadienylation of the aldehydes appeared to be markedly *anti*-stereoselective.[10] The stereoselectivity of the reaction employing PhCHO can slightly be increased by introducing a bulky OX group in the ether. Whereas the diastereomeric ratio remains almost constant for X=Bn, Me and Si*t*-BuMe$_2$ (entries 1–3), an improvement in the *anti* diastereoselection was observed for X=Si*t*-BuPh$_2$ (entry 4). The stereoselectivity of the reaction was increased further by adding the aldehyde at −78 °C rather than at 20 °C. Two examples employing the ether **4a** and benzaldehyde are given (entries 1 and 5). In these conditions, a high *anti*/*syn* ratio remains almost constant (92:8 to >95:5) for the aromatic, α,β-unsaturated as well as the aliphatic aldehydes (entries 5–9). Both regio- and stereochemistry of the reaction are consistent with a conventional six-membered chair-like transition state, as proposed for the simpler allylzirconation reactions.[1] The primary alcohol **5f** and the tertiary alcohol **5g** (a terpene, santolina alcohol) can finally be obtained by employing respectively paraformaldehyde and acetone (entries 10 and 11).

2.2. Ether components

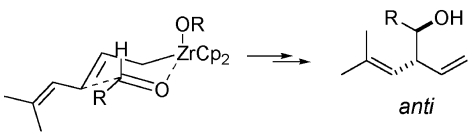
The synthetic utility of the reaction is also displayed by the possible use of various penta-1,4-dienyl ethers as substrates. Both 1- and 2-substituted pentadienyl ethers were employed, and the examples of these reactions are depicted in Table 2.

As for the non-substituted and 1,1-disubstituted pentadienyl ether, also in these cases γ-regioisomers were obtained solely in good yields. All the reactions involving 1-substituted ethers (entries 1–4) proceeded with a high *anti* diastereoselectivity (*anti*/*syn*≅ 95:5). The high level of *anti* selection appeared to be independent both of the nature of the aldehyde (aromatic, α,β-unsaturated or aliphatic, entries 1–3, respectively), and of the alkoxy group in the ether (X=Si*t*-BuMe$_2$ or Bn, entries 1–3 vs 4). We observed a partial *E* to *Z* isomerization of the double bond in alcohols **7d** and **7e** derived from the ether **6b**. Finally, only a moderate decrease in *anti* selectivity has been noticed when using a 2-substituted ether instead of the 1-substituted analogue (alcohols **7d** and **7f**, entries 4 and 6).

Table 2. Zr-mediated pentadienylations (following)

Entry	Ether	Aldehyde	Product[a]	Yield (%)[b] (*anti*/*syn*)[c]
1	**6a** 	PhCHO	**7a** 	90 (>95:5)
2	**6a**	PhCH=CHCHO	**7b** 	81 (>95:5)
3	**6a**	EtCHO	**7c** 	90 (93:7)
4	**6b** 	PhCHO	**7d** 	85 (>95:5)[d]
5	**6b**	$(HCHO)_n$	**7e** 	62 (−)[e]
6	**6c** 	PhCHO	**7f** 	76 (88:12)

[a] Only the major stereoisomer is shown.
[b] Isolated yield.
[c] *anti*/*syn* Ratio determinated by ^{1}H NMR.
[d] *E*/*Z* isomers=80:20.
[e] *E*/*Z* isomers=71:29.



Scheme 3.

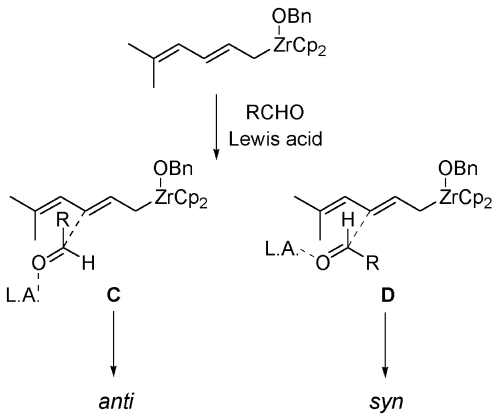
2.3. Reversal of *anti* to *syn* diastereoselectivity

At this stage, the synthetic limitation of the pentadienylation reactions lied in their invariably predominant *anti* stereochemistry. We made efforts to control the stereochemistry of these reactions, i.e. to ensure that it could be reversed leading mainly to the *syn* configurated alcohols. The *anti* stereochemistry can be explained by assuming a conventional six-membered chair-like transition state, as for the simpler allylzirconation reactions (Scheme 3). We then examined whether it was possible to modify the reaction conditions to favour a non-cyclic mechanism[1] over the cyclic one.

Lewis acids[11] and polar solvents, especially HMPA,[12] have been shown to affect the stereochemistry of the reactions originally proceeding through a six-membered transition state. We first examined the effect of HMPA as co-solvent and noticed that no change in stereochemistry took place. To promote a non-cyclic mechanism for the pentadienylation reactions, we then turned to the use of a Lewis acid. After the complex had been generated, $BF_3{\cdot}OEt_2$ (1 equiv.) was added at −78 °C, followed by the aldehyde, and the reaction mixture was allowed to warm to 20 °C. We noticed that a reversal of *anti* to *syn* stereoselectivity took place by applying this modified procedure (Procedure B, Section 3).[13] The results of the reactions with or without BF_3, employing ethers **4a** and **6a**–**c**, as well as the aromatic, α,β-unsaturated and aliphatic aldehydes are summarized in Table 3.

We noticed that a spectacular reversal of *anti* to *syn* stereoselectivity invariably took place when using the aromatic or α,β-unsaturated aldehydes, i.e. benzaldehyde (entries 1, 6, 9, and 10), cinnamaldehyde (entries 3 and 7) and crotonaldehyde (entry 2). In contrast, the effect of modifying the stereoselectivity was only moderate for the aliphatic aldehydes (entries 4, 5, and 8).

The Lewis acid-induced reversal of *anti* to *syn* stereoselectivity in the reactions of η^1-allyltitaniums with



Scheme 4.

carbonyl compounds was observed by Reetz.[11] The predominant *syn* selectivity in the presence of a Lewis acid was considered to be consistent with a non-cyclic antiperiplanar transition state.[14] We assumed tentatively, that also in our case, the reversal of *anti* to *syn* selectivity can be explained by a non-cyclic mechanism operating with BF_3 as presented in Scheme 4.[15]

A higher *syn* selectivity for the aromatic or unsaturated than for the aliphatic aldehydes is not entirely clear at present. This could possibly be rationalized by additional destabilizing π–π interactions in the transition structure **C**, thus favouring all the more **D**. However, the mechanism of the Lewis acid-mediated reactions could even be more complicated.[16] Systematic mechanistic studies are needed to fully elucidate the effect of Lewis acids on the stereoselectivity.

In summary, we have presented a practical procedure for preparing bis(homoallylic) alcohols in a highly γ-regioselective and *anti*-stereoselective manner. Furthermore, in the presence of a Lewis acid, the stereochemistry can be reversed leading predominantly to the *syn*-configurated products.

3. Experimental

3.1. General

All reactions were conducted under an atmosphere of dry

Table 3. Effect of $BF_3{\cdot}OEt_2$ on the *anti* vs *syn* diastereoselectivity

Entry	Ether	Carbonyl compound	Product	*anti*/*syn*[a]	$BF_3{\cdot}OEt_2$ *anti*/*syn*[a]
1	**4a**	PhCHO	**5a**	92:8	26:74
2	**4a**	MeCH=CHCHO	**5b**	93:7	18:82
3	**4a**	PhCH=CHCHO	**5c**	92:8	20:80
4	**4a**	EtCHO	**5d**	>95:5	68:32
5	**4a**	*i*-PrCHO	**5e**	>95:5	57:43
6	**6a**	PhCHO	**7a**	>95:5	16:84
7	**6a**	PhCH=CHCHO	**7b**	>95:5	18:82
8	**6a**	EtCHO	**7c**	93:7	50:50
9	**6b**	PhCHO	**7d**	>95:5	21:79
10	**6c**	PhCHO	**7f**	88:12	35:65[b]

[a] *anti*/*syn* Ratio determinated by ^{1}H NMR.
[b] ε-Addition product, i.e. 3-methyl-1-phenylhexa-3,5-dien-1-ol (**8**), was also formed in 29% yield.

argon using standard Schlenk techniques. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-250 or DRX-500 spectrometer. IR spectra were recorded on a Nicolet Avatar 320 instrument. Mass spectra were recorded on a ThermoFinnigan Trace MS spectrometer. Cp_2ZrCl_2 and vinylmagnesium bromide reagents were used as received. *n*-BuLi was titrated with diphenylacetic acid in THF prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use.

3.2. Preparation of ethers

3.2.1. 4-Benzyloxy-2-methylhexa-2,5-diene (4a). A solution of 3-methylbut-2-enal (7.7 mL, 80 mmol) in THF (20 mL) was added dropwise at room temperature to a solution of vinylmagnesium bromide (100 mL, 100 mmol, 1.0 M in THF) in THF (50 mL). After stirring for 1 h, 5 mL of water was added to the reaction mixture to produce a viscous paste in the walls of the flask. The organic layer was separated. The paste was washed twice with Et_2O. The combined organic phases were dried over $MgSO_4$. Filtration and removal of the solvent gave 8.5 g (95%) of the crude alcohol which was sufficiently pure (according to NMR) to be used in the next step. NaH (0.87 g, 36 mmol, oil removed by washing with pentane) was added to a solution of the crude alcohol (3.36 g, 30 mmol) in THF (30 mL). After stirring for 1 h, benzyl bromide (3.36 mL, 30 mmol) was added. After stirring overnight, water was poured into the mixture and extracted twice with Et_2O. The combined organic phases were dried over $MgSO_4$. Filtration and removal of the solvent gave a light yellow oil which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 99:1). Yield 4.36 g (72%). ^{1}H NMR (250 MHz): δ (ppm)=1.65 (s, 3H), 1.79 (s, 3H), 4.51 (s, 2H), 4.52–4.58 (m, 1H), 5.15–5.29 (m, 3H), 5.86 (ddd, J=17.3, 10.3, 6.7 Hz, 1H), 7.25–7.39 (m, 5H). ^{13}C NMR (63 MHz): δ (ppm)=18.3 (CH_3), 25.9 (CH_3), 69.3 (CH_2), 76.5 (CH), 115.7 (CH_2), 124.3 (CH), 127.3 (CH), 127.7 (CH), 128.2 (CH), 136.2 (C), 138.1 (CH), 138.7 (C). IR (film): ν (cm^{-1})=3064, 2859, 1672, 1454, 1380. MS (EI): *m*/*z* (%)=202 (1, $M^{+\cdot}$), 108 (64), 94 (64), 79 (100).

Ethers **4b**–**d** were obtained following the procedure described for the preparation of the ether **4a**, by using MeI, *t*-$BuMe_2SiCl$ and *t*-$BuPh_2SiCl$, respectively, instead of BnBr.

3.2.2. 4-Methoxy-2-methylhexa-2,5-diene (4b). ^{1}H NMR (250 MHz): δ (ppm)=1.70 (s, 3H), 1.77 (s, 3H), 3.28 (s, 3H), 4.32 (t, J=7.7 Hz, 1H), 5.08–5.27 (m, 3H), 5.77 (ddd, J=17.2, 10.3, 6.8 Hz, 1H). ^{13}C NMR (63 MHz): δ (ppm)=18.3 (CH_3), 25.8 (CH_3), 55.4 (CH_3), 79.0 (CH), 115.7 (CH_2), 124.2 (CH), 136.3 (C), 137.9 (CH). IR (film): ν (cm^{-1})=2975, 1686, 1449, 1378. MS (EI): *m*/*z* (%)=126 (6, $M^{+\cdot}$), 111 (28), 94 (85), 79 (100).

3.2.3. 4-*t*-Butyldimethylsilyloxy-2-methylhexa-2,5-diene (4c). ^{1}H NMR (250 MHz): δ (ppm)=0.05 (s, 6H), 0.89 (s, 9H), 1.65 (s, 3H), 1.71 (s, 3H), 4.80–4.87 (m, 1H), 4.99 (dd, J=10.3, 1.4 Hz, 1H), 5.08–5.22 (m, 2H), 5.80 (ddd, J=17.1, 10.3, 5.2 Hz, 1H). ^{13}C NMR (63 MHz): δ (ppm)=−4.7 (CH_3), −4.5 (CH_3), 18.2 (CH_3), 18.3 (C), 25.7 (CH_3), 25.9 (CH_3), 70.8 (CH), 112.4 (CH_2), 127.6 (CH), 131.9 (C), 140.7 (CH). IR (film): ν (cm^{-1})=2947, 2864, 1466 cm^{-1}. MS (EI): *m*/*z* (%)=211 (3, M−Me), 169 (50, M−*t*-Bu), 95 (22), 75 (100).

3.2.4. 4-*t*-Butyldiphenylsilyloxy-2-methylhexa-2,5-diene (4d). ^{1}H NMR (250 MHz): δ (ppm)=1.05 (s, 9H), 1.14 (s, 3H), 1.57 (s, 3H), 4.76–4.84 (m, 1H), 4.99 (dt, J=10.3, 1.5 Hz, 1H), 5.10–5.20 (m, 2H), 5.82 (ddd, J=17.1, 10.3, 5.2 Hz, 1H), 7.30–7.46 (m, 6H), 7.65–7.74 (m, 4H). ^{13}C NMR (63 MHz): δ (ppm)=17.8 (CH_3), 19.3 (C), 25.5 (CH_3), 26.9 (CH_3), 71.5 (CH), 112.7 (CH_2), 127.0 (CH), 127.2 (CH), 127.4 (CH), 129.3 (CH), 129.4 (CH), 132.5 (C), 134.2 (C), 134.3 (C), 135.9 (CH), 136.0 (CH), 140.3 (CH). IR (film): ν (cm^{-1})=3072, 2926, 2844, 1676, 1641, 1591. MS (EI): *m*/*z* (%)=293 (30, M−*t*-Bu), 199 (100).

3.2.5. 3-*t*-Butyldimethylsilyloxy-1-phenylpenta-1,4-diene (6a). A solution of cinnamaldehyde (7.5 mL, 60 mmol) in THF (20 mL) was added dropwise at room temperature to a solution of vinylmagnesium bromide (80 mL, 80 mmol, 1.0 M in THF) in THF (15 mL). After stirring for 1 h, ca. 5 mL of water was added to the reaction mixture to produce a viscous paste in the walls of the flask. The organic layer was separated. The paste was washed twice with Et_2O. The combined organic phases were dried over $MgSO_4$. Filtration and removal of the solvent followed by purification by column chromatography (silica gel, petroleum ether/ethyl acetate 90:10) gave 14.6 g (89%) of 1-phenylpenta-1,4-dien-3-ol. ^{1}H NMR (250 MHz): δ (ppm)=1.83 (br s, OH), 4.78–4.85 (m, 1H), 5.21 (dd, J=10.3, 1.0 Hz, 1H), 5.36 (dd, J=17.3, 1.0 Hz, 1H), 5.98 (ddd, J=17.3, 10.3, 6.2 Hz, 1H), 6.25 (dd, J=16.0, 6.5 Hz, 1H), 6.63 (d, J=16.0 Hz, 1H), 7.20–7.45 (m, 5H). ^{13}C NMR (63 MHz): δ (ppm)=73.5 (CH), 115.2 (CH_2), 126.4 (CH), 127.6 (CH), 128.4 (CH), 130.3 (CH), 130.5 (CH), 136.4 (C), 139.1 (CH). IR (film): ν (cm^{-1})=3356, 1655, 1597, 1495, 1454. To the alcohol (0.96 g, 6 mmol) in Et_2O (20 mL) was added *t*-$BuMe_2SiCl$ (1.0 g, 6.6 mmol) and 4-(dimethylamino)pyridine (0.85 g, 6.6 mmol). After stirring overnight, the precipitate was eliminated by filtration. Removal of the solvent and purification by column chromatography (silica gel, petroleum ether/ethyl acetate 99:1) furnished 1.38 g (84%) of **6a**. ^{1}H NMR (250 MHz): δ (ppm)=0.11 (s, 6H), 0.91 (s, 9H), 4.78 (br t, J=5.6 Hz, 1H), 5.12 (d, J=10.3 Hz, 1H), 5.29 (d, J=17.1 Hz, 1H), 5.89 (ddd, J=17.1, 10.3, 5.4 Hz, 1H), 6.18 (dd, J=15.9, 5.9 Hz, 1H), 6.56 (d, J=15.9 Hz, 1H), 7.20–7.41 (m, 5H). ^{13}C NMR (63 MHz): δ (ppm)=−4.7 (CH_3), −4.6 (CH_3), 18.4 (C), 25.9 (CH_3), 74.4 (CH), 113.8 (CH_2), 126.4 (CH), 127.4 (CH), 128.5 (CH), 129.0 (CH), 131.6 (CH), 136.9 (C), 140.1 (CH). IR (film): ν (cm^{-1})=2956, 2857, 1472, 1252. MS (EI): *m*/*z* (%)=217 (13, M−*t*-Bu), 143 (35), 142 (30), 81 (100).

3.2.6. (*E*)-3-Benzyloxyhexa-1,4-diene (6b). Ether **6b** was obtained in 82% yield from crotonaldehyde (two steps) following the procedure described for the preparation of ether **4a**. ^{1}H NMR (250 MHz): δ (ppm)=1.75 (d, J=6.3 Hz, 3H), 4.23 (t, J=6.8 Hz, 1H), 4.51 (s, 2H), 5.20 (d, J=10.3 Hz, 1H), 5.26 (d, J=17.3 Hz, 1H), 5.50 (ddq, J=15.4, 7.1, 1.5 Hz, 1H), 5.71 (dq, J=15.4, 6.3 Hz, 1H), 5.85 (ddd, J=17.3, 10.3, 6.6 Hz, 1H), 7.25–7.35 (m, 5H). ^{13}C NMR (63 MHz): δ (ppm)=17.8 (CH_3), 69.5 (CH_2), 80.6 (CH), 116.3 (CH_2), 127.3 (CH), 127.6 (CH), 128.2 (CH), 128.7

(CH), 130.5 (CH), 138.1 (CH), 138.6 (C). IR (film): ν (cm^{-1})=3029, 2857, 1668, 1454. MS (EI): *m/z* (%)=170 (1, M−H_2O), 144 (6), 130 (10), 91 (90), 79 (100).

3.2.7. 3-Benzyloxy-2-methylhexa-1,4-diene (6c). Ether **6c** was obtained in 78% yield from methacroleine (2 steps), following the procedure described for the preparation of **4a**. ^1H NMR (250 MHz): δ (ppm)=1.72 (s, 3H), 4.24 (d, *J*=6.1 Hz, 1H), 4.46 (d, *J*=12.0 Hz, 1H), 4.52 (d, *J*=12.0 Hz, 1H), 4.98 (s, 1H), 5.05 (s, 1H), 5.23 (d, *J*=10.4 Hz, 1H), 5.31 (d, *J*=17.3 Hz, 1H), 5.84 (ddd, *J*=17.3, 10.4, 6.1 Hz, 1H), 7.25–7.45 (m, 5H). ^{13}C NMR (63 MHz): δ (ppm)=17.6 (CH_3), 69.6 (CH_2), 83.5 (CH), 113.0 (CH_2), 116.5 (CH_2), 127.3 (CH), 127.5 (CH), 128.3 (CH), 137.3 (CH), 138.6 (C), 144.1 (C). IR (film): ν (cm^{-1})=3070, 2859, 1644, 1454. MS (EI): *m/z* (%)=170 (4, M−H_2O), 97 (28), 91 (100).

4. Zr-mediated pentadienylation of carbonyl compounds

4.1. General procedure for the preparation of bis(homoallylic) alcohols (procedure A)

To a solution of the dienyl ether (1 mmol) and Cp_2ZrCl_2 (321 mg, 1.1 mmol) in THF (5 mL) at 0 °C, was added dropwise *n*-BuLi (2.2 mmol, 2–2.5 M in hexanes). After stirring for 10 min at this temperature, the yellow solution was refluxed for 0.5 h, and cooled to −78 °C (or 20 °C, see Table 1). The carbonyl compound (1.5 mmol) was added, and the mixture warmed slowly to room temperature (about 1 h). HCl 1N (5 mL) and Et_2O (10 mL) were added to the solution. The organic layer was separated and washed with aq. $NaHCO_3$, then dried over $MgSO_4$. Filtration and removal of the solvent gave a yellow oil, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 92:8).

4.2. General procedure for the preparation of bis(homoallylic) alcohols in the presence of $BF_3{\cdot}OEt_2$ (procedure B)

Procedure A was modified by the addition of $BF_3{\cdot}OEt_2$ (125 L, 1 mmol) at −78 °C; the mixture was stirred for 15 min at this temperature before the addition of the carbonyl compound.

4.2.1. 4-Methyl-1-phenyl-2-vinylpent-3-en-1-ol (5a).[4] *Procedure A*. Yield 78% from **4a** (*anti*/*syn* 92:8).

Procedure B. Yield 72% from **4a** (*anti*/*syn* 26:74). IR (film): ν (cm^{-1})=3428, 1636, 1453, 1380. MS (EI): *m/z* (%)=184 (4, M−H_2O), 169 (10), 106 (48), 105 (52), 94 (39), 77 (100).

anti-**5a**. ^1H NMR (500 MHz): δ (ppm)=1.33 (s, 3H), 1.61 (s, 3H), 2.25 (br s, OH), 3.24 (br q, *J*=8.3 Hz, 1H), 4.49 (d, *J*=7.6 Hz, 1H), 5.02 (d, *J*=9.4 Hz, 1H), 5.16 (d, *J*=16.0 Hz, 1H), 5.17 (d, *J*=11.3 Hz, 1H), 5.78 (ddd, *J*=16.0, 11.3, 8.0 Hz, 1H), 7.20–7.35 (m, 5H). ^{13}C NMR (125 MHz): δ (ppm)=17.9 (CH_3), 26.8 (CH_3), 51.6 (CH), 76.4 (CH), 117.0 (CH_2), 122.0 (CH), 126.7 (CH), 127.3 (CH), 127.8 (CH), 134.5 (C), 138.0 (CH), 142.1 (C).

Syn-**5a**. ^1H NMR (250 MHz): δ (ppm)=1.61 (s, 3H), 1.78 (s, 3H), 2.25 (br s, OH), 3.27 (br q, *J*=7.7 Hz, 1H), 4.46 (d, *J*=7.5 Hz, 1H), 4.88–5.16 (m, 3H), 5.60 (ddd, *J*=17.2, 10.4, 6.9 Hz, 1H), 7.20–7.35 (m, 5H). ^{13}C NMR (125 MHz): δ (ppm)=18.3 (CH_3), 26.1 (CH_3), 51.0 (CH), 77.0 (CH), 116.1 (CH_2), 122.3 (CH), 127.0 (CH), 127.5 (CH), 128.0 (CH), 136.6 (C), 137.4 (CH), 141.9 (C).

4.2.2. (*E*)-7-Methyl-5-vinylocta-2,6-dien-4-ol (5b). *Procedure A*. Yield 83% (*anti*/*syn* 93:7).

Procedure B. Yield 93% (*anti*/*syn* 18:82). IR (film): ν (cm^{-1})=3405, 672, 1636, 1451, 1376. MS (EI): *m/z* (%)=148 (5, M−H_2O), 133 (8), 96 (59), 81 (100).

anti-**5b**. ^1H NMR (250 MHz): δ (ppm)=1.63 (s, 3H), 1.70 (d, *J*=6.5 Hz, 3H), 1.74 (s, 3H), 1.78 (br s, OH), 3.06 (br q, *J*=8.0 Hz, 1H), 3.94 (t, *J*=6.7 Hz, 1H), 5.03–5.13 (m, 3H), 5.47 (ddq, *J*=15.3, 6.8, 1.6 Hz, 1H), 5.69 (dq, *J*=15.3, 6.5 Hz, 1H), 5.69–5.77 (m, 1H). ^{13}C NMR (63 MHz): δ (ppm)=17.6 (CH_3), 18.1 (CH_3), 25.8 (CH_3), 49.6 (CH), 74.8 (CH), 116.0 (CH_2), 122.1 (CH), 127.2 (CH), 131.3 (CH), 134.3 (C), 137.9 (CH).

syn-**5b**. ^1H NMR (250 MHz): δ (ppm)=1.66 (s, 3H), 1.71 (d, *J*=6.3 Hz, 3H), 1.73 (br s, OH), 1.78 (s, 3H), 3.06 (br q, *J*=7.8 Hz, 1H), 3.90 (t, *J*=7.0 Hz, 1H), 5.01–5.15 (m, 3H), 5.48 (ddq, *J*=15.3, 7.2, 1.4 Hz, 1H), 5.62–5.81 (m, 2H). ^{13}C NMR (63 MHz): δ (ppm)=17.5 (CH_3), 18.0 (CH_3), 25.8 (CH_3), 49.2 (CH), 75.0 (CH), 115.5 (CH_2), 122.3 (CH), 128.0 (CH), 131.3 (CH), 135.0 (C), 137.5 (CH).

4.2.3. (*E*)-6-Methyl-1-phenyl-4-vinylhepta-1,5-dien-3-ol (5c). *Procedure A*. Yield 93% (*anti*/*syn* 92:8).

Procedure B. Yield 84% (*anti*/*syn* 20:80). IR (film): ν (cm^{-1})=3413, 1671, 1635, 1495, 1449, 1376. MS (EI): *m/z* (%)=228 (2, $M^{+\cdot}$), 210 (9), 132 (58), 131 (100).

anti-**5c**. ^1H NMR (250 MHz): δ (ppm)=1.64 (s, 3H), 1.74 (s, 3H), 1.85 (br s, OH), 3.19 (br q, *J*=7.9 Hz, 1H), 4.19 (t, *J*=6.4 Hz, 1H), 5.08–5.21 (m, 3H), 5.80 (ddd, *J*=17.6, 9.7, 7.6 Hz, 1H), 6.23 (dd, *J*=15.9, 6.0 Hz, 1H), 6.62 (d, *J*=15.9 Hz, 1H), 7.20–7.45 (m, 5H). ^{13}C NMR (63 MHz): δ (ppm)=18.3 (CH_3), 25.9 (CH_3), 49.8 (CH), 74.6 (CH), 116.5 (CH_2), 121.7 (CH), 126.3 (CH), 127.4 (CH), 128.4 (CH), 129.8 (CH), 130.6 (CH), 135.0 (C), 136.8 (C), 137.7 (CH).

syn-**5c**. ^1H NMR (250 MHz): δ (ppm)=1.68 (d, *J*=1.3 Hz, 3H), 1.79 (d, *J*=1.2 Hz, 3H), 1.96 (br d, *J*=3.3 Hz, OH), 3.19 (br q, *J*=7.7 Hz, 1H), 4.15 (td, *J*=6.1, 3.3 Hz, 1H), 5.06–5.20 (m, 3H), 5.79 (ddd, *J*=17.6, 9.8, 7.3 Hz, 1H), 6.23 (dd, *J*=15.9, 6.6 Hz, 1H), 6.62 (d, *J*=15.9 Hz, 1H), 7.20–7.45 (m, 5H). ^{13}C NMR (63 MHz): δ (ppm)=18.2 (CH_3), 25.9 (CH_3), 49.6 (CH), 74.9 (CH), 116.0 (CH_2), 122.1 (CH), 126.3 (CH), 127.3 (CH), 128.3 (CH), 129.9 (CH), 131.1 (CH), 135.4 (C), 136.7 (C), 137.4 (CH).

4.2.4. 6-Methyl-4-vinylhept-5-en-3-ol (5d). *Procedure A*. Yield 57% (*anti*/*syn* >95:5).

Procedure B. Yield 61% (*anti*/*syn* 68:32). IR (film): ν

(cm^{-1})=3403, 1635, 1454, 1379. MS (EI): *m/z* (%)=136 (1, M−H_2O), 107 (3), 96 (84), 81 (100).

anti-**5d**. ^1H NMR (250 MHz): δ (ppm)=0.96 (t, *J*=7.4 Hz, 3H), 1.28–1.36 (m, 1H), 1.56–1.65 (m, 1H), 1.63 (s, 3H), 1.71 (br s, OH), 1.73 (s, 3H), 2.97 (br q, *J*=8.3 Hz, 1H), 3.35 (td, *J*=7.9, 3.2 Hz, 1H), 5.05 (d, *J*=9.4 Hz, 1H), 5.09–5.12 (m, 2H), 5.72 (ddd, *J*=15.9, 10.7, 8.3 Hz, 1H). ^{13}C NMR (63 MHz): δ (ppm)=10.1 (CH_3), 18.1 (CH_3), 25.9 (CH_3), 26.9 (CH_2), 49.7 (CH), 75.1 (CH), 116.0 (CH_2), 123.0 (CH), 133.6 (C), 138.3 (CH).

syn-**5d**. ^1H NMR (250 MHz): δ (ppm)=0.96 (t, *J*=7.4 Hz, 3H), 1.20–1.40 (m, 2H), 1.66 (s, 3H), 1.71 (br s, OH), 1.77 (s, 3H), 3.02 (br q, *J*=8.2 Hz, 1H), 3.35 (td, *J*=7.9, 3.2 Hz, 1H), 5.02–5.16 (m, 3H), 5.65–5.82 (m, 1H). ^{13}C NMR (63 MHz): δ (ppm)=10.0 (CH_3), 18.1 (CH_3), 26.0 (CH_3), 26.8 (CH_2), 48.9 (CH), 75.2 (CH), 115.4 (CH_2), 122.4 (CH), 135.2 (C), 138.4 (CH).

4.2.5. 2,6-Dimethyl-4-vinylhept-5-en-3-ol (5e). *Procedure A*. Yield 64% (*anti*/*syn* >95:5).

Procedure B. Yield 50% (*anti*/*syn* 57:43). IR (film): ν (cm^{-1})=3437, 1630, 1466, 1379. MS (EI): *m/z* (%)=150 (12, M−H_2O), 135 (24), 107 (50), 96 (52), 79 (100).

anti-**5e**. ^1H NMR (250 MHz): δ (ppm)=0.85 (d, *J*=6.7 Hz, 3H), 0.97 (d, *J*=6.9 Hz, 3H), 1.58 (br s, OH), 1.62 (s, 3H), 1.71 (s, 3H), 1.65–1.80 (m, 1H), 3.03 (br q, *J*=8.5 Hz, 1H), 3.22 (dd, *J*=7.8, 4.0 Hz, 1H), 4.99–5.15 (m, 3H), 5.73 (ddd, *J*=17.7, 9.8, 8.3 Hz, 1H). ^{13}C NMR (63 MHz): δ (ppm)= 15.6 (CH_3), 18.1 (CH_3), 20.2 (CH_3), 25.9 (CH_3), 30.0 (CH), 47.6 (CH), 77.9 (CH), 116.0 (CH_2), 123.3 (CH), 132.9 (C), 138.5 (CH).

syn-**5e**. ^1H NMR (250 MHz): δ (ppm)=0.94 (d, *J*=6.6 Hz, 6H), 1.58 (br s, OH), 1.65 (d, *J*=1.4 Hz, 3H), 1.77 (d, *J*= 1.3 Hz, 3H), 1.65–1.82 (m, 1H), 3.12 (br q, *J*=8.2 Hz, 1H), 3.20–3.28 (m, 1H), 4.99–5.17 (m, 3H), 5.72 (ddd, *J*=17.0, 10.3, 7.2 Hz, 1H). ^{13}C NMR (63 MHz): δ (ppm)=16.3 (CH_3), 18.2 (CH_3), 19.9 (CH_3), 26.0 (CH_3), 30.1 (CH), 46.8 (CH), 78.3 (CH), 115.3 (CH_2), 122.3 (CH), 135.2 (C), 138.7 (CH).

4.2.6. 4-Methyl-2-vinylpent-3-en-1-ol (5f). *Procedure A*. Yield 81%. ^1H NMR (250 MHz): δ (ppm)=1.52 (br s, OH), 1.67 (s, 3H), 1.74 (s, 3H), 3.18 (quint., *J*=7.6 Hz, 1H), 3.45 (dd, *J*=10.3, 6.9 Hz, 1H), 3.52 (dd, *J*=10.3, 7.3 Hz, 1H), 5.00 (d, *J*=9.1 Hz, 1H), 5.11 (d, *J*=10.3 Hz, 1H), 5.12 (d, *J*=17.2 Hz, 1H), 5.69 (ddd, *J*=17.2, 10.3, 7.2 Hz, 1H). ^{13}C NMR (63 MHz): δ (ppm)=18.1 (CH_3), 25.9 (CH_3), 45.7 (CH), 65.4 (CH_2), 115.8 (CH_2), 122.6 (CH), 135.3 (C), 138.1 (CH). MS (EI): *m/z* (%)=126 (2, $M^{+\cdot}$), 108 (23), 93 (65), 91 (68), 79 (100).

4.2.7. 2,5-Dimethyl-3-vinylhex-4-en-2-ol (5g).[2i] *Procedure A*. Yield 70%. ^1H NMR (250 MHz): δ (ppm)=1.17 (s, 3H), 1.18 (s, 3H), 1.65 (s, 3H), 1.70 (br s, OH), 1.78 (s, 3H), 2.98 (dd, *J*=9.4, 8.8 Hz, 1H), 5.05–5.20 (m, 3H), 5.72–5.86 (m, 1H). ^{13}C NMR (63 MHz): δ (ppm)=18.2 (CH_3), 26.1 (CH_3), 26.5 (CH_3), 26.9 (CH_3), 54.4 (CH), 72.5 (C), 116.3 (CH_2), 122.5 (CH), 134.6 (C), 137.9 (CH). MS (EI): *m/z* (%)=136 (18, M−H_2O), 121 (65), 93 (81), 91 (65), 79 (100).

4.2.8. (*E*)-1,4-Diphenyl-2-vinylbut-3-en-1-ol (7a).[2o] *Procedure A*. Yield 90% (*anti*/*syn* >95:5).

Procedure B. Yield 80% (*anti*/*syn* 16:84). IR (film): ν (cm^{-1})=3423, 1636, 1599, 1494, 1451. MS (EI): *m/z* (%)= 232 (2, M−H_2O), 144 (42), 129 (94), 128 (66), 77 (100).

anti-**7a**. ^1H NMR (500 MHz): δ (ppm)=2.31 (br s, OH), 3.25 (br q, *J*=7.4 Hz, 1H), 4.67 (d, *J*=6.8 Hz, 1H), 5.22 (d, *J*=17.2 Hz, 1H), 5.26 (d, *J*=10.2 Hz, 1H), 5.91 (ddd, *J*= 17.2, 10.2, 8.1 Hz, 1H), 6.06 (dd, *J*=16.0, 7.4 Hz, 1H), 6.33 (d, *J*=16.0 Hz, 1H), 7.18–7.33 (m, 10H). ^{13}C NMR (125 MHz): δ (ppm)=55.4 (CH), 76.4 (CH), 118.4 (CH_2), 126.1 (CH), 126.7 (CH), 127.3 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 132.0 (CH), 136.9 (CH), 137.1 (C), 141.7 (C).

syn-**7a**. ^1H NMR (250 MHz): δ (ppm)=2.26 (br d, *J*= 3.0 Hz, OH), 3.27 (br q, *J*=8.0 Hz, 1H), 4.69 (dd, *J*=6.9, 3.0 Hz, 1H), 5.07 (d, *J*=17.1 Hz, 1H), 5.09 (d, *J*=10.8 Hz, 1H), 5.78 (ddd, *J*=17.1, 10.8, 7.1 Hz, 1H), 6.23 (dd, *J*=16.0, 8.0 Hz, 1H), 6.50 (d, *J*=16.0 Hz, 1H), 7.20–7.41 (m, 10H). ^{13}C NMR (63 MHz): δ (ppm)=55.4 (CH), 76.5 (CH), 117.2 (CH_2), 126.3 (CH), 126.8 (CH), 127.5 (CH), 127.7 (CH), 128.0 (CH), 128.2 (CH), 128.5 (CH), 133.2 (CH), 136.9 (CH), 137.0 (C), 141.8 (C).

4.2.9. (1*E*,6*E*)-1,6-Diphenyl-4-vinylhexa-1,5-dien-3-ol (7b). *Procedure A*. Yield 81% (*anti*/*syn* >95:5).

Procedure B. Yield 68% (*anti*/*syn* 18:82). IR (film): ν (cm^{-1})=3412, 1637, 1599, 1495, 1449. MS (EI): *m/z* (%)=276 (3, $M^{+\cdot}$), 258 (3), 172 (6), 144 (16), 143 (100), 128 (75).

anti-**7b**. ^1H NMR (250 MHz): δ (ppm)=2.00 (br s, OH), 3.17 (br q, *J*=7.3 Hz, 1H), 4.34 (br t, *J*=5.7 Hz, 1H), 5.24 (d, *J*=16.9 Hz, 1H), 5.26 (d, *J*=10.5 Hz, 1H), 5.95 (ddd, *J*=16.9, 10.5, 7.7 Hz, 1H), 6.24 (dd, *J*=15.9, 7.8 Hz, 1H), 6.28 (dd, *J*=15.9, 6.3 Hz, 1H), 6.50 (d, *J*=15.9 Hz, 1H), 6.64 (d, *J*=15.9 Hz, 1H), 7.15–7.45 (m, 10H). ^{13}C NMR (63 MHz): δ (ppm)=54.2 (CH), 74.7 (CH), 118.1 (CH_2), 126.2 (CH), 126.5 (CH), 127.4 (CH), 127.7 (CH), 127.9 (CH), 128.5 (CH), 128.5 (CH), 129.5 (CH), 131.6 (CH), 132.7 (CH), 136.6 (C), 136.8 (CH), 137.0 (C).

syn-**7b**. ^1H NMR (250 MHz): δ (ppm)=2.04 (br s, OH), 3.16 (br q, *J*=6.9 Hz, 1H), 4.30–4.38 (m, 1H), 5.17–5.25 (m, 2H), 5.94 (ddd, *J*=17.7, 9.5, 7.5 Hz, 1H), 6.26 (dd, *J*= 16.0, 8.0 Hz, 1H), 6.27 (dd, *J*=16.0, 6.4 Hz, 1H), 6.52 (d, *J*=16.0 Hz, 1H), 6.64 (d, *J*=16.0 Hz, 1H), 7.18–7.41 (m, 10H). ^{13}C NMR (63 MHz): δ (ppm)=54.2 (CH), 74.8 (CH), 117.7 (CH_2), 126.3 (CH), 126.5 (CH), 127.5 (CH), 127.7 (CH), 127.9 (CH), 128.5 (CH), 128.5 (CH), 129.6 (CH), 131.6 (CH), 132.9 (CH), 136.6 (C), 136.8 (CH), 137.0 (C).

4.2.10. (*E*)-6-Phenyl-4-vinylhex-5-en-3-ol (7c). *Procedure A*. Yield 90% (*anti*/*syn* 93:7).

Procedure B. Yield 80% (*anti*/*syn* 50:50). IR (film): ν

(cm^{-1})=3415, 1637, 1599, 1495, 1449. MS (EI): *m/z* (%)= 184 (2, M−H_2O), 144 (91), 129 (100), 128 (96), 115 (85).

anti-**7c**. ^1H NMR (250 MHz): δ (ppm)=1.00 (t, *J*=7.4 Hz, 3H), 1.60–1.75 (m, 3H), 2.98 (br q, *J*=8.0 Hz, 1H), 3.51–3.60 (m, 1H), 5.21 (d, *J*=17.0 Hz, 1H), 5.23 (d, *J*=10.5 Hz, 1H), 5.90 (ddd, *J*=17.0, 10.5, 8.0 Hz, 1H), 6.19 (dd, *J*=16.0, 8.0 Hz, 1H), 6.47 (d, *J*=16.0 Hz, 1H), 7.17–7.38 (m, 5H). ^{13}C NMR (63 MHz): δ (ppm)=10.1 (CH_3), 27.2 (CH_2), 53.9 (CH), 74.9 (CH), 117.6 (CH_2), 126.1 (CH), 127.3 (CH), 128.5 (CH), 129.1 (CH), 131.8 (CH), 137.2 (C), 137.2 (CH).

syn-**7c**. ^1H NMR (250 MHz): δ (ppm)=1.00 (t, *J*=7.4 Hz, 3H), 1.56–1.71 (m, 2H), 1.74 (br s, OH), 2.94–3.02 (m, 1H), 3.51–3.60 (m, 1H), 5.18 (d, *J*=17.5 Hz, 1H), 5.22 (d, *J*=10.3 Hz, 1H), 5.89 (ddd, *J*=17.5, 10.3, 8.4 Hz, 1H), 6.23 (dd, *J*=16.0, 8.4 Hz, 1H), 6.49 (d, *J*=16.0 Hz, 1H), 7.17–7.38 (m, 5H). ^{13}C NMR (63 MHz): δ (ppm)=10.1 (CH_3), 27.2 (CH_2), 53.6 (CH), 75.0 (CH), 116.9 (CH_2), 126.2 (CH), 127.4 (CH), 128.2 (CH), 128.5 (CH), 132.6 (CH), 137.1 (C), 137.9 (CH).

4.2.11. 1-Phenyl-2-vinylpent-3-en-1-ol (7d).[2o] *Procedure A*. Yield 85% ((*E*)-*anti*/(*Z*)-*anti*/(*E*)-*syn*/(*Z*)-*syn* 76:20:4:0).

Procedure B. Yield 70% (20:1:60:19). IR (film): ν (cm^{-1})= 3412, 1630, 1454. MS (EI): *m/z* (%)=170 (4, M−H_2O), 155 (10), 106 (61), 105 (61), 79 (80), 77 (100).

(*E*)-*anti*-**7d**. ^1H NMR (500 MHz): δ (ppm)=1.59 (d, *J*= 6.3 Hz, 3H), 2.32 (br s, OH), 3.02 (br q, *J*=7.4 Hz, 1H), 4.57 (d, *J*=6.9 Hz, 1H), 5.11 (d, *J*=17.3 Hz, 1H), 5.16 (d, *J*= 10.2 Hz, 1H), 5.28 (ddq, *J*=15.4, 7.2, 1.3 Hz, 1H), 5.39 (dq, *J*=15.4, 6.3 Hz, 1H), 5.79 (ddd, *J*=17.3, 10.2, 8.1 Hz, 1H), 7.24–7.32 (m, 5H). ^{13}C NMR (125 MHz): δ (ppm)=18.0 (CH_3), 55.1 (CH), 76.2 (CH), 117.6 (CH_2), 126.8 (CH), 127.3 (CH), 127.8 (CH), 127.9 (CH), 129.1 (CH), 137.4 (CH), 141.9 (C).

(*Z*)-*anti*-**7d**. ^1H NMR (500 MHz): δ (ppm)=1.38 (dd, *J*= 6.8, 1.7 Hz, 3H), 2.25 (br s, OH), 3.41 (br q, *J*=8.3 Hz, 1H), 4.53 (d, *J*=7.7 Hz, 1H), 5.19–5.25 (m, 2H), 5.29 (ddq, *J*= 10.7, 9.7, 1.7 Hz, 1H), 5.47 (dq, *J*=10.7, 6.8 Hz, 1H), 5.80–5.88 (m, 1H), 7.25–7.35 (m, 5H). ^{13}C NMR (125 MHz): δ (ppm)=12.8 (CH_3), 50.2 (CH), 76.2 (CH), 117.1 (CH_2), 126.3 (CH), 126.8 (CH), 127.4 (CH), 127.9 (CH), 128.0 (CH), 137.6 (CH), 142.0 (C).

(*E*)-*syn*-**7d**. ^1H NMR (500 MHz): δ (ppm)=1.74 (dd, *J*=6.4, 1.5 Hz, 3H), 2.28 (br d, *J*=2.5 Hz, OH), 3.02 (br q, *J*= 7.7 Hz, 1H), 4.49 (dd, *J*=7.5, 2.5 Hz, 1H), 4.92–5.01 (m, 1H), 5.45 (ddq, *J*=15.4, 8.4, 1.5 Hz, 1H), 5.59–5.68 (m, 2H), 7.25–7.34 (m, 5H). ^{13}C NMR (125 MHz): δ (ppm)= 18.2 (CH_3), 55.4 (CH), 76.3 (CH), 116.5 (CH_2), 126.9 (CH), 127.5 (CH), 128.0 (CH), 129.3 (CH), 129.6 (CH), 137.3 (CH), 141.9 (C).

(*Z*)-*syn*-**7d**. ^1H NMR (500 MHz): δ (ppm)=1.59 (d, *J*= 6.8 Hz, 3H), 2.23 (br s, OH), 3.44 (br q, *J*=7.8 Hz, 1H), 4.53–4.57 (m, 1H), 4.92–5.02 (m, 2H), 5.40–5.46 (m, 1H), 5.60–5.65 (m, 1H), 5.75 (dq, *J*=10.9, 6.8 Hz, 1H), 7.25–7.35 (m, 5H). ^{13}C NMR (125 MHz): δ (ppm)=13.2 (CH_3), 49.5 (CH), 76.7 (CH), 116.4 (CH_2), 126.8 (CH), 127.5 (CH), 128.0 (3 CH), 137.0 (CH), 141.9 (C).

4.2.12. 2-Vinylpent-3-en-1-ol (7e). *Procedure A*. Yield 62% (*E*/*Z* 71:29). IR (film): ν (cm^{-1})=3356, 1638, 1453, 1377. MS (EI): *m/z* (%)=95 (2), 81 (54), 79 (100).

(*E*)-**7e**. ^1H NMR (250 MHz): δ (ppm)=1.50 (br s, OH), 1.71 (d, *J*=6.4 Hz, 3H), 2.91 (quint., *J*=7.2 Hz, 1H), 3.46–3.55 (m, 2H), 5.11–5.17 (m, 2H), 5.36 (ddq, *J*=15.4, 7.8, 1.5 Hz, 1H), 5.59 (dq, *J*=15.4, 6.4 Hz, 1H), 5.66–5.76 (m, 1H). ^{13}C NMR (63 MHz): δ (ppm)=18.1 (CH_3), 49.8 (CH), 65.1 (CH_2), 116.4 (CH_2), 128.2 (CH), 129.6 (CH), 137.9 (CH).

(*Z*)-**7e**. ^1H NMR (250 MHz): δ (ppm)=1.65 (br s, OH), 1.67 (dd, *J*=6.8, 1.7 Hz, 3H), 3.33 (quint., *J*=7.5 Hz, 1H), 3.46–3.55 (m, 2H), 5.11–5.17 (m, 2H), 5.27 (ddq, *J*=10.8, 9.4, 1.7 Hz, 1H), 5.66–5.76 (m, 2H). ^{13}C NMR (63 MHz): δ (ppm)=13.2 (CH_3), 44.6 (CH), 65.3 (CH_2), 116.6 (CH_2), 127.4 (CH), 128.5 (CH), 137.5 (CH).

4.2.13. 3-Methyl-1-phenyl-2-vinylbut-3-en-1-ol (7f). *Procedure A*. Yield 76% (*anti*/*syn* 88:12).

Procedure B. Yield 48% (*anti*/*syn* 35:65) accompanied with 29% of the linear isomer **8**. IR (film): ν (cm^{-1})=3424, 1644, 1494, 1453. MS (EI): *m/z* (%)=170 (3, M−H_2O), 155 (8), 106 (98), 105 (99), 77 (100).

anti-**7f**. ^1H NMR (500 MHz): δ (ppm)=1.61 (s, 3H), 2.18 (br d, *J*=2.0 Hz, OH), 2.98 (t, *J*=8.4 Hz, 1H), 4.70 (dd, *J*=7.8, 2.0 Hz, 1H), 4.73 (s, 1H), 4.77 (br s, 1H), 5.18 (d, *J*=17.1 Hz, 1H), 5.21 (dd, *J*=10.2, 1.7 Hz, 1H), 6.01 (ddd, *J*=17.1, 10.2, 9.2 Hz, 1H), 7.25–7.34 (m, 5H). ^{13}C NMR (125 MHz): δ (ppm)=21.8 (CH_3), 59.9 (CH), 74.9 (CH), 113.1 (CH_2), 118.1 (CH_2), 126.8 (CH), 127.6 (CH), 128.1 (CH), 137.1 (CH), 142.0 (C), 144.5 (C).

syn-**7f**. ^1H NMR (500 MHz): δ (ppm)=1.81 (s, 3H), 2.29 (br d, *J*=2.1 Hz, OH), 3.07 (t, *J*=8.6 Hz, 1H), 4.64 (dd, *J*=9.4, 2.1 Hz, 1H), 4.86 (d, *J*=17.1 Hz, 1H), 4.91 (d, *J*=10.3 Hz, 1H), 5.01 (s, 1H), 5.05 (br s, 1H), 6.01 (ddd, *J*=17.1, 10.3, 8.1 Hz, 1H), 7.25–7.34 (m, 5H). ^{13}C NMR (125 MHz): δ (ppm)=20.0 (CH_3), 60.3 (CH), 74.5 (CH), 114.1 (CH_2), 117.1 (CH_2), 127.0 (CH), 127.6 (CH), 128.0 (CH), 135.9 (CH), 141.9 (C), 145.0 (C).

4.2.14. 3-Methyl-1-phenylhexa-3,5-dien-1-ol (8). ^1H NMR (500 MHz): δ (ppm)=1.83 (s, 3H), 2.10 (br s, OH), 2.42 (dd, *J*=13.7, 9.1 Hz, 1H), 2.45 (dd, *J*=13.7, 4.4 Hz, 1H), 4.82 (dd, *J*=9.1, 4.4 Hz, 1H), 5.07 (dd, *J*=10.2, 1.5 Hz, 1H), 5.16 (dd, *J*=16.9, 1.5 Hz, 1H), 5.97 (d, *J*=10.0 Hz, 1H), 6.59 (dt, *J*=16.9, 10.5 Hz, 1H), 7.25–7.34 (m, 5H). ^{13}C NMR (125 MHz): δ (ppm)=16.7 (CH_3), 50.3 (CH_2), 71.7 (CH), 116.3 (CH_2), 125.7 (CH), 127.5 (CH), 128.4 (CH), 129.1 (CH), 132.7 (CH), 135.2 (C), 144.0 (C).

References and notes

1. (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Roush, W. *Comprehensive Organic Synthesis*; Trost, B. M.,

Fleming, I., Heathcock, C. W., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1.

2. Leading references for pentadienylmetals: Li: (a) Gérard, F.; Miginiac, P. *Bull. Soc. Chim. Fr.* **1974**, 1924. Li and K: (b) Schlosser, M.; Zellner, A.; Leroux, F. *Synlett* **2001**, 1830. Mg: (c) Yasuda, H.; Yamauchi, M.; Nakamura, A.; Sei, T.; Kai, Y.; Yasuoka, N.; Kasai, N. *Bull. Chem. Soc. Jpn* **1980**, *53*, 1089. Zn: (d) Gérard, F.; Miginiac, P. *Bull. Soc. Chim. Fr.* **1974**, 2527. (e) Ghosez, L.; Marko, I.; Hesbain-Frisque, A. M. *Tetrahedron Lett.* **1986**, *27*, 5211. (f) Jung, M. E.; Nichols, C. J. *Tetrahedron Lett.* **1996**, *37*, 7667. (g) Fuijta, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258. (h) Suginome, M.; Yamamoto, Y.; Fujii, K.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9608. Ti: (i) Okamoto, S.; Sato, F. *J. Organomet. Chem.* **2001**, *624*, 151. (j) Zellner, A.; Schlosser, M. *Synlett* **2001**, 1016. Cr: (k) Sodeoka, M.; Yamada, H.; Shimizu, T.; Watanuki, S.; Shibasaki, M. *J. Org. Chem.* **1994**, *59*, 712. Sn: (l) Nishigaichi, Y.; Fujimoto, M.; Takuwa, A. *Synlett* **1994**, 731. Si: (m) Kobayashi, S.; Nishio, K. *Chem. Lett.* **1994**, 1773. (n) Vallée, Y.; Pelloux-Léon, N.; Minassian, F. *Synlett* **2000**, *242*. In: (o) Hirashita, T.; Inoue, S.; Yamamura, H.; Kawai, M.; Araki, S. *J. Organomet. Chem.* **1997**, *549*, 305. (p) Melekhov, A.; Fallis, A. G. *Tetrahedron Lett.* **1999**, *40*, 7867.

3. The use of alcohol derivatives, i.e. acetates or carbonates, for preparing pentadienylmetals is limited to titanium and chromium complexes, see Refs. 2i,k.

4. Bertus, P.; Cherouvrier, F.; Szymoniak, J. *Tetrahedron Lett.* **2001**, *42*, 1677.

5. For reviews of 'Cp_2Zr' chemistry, see: (a) Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn* **1998**, *71*, 755. (b) Negishi, E.; Kondakov, D. Y. *Chem. Soc. Rev.* **1996**, *26*, 417. (c) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124.

6. (a) Negishi, E.; Huo, S. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; p 1. (b) Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5105. (c) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295. (d) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* **1995**, *51*, 4507.

7. The pentadienyl ethers are stable compounds in comparison with pentadienyl bromides.

8. For the 1,3-metallotropic rearrangement with Zr, see: (a) Ref. 5. (b) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853, and references therein.

9. We have noticed that this procedure is also useful for the preparation of allylzirconocenes from allylic ethers.

10. The *anti* configuration was defined with reference to the simpler allylmetalation reactions, by considering pentadienylzirconiums as alkenyl-substituted allylmetals. The *anti* configuration was undoubtedly assigned to the major isomers by a cyclization method. For an example see Ref. 4.

11. Reetz, M. T.; Sauerwald, M. *J. Org. Chem.* **1984**, *49*, 2292.

12. (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Szymoniak, J.; Thery, N.; Moïse, C. *Synlett* **1997**, 1239.

13. Similar reversal of *anti* to *syn* stereoselectivity was also obtained with $TiCl_4$. The reversal of *anti* to *syn* selectivity was found to be less stronger when the solution of the aldehyde and BF_3 in THF was added to the reaction mixture.

14. The predominant *syn* diastereoselection in the Lewis acid-mediated allylic tin-aldehyde condensation reactions was rationalized similarly, see Ref. 1.

15. The formation of the ε-regioisomeric by-product **8** from the ether **6c** in the presence of a Lewis acid (see Table 3) also corroborates a non-cyclic mechanism.

16. For example, different open transition structures have been considered for the Lewis acid-mediated allylmetalation reactions, see: (a) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655. (b) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1385–1392
Tetrahedron

Construction of nitrogen-heterocyclic compounds through zirconium mediated intramolecular alkene-carbonyl coupling reaction of *N*-(*o*-alkenylaryl)carbamate derivatives

Yasushi Takigawa,[a] Hisanaka Ito,[b] Katsunori Omodera,[a] Maiko Ito[a] and Takeo Taguchi[a,*]

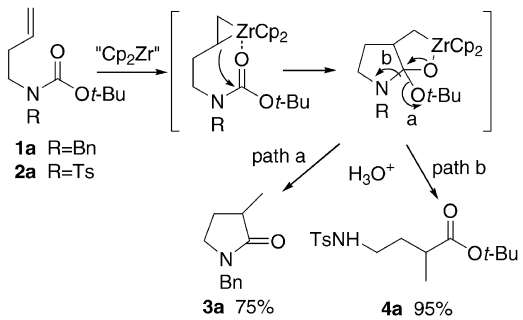
[a]*School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*
[b]*School of Life Science, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*

Received 20 June 2003; accepted 11 August 2003

Abstract—Intramolecular alkene-carbonyl coupling reaction of *N*-benzyl-*N*-(*o*-alkenylaryl)carbamate derivative derived from *o*-aminostyrene, *o*-(aminomethyl)styrene and *o*-aminoallylbenzene smoothly proceeded by treating with zirconocene–butene complex to give the corresponding lactam derivative.

1. Introduction

Low valent zirconium-mediated intramolecular coupling reaction of unsaturated functional groups has been extensively developed as a powerful mean for the construction of cyclic compounds.[1] While such zirconium-mediated intramolecular coupling reactions were limited to the cases of alkene, alkyne and imine derivatives,[2,3] we have recently demonstrated successful examples of intramolecular alkene-carbonyl coupling reaction by using *N*-alkenyl-*N*-substituted *tert*-butyl carbamate derivatives as the substrates.[4] One of the characteristic features of the present reaction is the effect of the substituent on the nitrogen atom on the reaction course. That is, as shown in Scheme 1,



Scheme 1.

depending on the ability as a leaving group (–NBn vs –NTs vs O*t*-Bu), lactam derivative **3a** is formed from the substrate **1a** having an electron donating group such as benzyl group (path a), while γ-aminobutyric acid derivative **4a** is obtained from the substrate **2a** having an electron withdrawing group such as sulfonyl group (path b).

Furthermore, not only electronic nature of the substituent on the nitrogen atom, steric effect of carbamate moiety maybe influences the reactivity and the reaction pathway. For example, the coupling reaction of sterically bulky *tert*-butyl carbamate of *N*-4-pentenyl-*N*-tosylamide **2b** proceeded after migration of zirconium into the inner site resulting in the formation of γ-aminobutyric acid derivative **4b**, while the benzyl carbamate **2c** gave δ-aminopentanoic acid derivative **4c** (Scheme 2).[4,5]

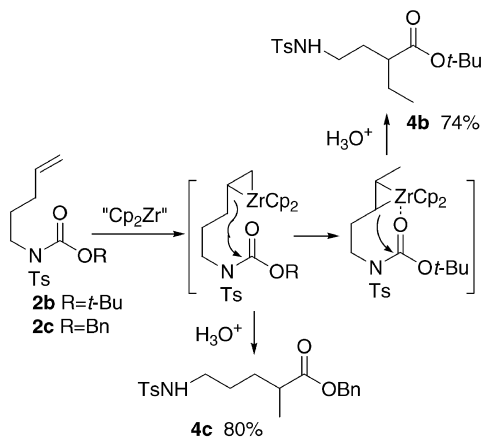
Based on our findings mentioned above, we extended the present zirconium-mediated intramolecular coupling reaction to *N*-(*o*-alkenylaryl)carbamate derivatives **1c–m** (*N*-benzyl derivatives), **2d–g** (*N*-tosyl derivatives) to examine the substituent effect of the carbamate moiety on the reactivity as well as to develop an efficient method for the preparation of nitrogen-containing heterocyclic compounds (Chart 1).[6]

2. Results and discussion

Since *N*-tosyl *tert*-butyl carbamates are good substrates in the zirconium mediated intramolecular alkene-carbonyl coupling reaction as reported in our preliminary results,[4] *N*-Boc-*N*-tosyl substituted *o*-aminostyrene **2d** and

Keywords: Zirconocene–butene complex; *N*-Aryl carbamate; Ester transfer; Indoline derivative; Quinolone derivative; Isoquinolone derivative.
* Corresponding author. Tel./fax: +81-426-76-3257;
e-mail address: taguchi@ps.toyaku.ac.jp

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.08.079



Scheme 2.

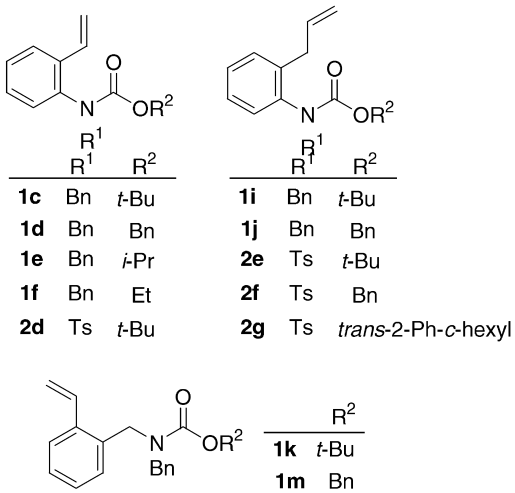
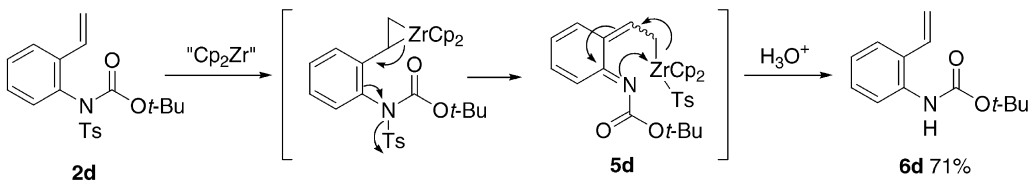


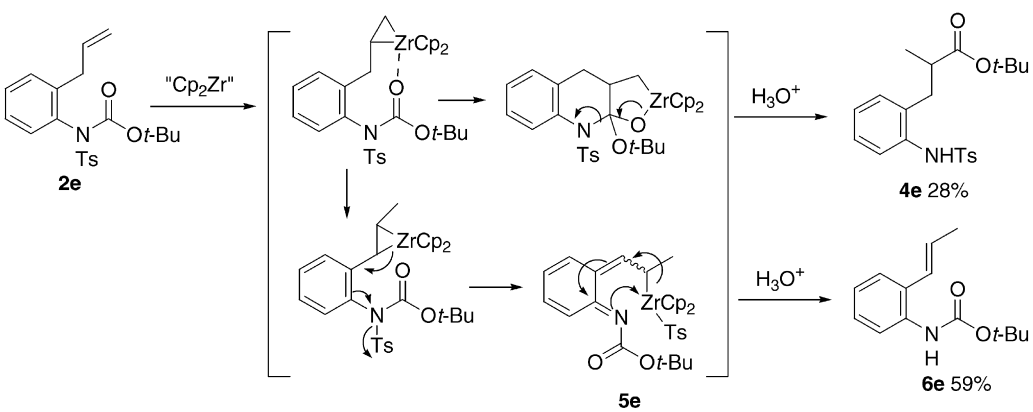
Chart 1.

o-aminoallylbenzene **2e** were chosen as a starting material. Reaction of *o*-aminostyrene derivative **2d** with zirconocene–butene complex[7] did not give the desired ester transfer product but exclusively afforded the desufonylated carbamate **6d** in 71% isolated yield. As shown in Scheme 3, the reaction pathway to the carbamate **6d** possibly involves the zirconium-promoted 1,4-elimination of sulfonyl group to form *o*-quinodimethane intermediate **5d** and the subsequent re-aromatization.[8] With one carbon elongated allylbenzene derivative **2e**, both alkene-carbonyl coupling reaction and desulfonylation reaction competitively proceeded. In this case, unlike the aliphatic substrate **2b** (Scheme 2), the alkene-carbonyl coupling reaction proceeded without migration of zirconium to give the α-methylated ester derivative **4e** as a minor product (28% yield) and the major product was the *E* isomer of desulfonylated compound **6e** (59% yield) derived after migration of zirconium (Scheme 4).

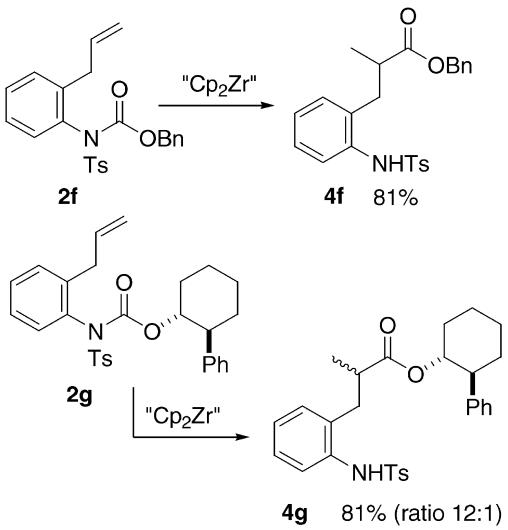
We found that in the case of allylbenzene derivatives, the desired alkene-carbonyl coupling reaction can be controlled to be a major reaction by using sterically less hindered carbamate by changing *tert*-butyl ester to primary or secondary alkyl ester such as benzyl carbamate **2f** and cyclohexyl carbamate **2g**. That is, with these substrates prior to migration of zirconium into the inner site (see Scheme 4), alkene-carbonyl coupling reaction smoothly occurred to give the ester transfer product **4f** and **4g** in good yields as shown in Scheme 5. It is also noted that reaction of *trans*-2-phenylcyclohexyl carbamate **2g** proceeded in a highly diastereoselective manner (isomer ratio 12:1) obtaining the α-methylated ester derivative **4g**, although the relative stereochemistry was not determined. In contrast to the allylbenzene derivatives mentioned above, desulfonylation was a major pathway in the reaction of benzyl carbamate of *o*-(tosylamino)styrene with zirconocene–butene complex.



Scheme 3.



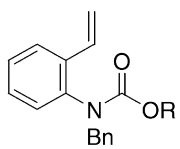
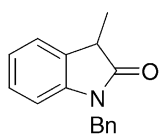
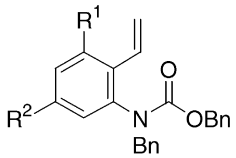
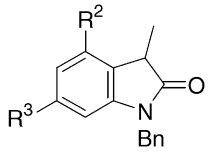
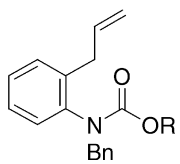
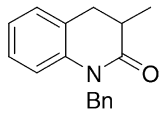
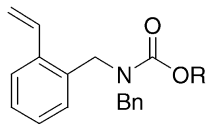
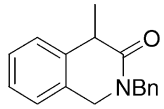
Scheme 4.



Scheme 5.

As mentioned above, since the present alkene-carbonyl coupling reaction cannot be applied to the *N*-sulfonyl carbamate of *o*-aminostyrene such as **2d** or the corresponding benzyl carbamate due to the facile desulfonylation reaction, *N*-benzyl derivatives were examined as substrates.

Table 1. 'Cp_2Zr' mediated coupling reaction of *N*-benzyl carbamate derivatives

Entry	Substrate	Product	Yield (%)
			
1	**1c** R=*t*-Bu	**3c**	51
2	**1d** R=Bn		59
3	**1e** R=*i*-Pr		48
4	**1f** R=Et		40
			
5	**1g** R^1=OMe R^2=H	**3g**	45
6	**1h** R^1=H R^2=OMe	**3h**	49
			
7	**1i** R=*t*-Bu	**3i**	69
8	**1j** R=Bn		88
			
9	**1k** R=*t*-Bu	**3k**	69
10	**1m** R=Bn		62

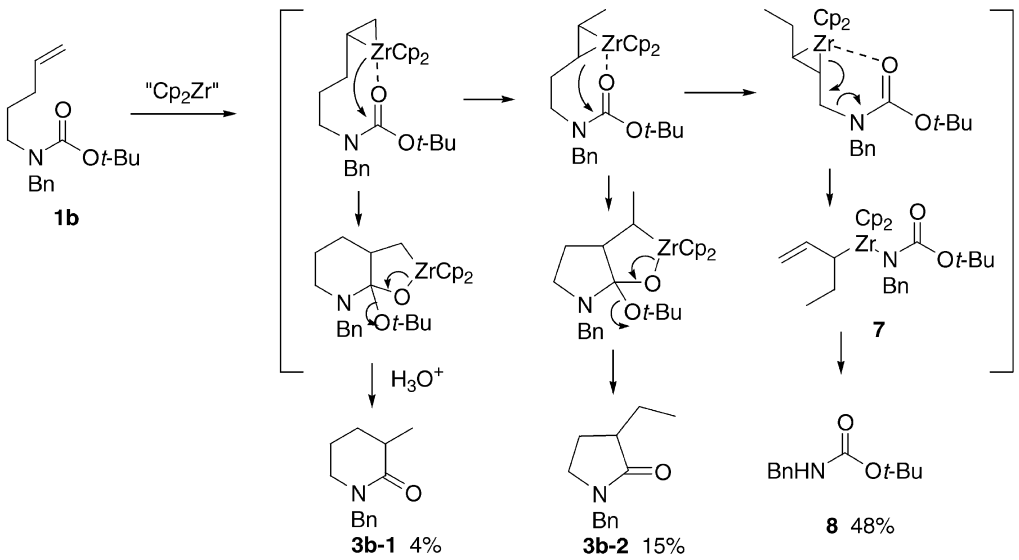
Thus, reaction of *N*-benzyl carbamates **1c**–**h** derived from *o*-aminostyrene, **1i**, **1j** from *o*-aminoallylbenzene and **1k**, **1m** from *o*-(aminomethyl)styrene with in situ generated zirconocene–butene complex were conducted and results are summarized in Table 1.

Contrary to the *N*-tosyl derivative **2d** (Scheme 3), *N*-benzyl derivative **1c** smoothly reacted with zirconocene–butene complex to give the intramolecular alkene-carbonyl coupling product **3c** in moderate yield (51%, entry 1, see also Scheme 7). Yield of the lactam derivative **3c** slightly varied by changing the steric demand of the ester part. Thus, the benzyl ester **1d** gave a higher yield of **3c** than either sterically hindered *tert*-butyl ester **1c** or less hindered ethyl ester **1f** (see entries 1, 2, 4). With the substrates **1g**, **1h** having an additional methoxyl group on the aromatic ring gave the corresponding 3-methylindoline derivatives **1g** and **1h**, respectively (entries 5, 6).

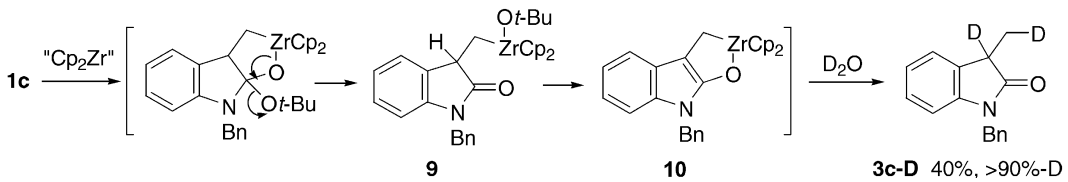
Six-membered ring forming reaction from *o*-aminoallylbenene derivatives **1i**, **1j** and *o*-(aminomethyl)styrene derivatives **1k**, **1m** proceeded much more effectively giving rise to the coupling product in good yields (entries 7–10). In the case of conversion into dihydroquinolone **3i**, benzyl ester **1j** gave a higher yield than *tert*-butyl ester **1i**, and in both cases 3-ethylindolinone derivative, possibly formed via migration of zirconium, was not detected (entries 7, 8). Efficient formation of these six-membered ring compounds **3i**, **3k** via alkene-carbonyl coupling reaction should be mainly due to *ortho*-substituted benzene structure of the substrate, because such an efficient cyclization reaction could not be achieved with the substrate of linear chain structure. For example, upon treating *N*-4-pentenyl benzyl carbamate **1b** with zirconocene–butene complex, two coupling products, piperidone **3b-1** (4%) and pyrrolidone **3b-2** (15%), were obtained in low yields along with the isolation of the pentenyl chain lacked *N*-benzyl carbamate **8** as a main product (48%). It is likely that formation of the dealkenylated product **8** involves the stepwise migration of zirconium leading to the intermediacy allylic zirconium species **7** (Scheme 6).[9]

To clarify the reaction pathway, deuterium oxide (D_2O) quenching of the reaction mixture was examined. After treatment of **1c** with zirconocene–butene complex under similar conditions as before (Table 1, entry 1), the reaction mixture was quenched with D_2O. High level (>90%) of deuterium incorporation was observed at both 3-position and at the methyl group of indoline derivative **3c-D** (Scheme 7). The reaction pathway possibly involves the intramolecular alkene-carbonyl coupling reaction followed by the formation of the lactam structure **9** having zirconated methyl substituent at the 3-position. In the next stage, it would be likely that zirconium *tert*-butoxide in the intermediate **9** acts as a base to deprotonate at the 3-position to form the five-membered zirconium enolate form **10**, which converted to the bisdeuterated indoline **3c-D**.

In the cases of six-membered ring forming reaction with the substrates **1j** and **1k**, deuterium incorporation was observed at the methyl group, giving rise to **3i-D** and **3k-D** in high yields (Scheme 8). When the reaction mixture was

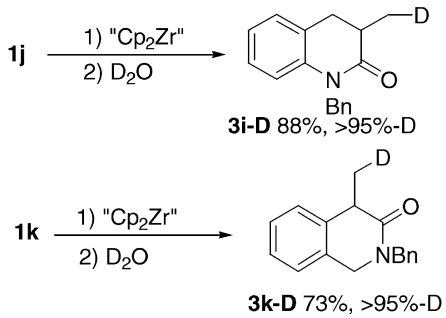


Scheme 6.

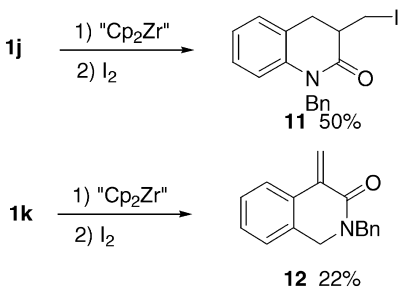


Scheme 7.

quenched by the addition of iodine instead of D_2O, iodomethyl derivative **11** was isolated in 50% yield in the case of **1j** and methylene derivative **12** was obtained in 22% yield in the case of **1k** (Scheme 9).



Scheme 8.



Scheme 9.

3. Conclusion

Zirconocene–butene complex mediated intramolecular alkene-carbonyl coupling reaction can be applied to *N*-benzyl carbamate derivatives derived from *o*-aminostyrene, *o*-aminoallylbenzene and *o*-(aminomethyl)styrene to give the corresponding nitrogen-heterocyclic compounds.

4. Experimental

4.1. General

Toluene (dehydrated), THF (dehydrated, no stabilizer) and zirconocene dichloride are available commercially. All reactions were conducted under an argon atmosphere. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and the chemical shifts are given in ppm using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^1H NMR and $CDCl_3$ (77.01 ppm) for ^{13}C NMR as internal standard, respectively. Mass spectra and HRMS were recorded by electrospray ionization. Column chromatography was performed on silica gel (70–230 mesh). Medium-pressure liquid chromatography (MPLC) was performed on a 30 cm×2.2 cm i.d. prepacked column (silica gel, 50 μm) with a UV or RI detector.

4.2. Procedure for the preparation of the carbamate derivative 1 and 2

To a mixture of 2-vinylbenzoic acid (741 mg, 5 mmol), triethylamine (1.05 ml, 7.5 mmol) in benzene (50 ml) was

added diphenylphosphoryl azide (DPPA, 1.62 ml, 7.5 mmol) at room temperature. After being stirred for 1 h at the same temperature, 2-methyl-2-propanol (4.8 ml, 50 mmol) was added and the reaction mixture was heated at reflux. After being stirred for 3 h until gas evolution had ceased, the reaction mixture was poured into sat. $NaHCO_3$ and then extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt=20:1) to give *tert*-butyl 2-vinylphenylcarbamate **6d** (800 mg, 73% yield) whose ^{1}H NMR data were in good agreement with those described in the literature.[10] The above carbamate (439 mg, 2 mmol) dissolved in DMF was added dropwise to sodium hydride (96.0 mg, 2.4 mmol) in DMF (20 ml) at room temperature. After being stirred for 30 min at the same temperature, benzyl bromide (0.36 ml, 3 mmol) was added and the whole was stirred overnight. The reaction mixture was quenched by the addition of 1N HCl and extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt=20:1) to give **1c** (616 mg, quantitative yield).

4.2.1. *tert*-Butyl benzyl(2-vinylphenyl)carbamate 1c. Colorless oil. IR (neat) ν; 1698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ; 7.58 (1H, d, J=7.6 Hz), 7.33–7.23 (6H, m), 7.18 (1H, t, J=7.2 Hz), 6.91 (1H, brs), 6.71(1H, dd, J=17.5, 11.1 Hz), 5.71 (1H, d, J=17.6 Hz), 5.29 (1H, d, J=11.0 Hz), 5.07 (1H, brs), 4.45 (1H, brs), 1.43 (9H, brs). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) δ; 115.1, 140.1, 138.1, 135.7, 133.0, 129.1, 128.8, 128.3, 128.1, 127.3, 127.2, 125.9, 115.4, 80.2, 53.8, 28.3. MS m/z: 310 $(M+H)^+$. Anal. calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.51; H, 7.63; N, 4.45.

4.2.2. Benzyl benzyl(2-vinylphenyl)carbamate 1d. Colorless oil. IR (neat) ν; 1704 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ; 7.56 (1H, d, J=7.8 Hz), 7.26–7.21 (11H, m), 7.15 (1H, t, J=7.6 Hz), 6.86 (1H, brs), 6.63 (1H, dd, J=17.5, 11.1 Hz), 5.66 (1H, d, J=17.5 Hz), 5.22 (1H, d, J=11.1 Hz), 5.16 (1H, brs), 4.41 (1H, brs). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) δ; 155.9, 139.2, 137.4, 136.8, 135.7, 132.4, 129.3, 129.0, 128.3, 128.3, 128.2, 127.8, 127.5, 126.2, 116.0, 67.3, 54.4. MS m/z: 366 $(M+Na)^+$. Anal. calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.36; H, 6.33; N, 4.13.

4.2.3. Isopropyl benzyl(2-vinylphenyl)carbamate 1e. Colorless oil. IR (neat) ν; 1696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ; 7.61 (1H, d, J=7.6 Hz), 7.34–7.26 (6H, m), 7.20 (1H, t, J=7.6 Hz), 6.92 (1H, brs), 6.70 (1H, dd, J=17.4, 11.1 Hz), 5.73 (1H, d, J=17.6 Hz), 5.30 (1H, d, J=11.0 Hz), 5.11–5.02 (2H, m), 4.47 (1H, brs), 1.22 (6H, brs). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) δ; 155.7, 139.6, 137.4, 137.8, 135.7, 132.7, 129.2, 129.0, 128.3, 128.1, 127.5, 127.4, 126.1, 115.6, 69.2, 54.2, 22.0. MS m/z: 318 $(M+Na)^+$. Anal. calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.12; H, 7.30; N, 4.68.

4.2.4. Ethyl benzyl(2-vinylphenyl)carbamate 1f. Colorless oil. IR (neat) ν; 1702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ; 7.54 (1H, dd, J=7.8, 1.3 Hz), 7.28–7.18 (6H, m), 7.13 (1H, dd, J=7.6, 1.4 Hz), 6.84 (1H, d, J=7.4 Hz), 6.33 (1H, dd, J=17.5, 11.1 Hz), 5.65 (1H, dd, J=17.6, 0.9 Hz), 5.29 (1H, dd, J=11.0, 0.9 Hz), 5.05 (1H, brs), 4.40 (1H, brs), 4.14 (2H, brs), 1.14 (3H, brs). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) δ; 156.1, 139.4, 137.6, 135.7, 132.6, 129.2, 129.0, 128.3, 128.2, 127.6, 127.5, 126.1, 115.8, 61.7, 54.3, 14.6. MS m/z: 304 $(M+Na)^+$. Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.84; H, 6.81; N, 4.83.

4.2.5. Benzyl benzyl(3-methoxy-2-vinylphenyl)carbamate 1g. White solid: mp 64.0–65.0 °C. IR (KBr) ν; 1697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ; 7.39–7.14 (10H, m), 7.06 (1H, t, J=8.1 Hz), 6.83 (1H, d, J=8.2 Hz), 6.54 (1H, dd, J=17.9, 12.0 Hz), 6.48 (1H, brs), 5.79 (1H, dd, J=18.0, 2.2 Hz), 5.41 (1H, dd, J=6.0, 2.1 Hz), 5.17 (3H, brs), 4.23 (1H, d, J=14.0 Hz), 3.85 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) δ; 158.6, 155.9, 140.5, 137.6, 136.9, 129.0, 128.8, 128.3, 127.7, 127.4, 124.7, 122.2, 119.9, 110.4, 67.3, 55.8, 54.2. MS m/z: 396 $(M+Na)^+$. Anal. calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.19; H, 6.15; N, 3.73.

4.2.6. Benzyl benzyl(5-methoxy-2-vinylphenyl)carbamate 1h. Colorless oil. IR (neat) ν; 1703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ; 7.48 (1H, d, J=8.7 Hz), 7.26–7.22 (10H, m), 6.82 (1H, dd, J=8.7, 2.5 Hz), 6.55 (1H, dd, J=17.8, 11.1 Hz), 6.33 (1H, brs), 5.55 (1H, d, J=17.5 Hz), 5.16 (3H, brs), 5.11 (1H, d, J=11.1 Hz), 4.35 (1H, brs), 3.61 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) δ; 159.5, 155.8, 140.1, 137.5, 136.8, 131.9, 129.1, 128.3, 128.3, 127.8, 127.6, 127.0, 114.4, 114.3, 113.9, 67.4, 55.3, 54.3. MS m/z: 396 $(M+Na)^+$. Anal. calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.30; H, 6.09; N, 3.79.

4.2.7. *tert*-Butyl 2-allylphenyl(benzyl)carbamate 1i. Colorless oil. IR (neat) ν; 1697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ; 7.37–7.24 (7H, m), 7.18 (1H, t, J=6.8 Hz), 7.04–6.87 (1H, brs), 5.94–5.78 (1H, m), 5.13 (1H, d, J=10.0 Hz), 5.12 (1H, d, J=18.2 Hz), 5.02 (1H, d, J=14.6 Hz), 4.53 (1H, d, J=14.6 Hz), 3.40–3.12 (2H, m), 1.49 (9H, brs). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) δ; 155.0, 140.8, 138.2, 138.0, 136.7, 129.8, 128.9, 128.3, 127.4, 127.3, 126.7, 116.1, 80.1, 54.1, 35.2, 28.4. MS m/z: 324 $(M+H)^+$. Anal. calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.88; H, 7.79; N, 4.07.

4.2.8. Benzyl 2-allylphenyl(benzyl)carbamate 1j. Colorless oil. IR (neat) ν; 1703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ; 7.33–7.15 (13H, m), 6.95 (1H, brs), 5.77 (1H, brs), 5.22 (2H, brs), 5.09 (1H, d, J=14.8 Hz), 5.06 (1H, d, J=8.3 Hz), 5.04 (1H, d, J=15.3 Hz), 4.55 (1H, d, J=14.5 Hz), 3.31–3.07 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) δ; 155.9, 139.9, 138.1, 137.5, 136.8, 136.4, 130.0, 129.1, 129.0, 128.4, 127.7, 127.6, 126.9, 116.2, 67.3, 54.5, 35.2. MS m/z: 380 $(M+Na)^+$. Anal. calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.53; H, 6.60; N, 3.84.

4.2.9. *tert*-Butyl benzyl(2-vinylbenzyl)carbamate 1k. Colorless oil. IR (neat) ν; 1703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ; 7.48 (1H, d, J=7.5 Hz),

7.32–7.13 (8H, m), 6.91 (1H, dd, *J*=17.1, 11.1 Hz), 5.59 (1H, d, *J*=17.3 Hz), 5.26 (1H, d, *J*=11.0 Hz), 4.52 (2H, s), 4.33 (2H, s), 1.50 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) *δ*; 155.9, 138.2, 137.4, 134.9, 134.4, 128.5, 127.8, 127.6, 127.1, 126.3, 116.0, 80.1, 49.1, 47.1, 28.5. MS *m/z*: 346 $(M+Na)^+$. Anal. calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.93; H, 7.99; N, 4.38.

4.2.10. Benzyl benzyl(2-vinylbenzyl)carbamate 1m. Colorless oil. IR (neat) *ν*; 1699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) *δ*; 7.48 (1H, d, *J*=7.3 Hz), 7.34–7.12 (14H, m), 6.86 (1H, brs), 5.57 (1H, d, *J*=17.1 Hz), 5.26 (1H, s) 5.22 (1H, d, *J*=10.9 Hz), 4.59 (2H, brs), 4.41 (2H, brs). ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) *δ*; 156.6, 137.5, 136.8, 134.2, 128.5, 128.5, 128.0, 127.8, 127.7, 127.3, 126.4, 116.4, 67.6, 49.1, 47.2. MS *m/z*: 380 $(M+Na)^+$. Anal. calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.70; H, 6.76; N, 3.90.

4.2.11. *tert*-Butyl (4-methylphenyl)sulfonyl(2-vinylphenyl)carbamate 2d. White solid: mp 85.0–86.0 °C. IR (KBr) *ν*; 1739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*; 7.93 (2H, d, *J*=8.2 Hz), 7.67 (1H, d, *J*=7.8 Hz), 7.41–7.30 (4H, m), 7.18 (1H, d, *J*=7.8 Hz), 6.74 (1H, dd, *J*=17.4, 11.0 Hz), 5.79 (1H, d, *J*=17.4 Hz), 5.32 (1H, d, *J*=11.1 Hz), 2.47 (3H, s), 1.32 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*; 150.6, 144.6, 137.4, 136.6, 134.3, 131.9, 130.0, 129.3, 129.3, 129.1, 128.4, 125.9, 116.9, 84.2, 27.8, 21.7. MS *m/z*: 396 $(M+Na)^+$. Anal. calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.36; H, 6.09; N, 3.78.

4.2.12. *tert*-Butyl 2-allylphenyl[(4-methylphenyl)sulfonyl]carbamate 2e. White solid: mp 92.0–93.0 °C. IR (KBr) *ν*; 1730 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*; 8.03 (2H, d, *J*=8.3 Hz), 7.46–7.44 (4H, m), 7.37–7.33 (1H, m), 7.16 (1H, d, *J*=7.7 Hz), 6.04 (1H, ddt, *J*=16.9, 10.2, 6.8 Hz), 5.27 (1H, ddd, *J*=17.4, 3.3, 1.6 Hz), 5.21(1H, ddd, *J*=10.0, 2.7, 1.2 Hz), 3.63 (1H, dd, *J*=15.8, 7.0 Hz), 3.53 (1H, dd, *J*=15.7, 6.5 Hz), 2.57 (3H, s), 1.44 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*; 150.7, 144.6, 140.3, 136.8, 135.9, 135.4, 130.2, 129.3, 129.2, 128.9, 127.0, 116.8, 84.1, 35.7, 27.8, 21.7. MS *m/z*: 410 $(M+Na)^+$. Anal. calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 65.18; H, 6.46; N, 3.62.

4.2.13. Benzyl 2-allylphenyl[(4-methylphenyl)sulfonyl]carbamate 2f. White solid: mp 92.0–93.0 °C. IR (KBr) *ν*; 1736 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*; 8.04 (2H, d, *J*=8.3 Hz), 7.55–7.38 (8H, m), 7.25–7.20 (3H, m), 5.97 (1H, ddt, *J*=16.9, 10.2, 6.8 Hz), 5.26–5.15 (4H, m), 3.60 (1H, dd, *J*=16.1, 7.4 Hz), 3.54 (1H, dd, *J*=16.1, 6.9 Hz), 2.59 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*; 152.4, 145.3, 140.8, 136.5, 136.0, 135.3, 135.1, 130.8, 130.1, 129.8, 129.6, 129.6, 128.8, 128.7, 128.2, 127.5, 117.3, 69.0, 36.1, 22.1. MS *m/z*: 444 $(M+Na)^+$. Anal. calcd for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50; N, 3.32. Found: C, 68.45; H, 5.47; N, 3.35.

4.2.14. *trans*-2-Phenylcyclohexyl 2-allylphenyl[(4-methylphenyl)sulfonyl]carbamate 2g. White solid: mp 128.5–129.5 °C. IR (KBr) *ν*;1732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*; 7.87 (1H, d, *J*=8.2 Hz), 7.79 (1H, d, *J*=8.2 Hz), 7.34–7.02 (12H, m), 6.86–6.83 (3H, m), 6.78 (0.5H, d, *J*=7.8 Hz), 6.13 (1H, d, *J*=7.8 Hz), 5.88 (1H, ddt, *J*=16.9, 10.0, 6.9 Hz), 5.68–5.58 (0.5H, m), 5.16–4.99 (3H, m), 4.92–4.81 (1.5H, m), 3.44 (1H, dd, *J*=15.8, 7.1 Hz), 3.32 (1H, dd, *J*=15.7, 6.4 Hz), 3.07 (0.5H, dd, *J*=16.0, 6.2 Hz), 2.73 (0.5H, dd, *J*=16.0, 7.3 Hz), 2.50 (3H, s), 2.47 (1.5H, s), 2.44–2.31 (1.5H, m), 2.16–2.11 (1.5H, m), 1.82–1.78 (3H, m), 1.71–1.68 (1.5H, m), 1.49–1.16 (3H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*; 151.4, 151.3, 144.5, 142.4, 142.3, 140.2, 136.2, 135.8, 135.8, 129.9, 129.3, 129.2, 129.2, 129.1, 129.0, 128.9, 128.3, 128.0, 127.5, 127.3, 126.9, 126.7, 126.5, 126.2, 116.8, 116.7, 79.8, 79.3, 49.6, 49.2, 35.7, 34.7, 34.1, 33.9, 32.0, 31.9, 25.5, 24.6, 24.5, 21.7, 15.3. HRMS calcd for $C_{29}H_{31}NO_4S$: 512.1883 $(M+Na)^+$. Found: 512.1872.

4.3. General procedure for zirconocene–butene complex mediated reaction of carbamate derivatives

A solution of *N*-benzyl-*N*-benzyloxycarbonyl 2-aminostyrene **1d** (172 mg, 0.5 mmol) in THF (2 ml) was added to a solution of 'Cp_2Zr', prepared from Cp_2ZrCl_2 (175 mg, 0.6 mmol) and *n*-BuLi (1.30 M in hexane 0.92 ml, 1.2 mmol) in THF (2 ml) at −78 °C. After being stirred for 2 h at room temperature, the reaction mixture was quenched by the addition of 1 N HCl and then extracted with ether. The organic extracts were washed with brine and dried over $MgSO_4$. Purification of the residue obtained by evaporation of the solvent, by silica gel column chromatography (hexane–AcOEt, 10:1) gave the indoline derivative **3c** (71 mg, 59% yield).

4.3.1. 1-Benzyl-3-methyl-1,3-dihydro-*2H*-indol-2-one 3c.[11] White solid: mp 117.0–118.0 °C. IR (KBr) *ν*; 1715 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*; 7.34–7.24 (6H, m), 7.16 (1H, t, *J*=7.3 Hz), 7.02 (1H, t, *J*=7.5 Hz), 6.72 (1H, d, *J*=7.8 Hz), 4.91 (2H, s), 3.54 (1H, q, *J*=7.6 Hz), 1.54 (3H, d, *J*=7.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*; 178.7, 143.1, 136.0, 130.6, 128.7, 127.8, 127.5, 127.3, 123.5, 122.4, 108.9, 43.6, 40.5, 15.6. MS *m/z*: 238 $(M+H)^+$. HRMS calcd for $C_{16}H_{15}NO$: 238.1232 $(M+H)^+$. Found: 128.1222.

4.3.2. 1-Benzyl-4-methoxy-3-methyl-1,3-dihydro-*2H*-indol-2-one 3g. White solid: mp 88.0–89.0 °C. IR (KBr) *ν*; 1717 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*; 7.21–7.10 (5H, m), 7.00 (1H, t, *J*=8.2 Hz), 6.46 (1H, t, *J*=8.4 Hz), 6.27 (1H, d, *J*=7.8 Hz), 4.80 (1H, d, *J*=15.7 Hz), 4.74 (1H, d, *J*=15.7 Hz), 3.73 (3H, s), 3.46 (1H, q, *J*=7.5 Hz), 1.45 (3H, d, *J*=7.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*; 179.5, 156.4, 144.7, 136.6, 129.4, 129.1, 127.9, 127.6, 117.0, 105.9, 102.8, 55.7, 44.2, 40.0, 14.9. MS *m/z*: 268 $(M+H)^+$. Anal. calcd for $C_{17}H_{17}NO_2$: C,76.38; H, 6.41; N, 5.24. Found: C, 76.22; H, 6.47; N, 5.14.

4.3.3. 1-Benzyl-6-methoxy-3-methyl-1,3-dihydro-*2H*-indol-2-one 3h. White solid: mp 76.0–77.0 °C. IR (KBr) *ν*; 1694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*; 7.29–7.19 (5H, m), 7.08 (1H, dd, *J*=8.2, 0.8 Hz), 6.47 (1H, dd, *J*=8.1, 2.3 Hz), 6.27 (1H, d, *J*=2.2 Hz), 4.83 (2H, s), 3.68 (3H, s), 3.43 (1H, q, *J*=7.6 Hz), 1.46 (3H, d, *J*=7.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*; 179.4, 159.8, 144.2, 135.9, 128.7, 127.6, 127.3, 124.0, 122.7, 106.0, 97.2, 55.4, 43.7, 40.0, 15.9. MS *m/z*: 268 $(M+H)^+$. Anal. calcd for $C_{17}H_{17}NO_2$:

C,76.38; H, 6.41; N, 5.24. Found: C, 76.20; H, 6.49; N, 5.16.

4.3.4. 1-Benzyl-3-methyl-3,4-dihydro-2(*1H*)-quinolinone 3i.[12] White solid: mp 79.5–80.5 °C. IR (KBr) ν; 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.33–7.21 (5H, m), 7.17 (1H, d, J=7.3 Hz), 7.11 (1H, td, J=7.8, 1.2 Hz), 6.98 (1H, td, J=7.4, 0.6 Hz), 6.87 (1H, d, J=8.1 Hz), 5.28 (1H, d, J=16.2 Hz), 5.09 (1H, d, J=16.2 Hz), 3.06–2.98 (1H, m), 2.85–2.75 (2H, m), 1.35 (3H, d, J=6.5 Hz). ^{13}C NMR (100.6 Hz, $CDCl_3$) δ; 173.2, 139.7, 137.2, 128.7, 128.0, 127.3, 127.0, 126.3, 125.7, 122.8, 115.3, 46.4, 35.6, 33.4, 15.7. MS m/z: 252 $(M+H)^+$. Anal. calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.02; H, 6.79; N, 5.41.

4.3.5. 2-Benzyl-4-methyl-1,4-dihydro-3(*2H*)-isoquinolinone 3k. Pale yellow oil (unstable). IR (neat) ν; 1651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.35–7.18 (8H, m), 7.07 (1H, d, J=7.5 Hz), 4.79 (1H, d, J=14.8 Hz), 4.54 (1H, d, J=14.9 Hz), 4.44 (1H, d, J=15.7 Hz), 4.29 (1H, d, J=15.7 Hz), 3.66 (1H, q, J=7.3 Hz), 1.55 (3H, d, J=7.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 172.3, 137.9, 136.8, 131.0, 128.7, 127.8, 127.7, 127.5, 126.4, 126.2, 125.2, 50.1, 49.6, 41.6, 18.1. MS m/z: 274 $(M+Na)^+$. HRMS calcd for $C_{17}H_{17}NO$: 274.1208 $(M+H)^+$. Found: 174.1205.

4.3.6. *tert*-Butyl 2-methyl-3-(2-{[(4-methylphenyl)sulfonyl]amino}phenyl)-propanoate 4e. White solid: mp 113.0–114.0 °C. IR (KBr) ν; 3263, 1704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.92 (1H, brs), 7.62 (2H, d, J=8.3 Hz), 7.20 (2H, d, J=8.1 Hz), 7.16 (1H, td, J=7.6, 1.6 Hz), 7.10 (1H, td, J=7.4, 1.2 Hz), 7.04 (1H, dd, J=7.5, 1.6 Hz), 2.52–2.43 (2H, m), 2.38 (3H, s), 2.18–2.10 (2H, m), 1.32 (9H, s), 1.13 (3H, d, J=6.6 Hz). ^{13}C NMR (100.6 Hz, $CDCl_3$) δ; 176.7, 143.3, 137.3, 134.6, 133.6, 130.6, 129.4, 127.4, 127.1, 126.0, 125.6, 81.4, 42.6, 33.8, 27.9, 21.5, 18.5. MS m/z: 412 $(M+Na)^+$. Anal. calcd for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60. Found: C, 64.52; H, 6.88; N, 3.61.

4.3.7. *tert*-Butyl 2-[(*E*)-1-propenyl]phenylcarbamate 6e. Colorless oil. IR (KBr) ν; 3346, 1732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.79 (1H, d, J=6.9 Hz), 7.30 (1H, d, J=7.7 Hz), 7.21 (1H, t, J=7.5 Hz), 7.03 (1H, t, J=7.5 Hz), 6.45 (1H, d, J=15.6 Hz), 6.40 (1H, brs), 6.11 (1H, dq, J=15.6, 6.6 Hz), 1.93 (3H, dd, J=6.6, 1.6 Hz), 1.53 (9H, s). ^{13}C NMR (100.6 Hz, $CDCl_3$) δ; 153.1, 134.7, 130.0, 129.2, 127.6, 127.1, 126.0, 123.8, 121.3, 80.5, 28.4, 18.9. MS m/z: 178 $(M+Na)^+$. Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.90; H, 8.45; N, 5.82.

4.3.8. Benzyl 2-methyl-3-(2-{[(4-methylphenyl)sulfonyl]-amino}phenyl)propanoate 4f. White solid: mp 52.0–53.0 °C. IR (KBr) ν; 3330, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.70 (1H, brs), 7.61 (2H, d, J=8.3 Hz), 7.36–7.29 (4H, m), 7.20–7.14 (5H, m), 7. 09 (1H, td, J=7.4, 1.3 Hz), 7.04 (1H, td, J=7.6, 1.7 Hz), 5.07 (1H, d, J=12.3 Hz), 5.01 (1H, d, J=12.3 Hz), 2.70–2.59 (2H, m), 2.37 (3H, s), 2.32–2.24 (1H, m), 1.19 (3H, d, J=6.7 Hz). ^{13}C NMR (100.6 Hz, $CDCl_3$) δ; 176.9, 143.4, 137.2, 135.5, 134.6, 133.5, 130.6, 129.5, 128.5, 128.2, 128.0, 127.5, 127.1, 126.2, 125.7, 66.7, 41.5, 33.8, 21.5, 18.3. MS m/z: 424 $(M+H)^+$. Anal. calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 67.93; H, 6.06; N, 3.31.

4.3.9. *trans*-2-Phenylcyclohexyl 2-methyl-3-(2-{[(4-methylphenyl)sulfonyl]amino} phenyl)propanoate 4g. White solid: mp 110.0–112.0 °C. IR (KBr) ν; 3263, 1704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.86 (1H, brs), 7.59 (1H, d, J=8.3 Hz), 7.36 (2H, dd, J=8.0, 0.9 Hz), 7.23 (2H, d, J=7.0 Hz), 7.20–7.11 (6H, m), 7.04 (1H, dd, J=7.5, 1.2 Hz), 6.91(1H, dd, J=7.6, 1.4 Hz), 4.93 (1H, td, J=10.9, 4.2 Hz), 2.60 (1H, td, J=11.6, 3.4 Hz), 2.37 (3H, s), 2.31–2.24 (2H, m), 1.98 (1H, dd, J=13.1, 3.2 Hz), 1.94–1.88 (1H, m), 1.84–1.73 (3H, m), 1.53–1.16 (4H, m), 0.56 (3H, d, J=6.8 Hz). ^{13}C NMR (J=100.6 Hz, $CDCl_3$) δ; 176.6, 143.2, 142.9, 137.3, 134.5, 133.4, 130.5, 129.4, 128.3, 127.5, 127.3, 127.1, 126.5, 125.9, 125.4, 76.7, 49.4, 41.7, 34.0, 33.5, 32.1, 25.7, 24.7, 21.5, 17.8. MS m/z: 514 $(M+Na)^+$. Anal. calcd for $C_{29}H_{33}NO_4S$: C, 70.85; H, 6.77; N, 2.85. Found: C, 70.79; H, 6.84; N, 2.84.

4.4. Iodination reaction of the intermediate

After treating **1j** (179 mg, 0.5 mmol) with zirconocene–butene complex in THF as described in general procedure, to the reaction mixture was added iodine (508 mg, 2.0 mmol) dissolved in THF (2 ml), and then the whole was stirred for 1 h at −20 °C. Usual extractive work-up and purification of the crude material by silica gel column (hexane–AcOEt, 20:1) gave the iodide **11** in 50% yield.

4.4.1. 1-Benzyl-3-(iodomethyl)-3,4-dihydro-2(*1H*)-quinolinone 11. Light yellow solid: mp 92.0–93.0 °C. IR (KBr) ν; 1674 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.33–7.19 (6H, m), 7.14 (1H, t, J=7.8 Hz), 7.01 (1H, t, J=7.2 Hz), 6.89 (1H, d, J=8.1 Hz), 5.26 (1H, d, J=16.2 Hz), 5.09 (1H, d, J=16.2 Hz), 3.74 (1H, dd, J=10.1, 3.8 Hz), 3.38 (1H, dd, J=10.0, 8.8 Hz), 3.19 (1H, dd, J=15.3, 5.4 Hz), 3.01 (1H, dd, J=15.3, 11.3 Hz), 2.88 (1H, dddd, J=11.1, 8.9, 5.4, 3.6 Hz). ^{13}C NMR (100.6 Hz, $CDCl_3$) δ; 169.4, 139.2, 136.7, 128.8, 128.4, 127.8, 127.2, 126.3, 124.6, 123.3, 115.5, 46.6, 42.7, 32.1, 4.9. MS m/z: 400 $(M+Na)^+$. Anal. calcd for $C_{17}H_{16}INO$: C, 54.13; H, 4.28; N, 3.71. Found: C, 53.91; H, 4.53; N, 3.61.

4.4.2. Benzyl-4-methylene-1,4-dihydro-3(*2H*)-isoquinolinone 12. Pale yellow oil (unstable). IR (neat) ν; 1649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ; 7.66 (1H, d, J=7.5 Hz), 7.34–7.24 (7H, m), 7.08 (1H, d, J=7.3 Hz), 6.53 (1H, s), 6.09 (1H, s), 4.85 (2H, s), 4.47 (2H, s). ^{13}C NMR (100.6 Hz, $CDCl_3$) δ; 163.9, 136.6, 134.6, 131.1, 129.5, 128.7, 128.2, 128.1, 127.7, 127.6, 125.6, 123.8, 119.6, 50.5, 49.7. MS m/z: 250 $(M+H)^+$. HRMS calcd for $C_{17}H_{15}NO$: 250.1232 $(M+H)^+$. Found: 250.1234.

References and notes

1. Negishi, E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 1163.
2. Zirconium-mediated intermolecular coupling reaction of

alkyne with chloroformate to obtain the α,β-unsaturated esters was reported Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 3228.

3. For reviews on titanium-mediated alkene-carbonyl coupling reactions, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.
4. Ito, H.; Omodera, K.; Takigawa, Y.; Taguchi, T. *Org. Lett.* **2002**, *4*, 1499.
5. (a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115. (b) Negishi, E.; Maye, J. P.; Choueiry, D. *Tetrahedron* **1995**, *51*, 4447.
6. Zirconium mediated synthesis of polyfunctionalized indole and indoline derivatives from *N*-allyl-*o*-bromoaniline derivative. (a) Tidwell, J. H.; Senn, D. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 4685. (b) Tidwell, J. H.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 6380. (c) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797.
7. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
8. Dealkoxylation reaction took place by treating *o*-alkoxymethyl styrene with an equimolar amount of zirconocene–butene complex Hanzawa, Y.; Ikeuchi, Y.; Nakamura, T.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 6503.
9. (a) Ito, H.; Hanzawa, Y.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 774. (b) See also, Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299.
10. Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968.
11. Rajasekaran, A.; Mahesh, R.; Parimoo, P. J. *Heterocycl. Chem.* **1998**, *8*, 151.
12. Nishio, T.; Asai, H.; Miyazaki, T. *Helv. Chim. Acta* **2000**, *83*, 1475.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1393–1400
Tetrahedron

Haloamidation of alkynes and related reactions using zirconacycles and isocyanates

Yanzhong Li,[a,b] Hiroshi Matsumura,[a,b] Masamichi Yamanaka[a,b] and Tamotsu Takahashi[a,b,*]

[a]*Catalysis Research Center and Graduate School of Pharmaceutical Science, Hokkaido University, Kita-ku, Sapporo 060-0811, Japan*
[b]*CREST, Science and Technology Corporation (JST), Sapporo 060-0811, Japan*

Received 12 August 2003; accepted 27 August 2003

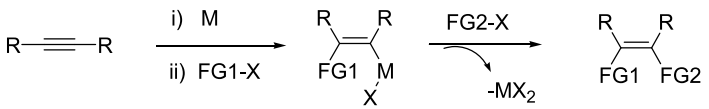
Abstract—Zirconacyclopentenes reacted with isocyanates to give aza- or oxazirconacycles which were conveniently coverted into the corresponding haloamidation products of alkynes after halogenation. 1,4-Bistrimethylsilyl substituted zirconacyclopentadiene afforded a low yield of iodoamidation product, whereas zirconium–alkyne complexes stabilized with phosphine gave the iodoamidation products in moderate yields. On the other hand, zirconacyclopentanes reacted with isocyanates to give trimerization products of isocyanate, isocyanurates.

1. Introduction

Metallacycles are very useful intermediates in organic synthesis since they can be readily prepared from alkynes or alkenes and low-valent metal species.[1] Zirconacycles, including zirconacyclopentanes,[2] zirconacyclopentenes,[3] and zirconacyclopentadienes,[4] have been conveniently prepared from Cp_2ZrEt_2 or Cp_2ZrBu_2. A variety of novel reactions have been developed by the reaction of zirconacycles with alkynes,[5] alkenes[6] and other unsaturated molecules.[7] Addition of two functional groups to alkynes is one of the most important and attractive reactions to obtain stereodefined bifunctionalized olefins from alkynes. Stepwise bifunctionalization of alkynes using Zr can be classified into two ways. One way is shown in Scheme 1 where M traps the leaving group X from FG1–X in the intermediate.

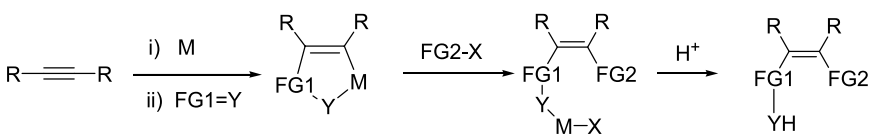
This way consists of allylzirconation of alkynes,[8] vinylzirconation of alkynes,[9] alkynylzirconation of alkynes[10] and metalloesterification of alkynes.[11] The other way is shown in Scheme 2 where coupling reaction of alkynes with unsaturated compounds on Zr affords zirconacycles. Haloamidation reaction we describe here belongs to this way.

Herein we would like to report haloamidation of alkynes by the reaction of zirconacyclopentenes with isocyanates (Scheme 3). Iodoamidation of trimethylsilyl substituted



FG1, FG2: functional groups

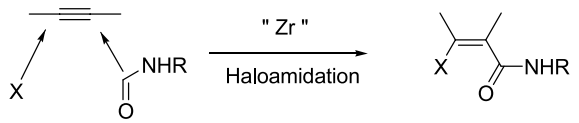
Scheme 1. FG1, FG2: functional groups.



Scheme 2.

Keywords: Zirconacyclopentene; Zirconacyclopentadiene; Zirconacyclopentane; Haloamidation; Isocyanate; Isocyanurate; Trimerization of isocyanate.
* Corresponding author at present address: Catalysis Research Center and Graduate School of Pharmaceutical Science, Hokkaido University, Kita-ku, Sapporo 060-0811, Japan. Fax: +81-11-706-3274; e-mail address: tamotsu@cat.hokudai.ac.jp

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.08.078



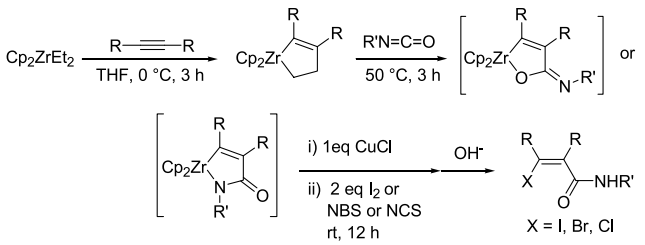
Scheme 3.

alkynes could be also achieved through zirconacylopentadienes. On the other hand, we found that zirconacyclopentane is a reactive catalyst for trimerization of isocyanates.

2. Results and discussion

2.1. Haloamidation of alkynes using zirconacyclopentenes and isocyanates

We have already reported that Cp_2ZrEt_2, prepared in situ from Cp_2ZrCl_2 and 2 equiv. of EtMgBr, reacted with an alkyne to give zirconacyclopentenes. The ethylene moiety of zirconacyclopentenes could be easily replaced by unsaturated compounds via β,β′ carbon–carbon bond cleavage reaction. We have also reported the formation of symmetrical or unsymmetrical zirconacyclopentadienes with the second alkynes,[4c] oxazirconacyclopentenes with aldehydes,[12] and azazirconacyclopentadienes with nitriles[12] using this strategy. In a similar way, as shown in Eq. 1, reaction of zirconacyclopentenes with isocyanates as unsaturated compounds smoothly gave oxa- or aza-zirconacycles[13d] which afforded the iodoamidation products of an alkyne by treatment with I_2 in the presence of CuCl followed by hydrolysis (Eq. 1). In the absence of CuCl, the reaction did not complete even when 4 equiv. of halogenation reagent was added.



(1)

Representative results were summarized in Table 1. Alkyl substituted alkynes (Table 1, entries 1, 3, and 4), such as 3-hexyne, 4-octyne, could be used in the reaction and gave moderate yields of the products (45, 48, 43% for **1a**, **1c**, **1d**, respectively). Aryl substituted alkynes, for example, dithienyl acetylene (Table 1, entry 12), bis(methoxyphenyl) acetylene (Table 1, entry 13) also gave the corresponding iodoamidation products (**1l**, **1m**) in good yields. In the case of diphenyl acetylene, phenyl isocyanate as well as butyl isocyanate could be employed in the reaction and resulted in the formation of the desired products (**1h**, **1i**) in high yields (Table 1, entries 8 and 9).

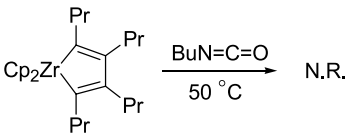
There were several reports on a coupling reaction of an alkyne and an isocyanate on early transition metals. However, only hydrolysis or other type of reaction have been reported.[13] Moreover, there is no information on the metal-containing species. In order to observe the intermediate, we monitored this reaction by NMR spectroscopy. When diphenyl substituted zirconacyclopentene reacted with butyl isocyanate at 50 °C for 3 h, ^{1}H NMR spectrum of the reaction mixture showed the peak of Cp protons at 6.05 ppm as a singlet. Its ^{13}C NMR spectrum showed the Cp at 112.38 ppm. Other signals appeared at 228.13 ppm (C–Zr), 152.18 ppm (β-carbon), 178.52 ppm (carbonyl- or imino-carbon), and four carbons for the butyl group at 14.45, 20.61, 32.09, 41.67 ppm, respectively. It indicated that there was only one kind of zirconacycle produced in the reaction mixture. Although we could not make clear whether it is an azazirconacycle or an oxazirconacycle. Effort was also made for preparing crystals suitable for X-ray analysis, but not successful so far.

When thus formed aza- or oxa-zirconacycles were treated with *N*-bromosuccinimide (NBS) in the presence of stoichiometric amount of CuCl, the corresponding bromoamidation products were obtained. Results of bromoamidation of various alkynes were also shown in Table 1. Not only the alkyl and aryl substituted alkynes (Table 1, entries 2, 5, 7, and 10) resulted in good yields of the bromoamidation products (**1b**, **1e**, **1g**, **1j**), but also the trimethyl silyl substituted alkynes (Table 1, entry 14) gave reasonable yields of the desired product (**1n**).

We applied the similar strategy for the chloroamidation of alkynes. It should be pointed out that EtMgCl was used instead of EtMgBr for the preparing of Cp_2ZrEt_2 in order to avoid the halogen exchange reaction.[11] When *N*-chlorosuccinimide (NCS) was employed instead of NBS in the reaction, the corresponding chloride derivatives (**1f**, **1k**) were produced in good to high yields (Table 1, entries 6 and 11).

2.2. Iodoamidation of alkynes using zirconacyclopentadienes and isocyanates

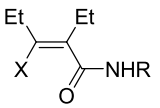
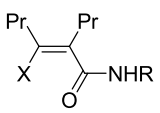
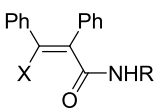
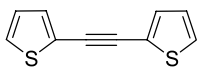
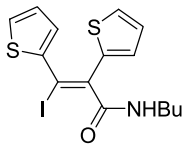
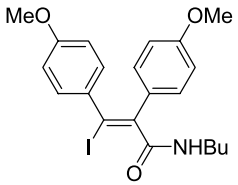
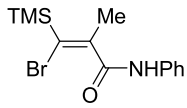
Tetrapropyl substituted zirconacyclopentadiene, prepared in situ from Cp_2ZrBu_2 and 2 equiv. of 4-octyne, did not react with butyl isocyanate. Zirconacyclopentadienes remained unreacted (Eq. 2).



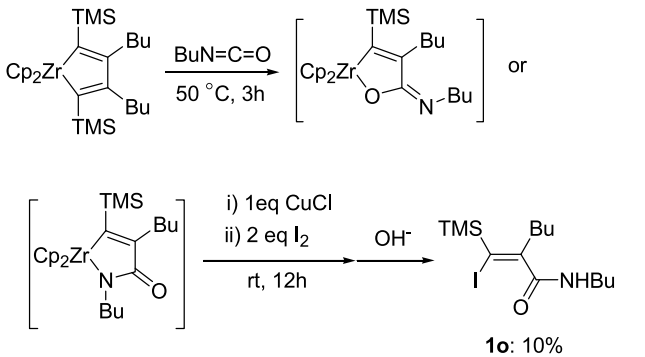
(2)

When 2 equiv. of CuCl or 1 equiv. of $NiCl_2(PPh_3)_2$ was added to the reaction mixture, the zirconacyclopentadiene was consumed, but no identified products were obtained. Yet if the 1,4-bis-trimethylsilyl substituted zirconacyclopentadiens were employed in the reaction, oxa- or aza-zirconacycle was formed, but around 50% of the zirconacyclopentadiene remained.[14] Therefore, iodoamidation product **1o** of alkyne was produced in low yield (10%) after iodination (Eq. 3).

Table 1. Haloamidation of alkynes using zirconacyclopentenes[a]

Entry	Alkyne	Isocyanate	Product	Yield (%)[b]
1	Et—≡—Et	RN=C=O	 (R=Ph, X=I: **1a**)	45
2			(R=Ph, X=Br: **1b**)	58
3			(R=Bu, X=I: **1c**)	48
4	Pr—≡—Pr	RN=C=O	 (R=Ph, X=I: **1d**)	43
5			(R=Ph, X=Br: **1e**)	62
6			(R=Ph, X=Cl: **1f**)	53
7			(R=Bn, X=Br: **1g**)	70
8	Ph—≡—Ph	RN=C=O	 (R=Ph, X=I: **1h**)	70
9			(R=Bu, X=I: **1i**)	57
10			(R=Bu, X=Br: **1j**)	46
11			(R=Bu, X=Cl: **1k**)	90
12		BuN=C=O	 (**1l**)	56
13	MeO—≡—OMe	BuN=C=O	 (**1m**)	82
14	TMS—≡—Me	PhN=C=O	 (**1n**)	38

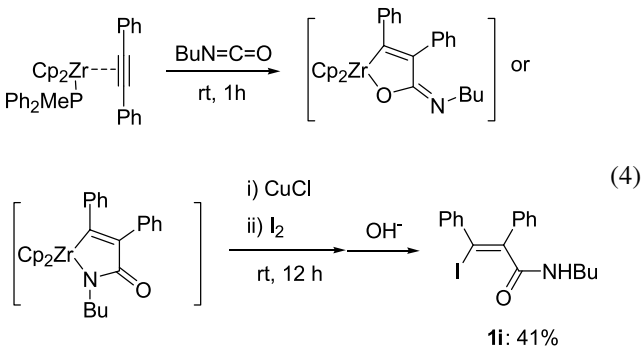
[a] Reaction conditons: 1:1.5:1:2 molar ratio of alkyne, isocyanete, CuCl and halogenation reagent, hydrolyzed with sat. $NaHCO_3$ aq.
[b] Isolated yield.



(3)

2.3. Iodoamidation of alkynes mediated by zirconium alkyne complexes

It is known that a zirconium alkyne complex stabilized by $MePPh_2$ reacted with isocyanate to give the corresponding oxa- or aza-zirconacycle.[15] Iodoamidation products were obtained after iodination (Eq. 4).



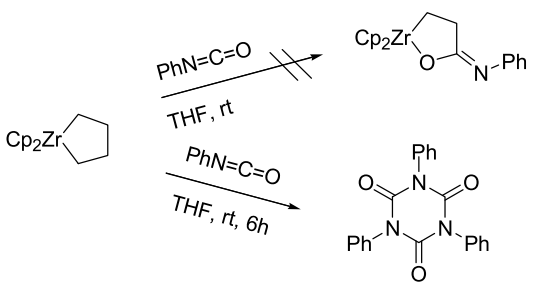
(4)

When diphenylacetylene was used in the reaction, compound **1i** was obtained in 41% isolated yield. Alkyl substituted alkynes usually are not suitable for this reaction because its zirconium alkyne complexes were not stable and gave homocoupling products.

2.4. Reaction of zirconacyclopentanes with isocyanates

In order to investigate the scope of the reaction of zirconacycles, we tried the reaction of zirconacyclopentane with isocyanates. Zirconacyclopentane has shown similar

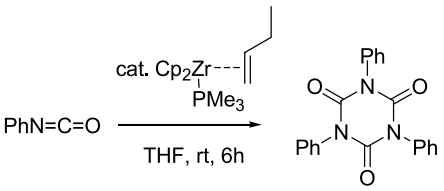
reactivity towards aldehydes or ketones to afford oxazirconacyclopentanes. We expected the similar oxa- or azazirconacycles would be formed in the case of isocyanates. However, cyclotrimerization compound **2a** of phenyl isocyanate was obtained as the sole product when phenyl isocyanate was employed (Eq. 5).



(5)

2a: 79%

Cyclotrimerization of phenyl isocyanate was reported by many groups using base or Lewis acid.[16] Catalytic cyclotrimerization of isocyanates using metallocene, however, has not been reported. This prompted us to investigate the trimerization using various zirconocene compounds. The use of catalytic amount (10 mol%) of the zirconium 1-butene complex stabilized with trimethyl phosphine afforded cyclotrimerization product in 71% yield (Eq. 6).

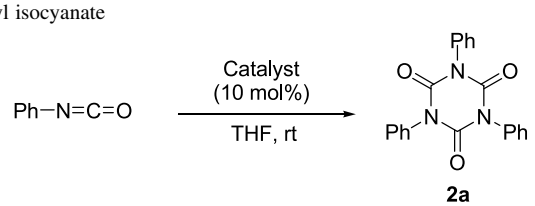


(6)

2a: 71%

Various group 4 metallocenes were used for the trimerization. The results were summarized in Table 2. Dibutylzirconocene and dibutyl hafnocene catalyzed the trimerization and both gave the product in 82% yields in 6 h. Dibutyltitanocene gave only 7% of the isocyanurate. This may be due to the instability of the titanocene complex. While zirconocene complex bearing bulky ligand such as *t*-butylcyclopentadienyl could catalyze the reaction smoothly. Metallocene dihalide of group 4 metals gave low yields of the corresponding trimer even after 48 h. In the case of dimethylzirconocene, product was obtained in 46% yield within 24 h.

Table 2. Group 4 metallocene complexes catalyzed cyclotrimerization of phenyl isocyanate

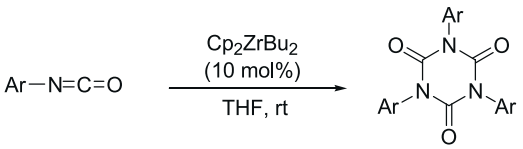


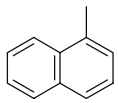
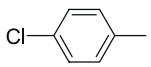
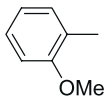
2a

Entry	Catalyst	Time (h)	Yield (%)[a]
1	Cp_2ZrBu_2	6	82
2	Cp_2TiBu_2	6	7
3	Cp_2HfBu_2	6	82
4	$(t\text{-}BuC_5H_4)_2ZrBu_2$	6	79
5	Cp_2ZrCl_2	48	28
6	Cp_2TiCl_2	48	28
7	Cp_2HfCl_2	48	20
8	Cp_2ZrMe_2	24	46

[a] Isolated yield.

Table 3. Zirconocene catalyzed cyclotrimerization of aryl isocyanates

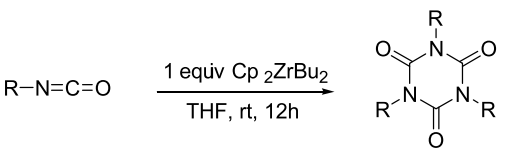


Entry	Ar	Time (h)	Product	Yield (%)[a]
1		6	**2b**	82
2		6	**2c**	78
3		24	**2d**	60

[a] Isolated yield.

Among all these catalysts, dibutyl zirconocene gave the best result. We applied these conditions to the trimerization of other aryl isocyanates. Results were given in Table 3. 1-Naphthyl isocyanate reacted smoothly to give the corresponding isocyanurate **2b** in 82% yield for 6 h. Isocyanate containing electron-withdrawing group such as *p*-chloro phenyl isocyanate also gave 78% (**2c**) yields, while 2-methoxyphenyl isocyanate gave moderate yield of the product (**2d**) even after prolonged reaction time (24 h).

Alkyl isocyanates are less reactive for the trimerization reaction compared with aryl isocyantes.[16g] Dibutylzirconocene could not catalyze its trimerization. Stoichiometric amount of the dibutyl zirconocene was necessary to achieve reasonable yields of the trimer (Eq. 7).



(7)

2e: R = Et, 61%
2f: R = Bn, 68%

3. Conclusion

Alkyl, aryl as well as trimethylsilyl substituted alkynes could be conveniently converted to the corresponding iodoamidation bromoamidation chloroamidation products in good to high yields using zirconacyclopentenes. Zirconacyclopentenes reacted with isocyanates to give oxa- or azazirconacycles. The intermediate was observed by NMR study. Aryl isocyanates were trimerized by a catalytic amount of zirconacyclopentane and dibutylzirconocene.

Trimerization of alkyl isocyanates required a stoichiometric amount of zirconocene complex.

4. Experimental

4.1. General

Unless otherwise noted, all starting materials were commercially available and were used without further purification All reactions were run under a slightly positive pressure of dry N_2. THF was refluxed and distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Zirconocene dichloride was purchased from Nichia Corporation. Ethylmagnesium bromide(THF solution), *n*-butyllithium(hexane solution), were purchased from Kanto Chemicals Co., Ltd. CuCl was purchased from Wako. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-400 or JEOL JNM-300 NMR spectrometer. GC analysis was performed on a gas chromatograph equipped with a flame ionization detector using a capillary column (CBP1-M25-025).

4.2. Haloamidation reaction

4.2.1. A typical procedure for iodoamidation of alkynes via zirconacyclopentenes. To a solution of Cp_2ZrCl_2 (1.75 g, 6.0 mmol) in 25 mL of THF, EtMgBr (0.89 M hexane solution, 13.5 mL, 12.0 mmol) was added at 78 °C. After stirring for 1 h at −78 °C, 4-octyne (0.734 mL, 5.0 mmol) was added and the reaction mixture was warmed to 0 °C for 3 h. Then phenyl isocyanate (0.815 mL, 7.5 mmol) was added and the reaction mixture was stirred at 50 °C for 3 h. And then CuCl (495 mg, 5.0 mmol) and iodine (2.53 g, 10.0 mmol) were added. The reaction mixture was stirred at room temperature for 12 h. Then it was quenched with saturated $NaHCO_3$ solution, filtrated through celite, extracted with AcOEt. The organic layer was dried over Na_2SO_4. Purification by flash column chromatography gave **1d** (43%).

4.2.2. A typical procedure for bromoamidation of alkynes via zirconacyclopentenes. A similar procedure as described above for iodoamidation. Using NBS instead of I_2 gave the bromination products.

4.2.3. A typical procedure for the chloroamidation of alkynes via zirconacyclopentenes. This reaction was also carried out in a similar manner as that for iodination. EtMgCl should be used instead of EtMgBr to avoid halogen exchange reaction.[11] The use of NCS instead of I_2 gave the desired products.

4.2.4. A typical procedure for the iodoamidation of alkynes via zirconacyclopentadiene. To a solution of Cp_2ZrCl_2 (351 mg, 1.2 mmol) in 5 mL of THF, *n*-BuLi (1.58 M hexane solution, 1.52 mL, 2.4 mmol) was added at −78 °C. After stirring for 1 h at −78 °C, 1-trimethylsilyl-1-hexyne (0.404 mL, 2.0 mmol) was added and the reaction mixture was warmed to room temperature for 1 h. Then butyl isocyanate (0.163 mL, 1.5 mmol) was added and the reaction mixture was heated to 50 °C for 3 h. Then CuCl (99 mg, 1.0 mmol) and I_2 (1012 mg, 4.0 mmol) were added. The resulting mixture was stirred for 12 h. After quenching with saturated $NaHCO_3$ solution the mixture was extracted with AcOEt. The organic layer was dried over Na_2SO_4. Purification by flash column chromatography gave the product in 40 mg (isolated yield 10%).

4.2.5. A typical procedure for the iodoamidation of alkynes via zirconium alkyne complexes. To a solution of Cp_2ZrCl_2 (351 mg, 1.2 mmol) in 5 mL of THF, *n*-BuLi (1.58 M hexane solution, 1.52 mL, 2.4 mmol) was added at −78 °C. After stirring for 1 h at −78 °C, $MePPh_2$ (0.223 mL, 1.2 mmol) was added and the reaction mixture was warmed to room temperature for 1 h. Then diphenyl acetylene (178 mg, 1.0 mmol) was added and the mixture was stirred for 1 h. Then butyl isocyanate (0.163 mL, 1.5 mmol) was added and the reaction mixture was stirred for 1 h. To the mixture CuCl (99 mg, 1.0 mmol) and I_2 (1012 mg, 4.0 mmol) were added and the mixture was stirred for 12 h. After quenching with saturated $NaHCO_3$ solution the mixture was extracted with AcOEt. The organic layer was dried over Na_2SO_4. Purification by flash column chromatography gave the product in 167 mg (isolated yield 41%).

4.3. Preparation of aza- or oxa-zirconacycle

To a THF solution of 2.0 mmol of Cp_2ZrEt_2, which was prepared from Cp_2ZrCl_2 (2.2 mmol, 643 mg) and EtMgBr (0.86 M THF solution, 5.2 mL, 4.4 mmol) in 5.0 mL THF at −78 °C, was added diphenylacetylene (356 mg, 2.0 mmol). After stirring the mixture at 0 °C for 3 h, buthyl isocyanate (0.335 mL, 3.0 mmol) was added to the reaction mixture at 0 °C. The mixture was kept at 50 °C for 3 h and evaporated to dry in vacuo. The residue was dissolved in 5.0 mL of benzene. After filtration, the resulting solid was dissolved in C_6D_6 and characterized by NMR.

4.3.1. 2-Ethyl-3-iodopent-2-enoic acid phenylamide (1a). Isolated yield 45%. Colorless solid: mp 109–112 °C. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.13 (t, J=7.6 Hz, 3H), 1.14 (t, J=7.4 Hz, 3H), 2.48 (q, J=7.6 Hz, 2H), 2.61 (q, J=7.4 Hz, 2H), 7.12–7.16 (m, 1H), 7.26 (bs, 1H), 7.32–7.37 (m, 2H), 7.56–7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.44, 14.12, 25.07, 34.24, 105.11, 120.12, 124.67, 129.00, 137.35, 145.54, 169.09; IR (nujol) 3193, 1647, 1592, 758 cm^{-1}; HRMS calcd for $C_{13}H_{16}INO$ 329.0277, found 329.0285.

4.3.2. 3-Bromo-2-ethylpent-2-enoic acid phenylamide (1b). Isolated yield 58%. Colorless solid: mp 104–106 °C. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.14 (t, J=7.6 Hz, 3H), 1.20 (t, J=7.3 Hz, 3H), 2.53 (q, J=7.6 Hz, 2H), 2.64 (q, J=7.3 Hz, 2H), 7.14–7.18 (m, 2H), 7.34–7.38 (m, 2H), 7.53–7.55 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 12.05, 13.88, 28.50, 32.74, 119.84, 124.86, 129.18, 132.84, 137.23, 138.33, 166.44; IR (nujol) 3252, 2988, 1636, 1539, 760 cm^{-1}; HRMS calcd for $C_{13}H_{16}BrNO$ 281.0415, found 281.0409.

4.3.3. 2-Ethyl-3-iodopent-2-enoic acid butylamide (1c). Isolated yield 48%. Pale yellow oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.95 (t, J=7.3 Hz, 3H), 1.07 (t, J=7.6 Hz, 3H), 1.09 (t, J=7.3 Hz, 3H), 1.37–1.46 (m, 2H), 1.53–1.62 (m, 2H), 2.39 (q, J=7.6 Hz, 2H), 2.55 (q, J=7.3 Hz, 2H), 3.31–3.36 (m, 2H), 5.46 (bs, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ

13.43, 13.71, 14.12, 20.23, 24.82, 31.23, 34.14, 39.30, 104.13, 145.75, 171.12; IR (neat) 3283, 2938, 1631, 1547 cm^{-1}; HRMS calcd for $C_{11}H_{20}INO$ 309.0590, found 309.0570.

4.3.4. 3-Iodo-2-propylhex-2-enoic acid phenylamide (1d). Isolated yield 43%. Colorless solid: mp 95–96 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.96 (t, J=7.3 Hz, 3H), 0.98 (t, J=7.4 Hz, 3H), 1.53–1.65 (m, 4H), 2.42–2.46 (m, 2H), 2.54–2.58 (m, 2H), 7.07 (bs, 1H), 7.13–7.17 (m, 1H), 7.34–7.38 (m, 2H), 7.55–7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.10, 13.19, 21.99, 22.61, 34.05, 42.39, 103.95, 120.12, 124.74, 129.06, 137.33, 145.18, 169.19; IR (nujol) 3249, 2973, 1599, 1539, 758 cm^{-1}. Anal. calcd for $C_{15}H_{20}INO$: C,50.43; H, 5.64; N, 3.92. Found: C, 50.71; H, 5.63; N, 3.60.

4.3.5. 3-Bromo-2-propylhex-2-enoic acid phenylamide (1e). Isolated yield 62%. Colorless solid: mp 72–74 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.95 (t, J=7.3 Hz, 3H), 0.96 (t, J=7.3 Hz, 3H), 1.52–1.67 (m, 4H), 2.37–2.41 (m, 2H), 2.49–2.52 (m, 2H), 7.10–7.14 (m, 1H), 7.30–7.34 (m, 2H), 7.58–7.59 (m, 2H), 7.65 (bs, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.19, 13.79, 21.34, 21.65, 33.76, 38.71, 120.04, 124.40, 124.81, 128.80, 137.47, 138.46, 167.67; IR (nujol) 3276, 2967, 1651, 1537, 754 cm^{-1}. Anal. Calcd for $C_{15}H_{20}BrNO$: C, 58.07; H, 6.50; Br, 25.76; N, 4.51. Found: C, 57.76; H, 6.46; Br, 25.69; N, 4.44.

4.3.6. 3-Chloro-2-propylhex-2-enoic acid phenylamide (1f). Isolated yield 53%. Colorless solid: mp 85–86.5 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.96 (t, J=7.4 Hz, 3H), 0.98 (t, J=7.4 Hz, 3H), 1.50–1.57 (m, 2H), 1.64–1.70 (m, 2H), 2.38–2.45 (m, 4H), 7.12–7.15 (m, 1H), 7.30 (bs, 1H), 7.32–7.36 (m, 2H), 7.55–7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.41, 13.87, 20.71, 21.88, 33.25, 37.03, 119.98, 124.53, 128.98, 132.98, 135.27, 137.52, 166.71; IR (nujol) 3268, 2977, 1659, 1618, 1537, 756 cm^{-1}; HRMS calcd for $C_{15}H_{20}ClNO$ 265.1233, found 265.1246.

4.3.7. 3-Bromo-2-propylhex-2-enoic acid benzylamide (1g). Isolated yield 70%. Colorless solid: mp 54–56 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.93 (t, J=7.3 Hz, 3H), 0.94 (t, J=7.3 Hz, 3H), 1.45–1.66 (m, 4H), 2.31–2.36 (m, 2H), 2.44–2.49 (m, 2H), 4.52 (d, J=5.7 Hz, 2H), 5.08 (bs, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.24, 13.84, 21.41, 21.77, 33.80, 38.77, 43.79, 124.40, 127.60, 128.15, 128.65, 137.67, 138.32, 169.51; IR (nujol) 3243, 3108, 1628, 1559, 1316, 731 cm^{-1}; HRMS calcd for $C_{16}H_{22}BrNO$ 323.0884, found 323.0877.

4.3.8. 3-Iodo-2,3,*N*-triphenylacrylamide (1h). Isolated yield 70%. Colorless solid: mp 222–223 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 7.13–7.25 (m, 11H), 7.33–7.37 (m, 3H), 7.58–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 100.82, 120.18, 124.89, 128.15, 128.18, 128.38, 128.45, 128.97, 129.08, 129.47, 135.28, 137.36, 142.35, 145.91, 167.71; IR (nujol) 2975, 2867, 1653, 1545, 754, 696 cm^{-1}; HRMS calcd for $C_{21}H_{16}INO$ 405.0590, found 405.0591.

4.3.9. *N*-Butyl-3-iodo-2,3-diphenylacrylamide (1i). Isolated yield 57%. Colorless solid: mp 131–132 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.92 (t, J=7.3 Hz, 3H), 1.36–1.41 (m, 2H), 1.54–1.62 (m, 2H), 3.34–3.39 (m, 2H), 5.78 (m, 1H), 7.09–7.20 (m, 10H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.68, 20.12, 31.18, 39.56, 99.63, 127.81, 127.99, 128.09, 128.17, 128.79, 129.43, 135.60, 142.48, 146.29, 169.86; IR (nujol) 2969, 1640, 1543, 694 cm^{-1}; HRMS calcd for $C_{19}H_{20}INO$ 405.0590, found 405.0591.

4.3.10. 3-Bromo-*N*-butyl-2,3-diphenylacrylamide (1j). Isolated yield 46%. Colorless solid: mp 138–139.5 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.93 (t, J=7.3 Hz, 3H), 1.34–1.45 (m, 2H), 1.53–1.62 (m, 2H), 3.35–3.41 (m, 2H), 5.77 (bs, 1H), 7.14–7.26 (m, 10H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.69, 20.09, 31.31, 39.52, 122.47, 127.94, 128.08, 128.31, 128.63, 128.78, 129.78, 135.60, 138.77, 140.00, 168.48; IR (nujol) 3279, 1628, 1543, 694 cm^{-1}; HRMS calcd for $C_{19}H_{20}BrNO$ 357.0728, found 357.0723.

4.3.11. *N*-Butyl-3-chloro-2,3-diphenylacrylamide (1k). Isolated yield 90%. Colorless solid: mp 152–155 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.74 (t, J=7.3 Hz, 3H), 0.92–1.01 (m, 2H), 1.08–1.15 (m, 2H), 3.01–3.06 (m, 2H), 5.39 (bs, 1H), 7.33–7.44 (m, 6H), 7.53–7.54 (m, 2H), 7.57–7.61 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.61, 19.71, 30.81, 39.47, 128.34, 128.37, 128.38, 128.41, 128.80, 129.42, 134.79, 136.08, 137.18, 138.13, 167.21; IR (nujol) 3241, 1626, 1543, 696 cm^{-1}; HRMS calcd for $C_{19}H_{20}ClNO$ 313.1254, found 313.1233.

4.3.12. 3-Iodo-*N*-phenyl-2,3-dithiophen-2-ylacrylamide (1l). Isolated yield 56%. Colorless solid: mp 104–107 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.96 (t, J=7.3 Hz, 3H), 1.41–1.47 (m, 2H), 1.60–1.67 (m, 2H), 3.42–3.47 (m, 2H), 5.79 (m, 1H), 6.86 (dd, J=5.1, 3.7 Hz, 1H), 6.98 (dd, J=5.1, 3.7 Hz, 1H), 7.03 (dd, J=3.7, 0.8 Hz, 1H), 7.12 (dd, J=3.7, 0.8 Hz, 1H), 7.20 (dd, J=5.1, 0.8 Hz, 1H), 7.42 (dd, J=5.1, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.69, 20.17, 31.08, 39.71, 86.18, 126.33, 127.23, 128.23, 128.28, 129.35, 129.58, 136.70, 142.32, 144.09, 169.03; IR (nujol) 2936, 1638, 1547, 702 cm^{-1}; HRMS calcd for $C_{15}H_{16}INOS_2$ 416.9736, found 416.9718.

4.3.13. 3-Iodo-2,3-bis (4-methoxyphenyl)-*N*-phenylacrylamide (1m). Isolated yield 82%. Colorless solid: mp 138–140 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.93 (t, J=7.3 Hz, 3H), 1.35–1.44 (m, 2H), 1.54–1.62 (m, 2H), 3.34–3.40 (m, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 5.62 (bt, J=5.3 Hz, 1H), 6.64–6.70 (m, 4H), 7.03–7.05 (m, 2H), 7.14–7.17 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.65, 20.09, 31.18, 39.48, 55.02, 55.11, 113.35, 113.53, 128.07, 130.12, 130.99, 134.96, 145.02, 158.82, 158.97, 170.42; IR (nujol) 2942, 1634, 1505, 1254 cm^{-1}; HRMS calcd for $C_{21}H_{24}INO_3$ 465.0795, found 465.0801.

4.3.14. 3-Bromo-2-methyl-*N*-phenyl-3-trimethylsilylacrylamide (1n). Isolated yield 38%. Colorless solid: mp 115–117 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.34 (s, 9H), 2.13 (s, 3H), 7.13–7.16 (m, 1H), 7.21 (bs, 1H), 7.33–7.37 (m, 2H), 7.56–7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 0.33, 20.12, 120.09, 124.69, 124.93, 129.05, 137.26, 146.58, 168.20; IR (nujol) 2934, 1657, 1615, 1250 cm^{-1}; HRMS calcd for $C_{13}H_{18}BrNOSi$ 311.0341, found 311.0361.

4.3.15. 2-(Iodotrimethylsilanylmethylene)hexanoic acid butylamide (1o). Isolated yield 10%. Pale yellow oil: ^1H

NMR ($CDCl_3$, Me_4Si) δ 0.16 (s, 9H), 0.74 (t, J=7.3 Hz, 3H), 0.79 (t, J=7.3 Hz, 3H), 1.12–1.21 (m, 2H), 1.23–1.33 (m, 4H), 1.39–1.47 (m, 2H), 2.25–2.29 (m, 2H), 3.16–3.21 (m, 2H), 5.49 (bt, J=5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 1.39, 13.56, 13.67, 20.09, 22.38, 30.93, 31.07, 35.13, 39.01, 104.62, 158.51, 171.32; IR (neat) 2965, 1631, 1615, 1250 cm^{-1}; HRMS calcd for $C_{14}H_{28}INOSi$ 381.0985, found 381.0980.

4.4. A typical procedure for the preparation of triphenyl isocyanurate

To a solution of Cp_2ZrCl_2 (29 mg, 0.1 mmol) in THF (5 mL) was added *n*-BuLi (1.58 M hexane solution, 0.13 mL, 0.2 mmol) at −78 °C and stirred for 1 h. The mixture was warmed to room temperature and stirred for 1 h. Phenyl isocyanate (357 mg, 3.0 mmol) was added and stirred for 6 h at room temperature. Then the reaction mixture was quenched with saturated $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel.

4.4.1. Triphenyl isocyanurate (2a).[16] Isolated yield 82%. Colorless solid: mp 279–280 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 7.33–7.51 (m, 15H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 128.21, 128.75, 129.16, 133.40, 148.45; HRMS calcd for $C_{21}H_{15}N_3O_3$ 357.1113, found 351.1154.

4.4.2. Tris(1-naphthyl) isocyanurate (2b). Isolated yield 82%. Colorless solid: mp >300 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 7.52 (d, J=7.3 Hz, 3H), 7.58 (d, J=8.1 Hz, 3H), 7.67 (d, J=7.5 Hz, 3H), 7.70 (d, J=6.9 Hz, 3H), 7.90–7.97 (m, 9H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 120.59, 125.45, 126.55, 127.28, 127.74, 129.03, 129.90, 129.99, 130.32, 134.58, 148.74; HRMS calcd for $C_{33}H_{21}N_3O_3$ 507.1583, found 507.1609.

4.4.3. Tris(*p*-chlorophenyl) isocyanurate (2c).[16a] Isolated yield 78%. Colorless solid: mp >300 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 7.31 (d, J=8.8 Hz, 6H), 7.47 (d, J=8.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 129.70, 129.73, 131.71, 135.59, 148.13; HRMS calcd for $C_{21}H_{12}Cl_3N_3O_3$ 458.9941, found 458.9930.

4.4.4. Tris(*o*-methoxyphenyl) isocyanurate (2d).[16a] Isolated yield 60%. Colorless solid: mp 259–261 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 3.86 (s, 9H), 6.86 (dd, J=7.6,1.3 Hz, 3H), 6.94–6.99 (m, 6H), 8.10 (dd, J=7.6, 1.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 55.66, 110.06, 119.56, 121.19, 122.82, 128.08, 148.08; HRMS calcd for $C_{24}H_{21}N_3O_6$ 447.1430, found 447.1462.

4.4.5. Triethyl isocyanurate (2e).[16g] Isolated yield 61%. Pale yellow solid: mp 92–94 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 1.20 (d, J=6.9 Hz, 9H), 3.91 (t, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.05, 38.08, 148.58; HRMS calcd for $C_9H_{15}N_3O_3$ 213.1103, found 213.1089.

4.4.6. Tribenzyl isocyanurate (2f). Isolated yield 68%. Colorless solid: mp 157–158 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 5.02 (s, 6H), 7.28–7.34 (m, 9H), 7.43 (dd, J=7.2, 1.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 46.24, 128.14, 128.61, 129.05, 135.76, 149.09; HRMS calcd for $C_{24}H_{21}N_3O_3$ 399.1583, found 399.1557.

References and notes

1. Grotjahn, D. B. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, pp 741–770 and references therein.
2. Takahashi, T.; Fischer, R.; Xi, Z.; Nakajima, K. *Chem. Lett.* **1996**, 357.
3. (a) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Neghishi, E. *Tetrahedron Lett.* **1993**, *34*, 687. (b) Takahashi, T.; Xi, Z.; Rousset, C. J.; Suzuki, N. *Chem. Lett.* **1993**, 1001.
4. (a) Negishi, E.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829. (b) Negishi, E.; Holms, S. J.; Tour, J.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336. (c) Xi, Z.; Hara, R.; Takahashi, T. *J. Org. Chem.* **1995**, *60*, 4444.
5. (a) Takahashi, T.; Kotora, M.; Xi, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 361. (b) Xi, Z.; Fischer, R.; Hara, R.; Sun, W.-H.; Obora, Y.; Suzuki, N.; Nakajima, K.; Takahashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 12842. (c) Takahashi, T.; Xi, C.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672. (d) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093. (e) Takahashi, T.; Kitamura, M.; Shen, B.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 12876.
6. Kotora, M.; Xi, C.; Takahashi, T. *Tetrahedron Lett.* **1998**, *39*, 4321.
7. (a) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 687. (b) Takahashi, T.; Tsai, F.-Y.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994. (c) Takahashi, T.; Li, Y.; Liu, Y.; Ito, T.; Xu, F.; Nakajima, K. *J. Am. Chem. Soc.* **2002**, *124*, 1144. (d) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, M.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059.
8. Suzuki, N.; Kondakov, D. Y.; Kageyama, M.; Kotora, M.; Hara, R.; Takahashi, T. *Tetrahedron* **1995**, *51*, 4519.
9. Takahashi, T.; Kondakov, D. Y.; Xi, Z.; Suzuki, N. *J. Am. Chem. Soc.* **1995**, *117*, 5871.
10. Liu, Y.; Zhong, Z.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2002**, *67*, 7451.
11. Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 3228.
12. Takahashi, T.; Xi, C.; Xi, Z.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. *J. Org. Chem.* **1998**, *63*, 6802.
13. (a) van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495. (b) Williams, A. C.; Sheffels, P.; Sheehan, D.; Livinghouse, T. *Organometallics* **1989**, *8*, 1566. (c) Takai, K.; Kataoka, Y.; Yoshizumi, K.; Oguchi, Y. *Chem. Lett.* **1991**, 1479. (d) Takahashi, T.; Li, Y.; Tsai, F.-Y.; Nakajima, K. *Orgamometallics* **2001**, *20*, 595.
14. Yield was determined by GC.
15. Unpublished data.
16. (a) Kogon, I. C. *J. Am. Chem. Soc.* **1956**, *78*, 4911. (b) Bloodworth, A. J.; Davies, A. G. *J. Chem. Soc.* **1965**, 6858. (c) Noltes, J. G.; Boersma, J. *J. Organomet. Chem.* **1967**, *7*, 6. (d) Taguchi, Y.; Shibuya, I.; Yasumoto, M.; Tsuchiya, T.; Yonemoto, K. *Bull. Chem. Soc. Jpn* **1990**, *63*, 3486. (e) Mizuya, J.; Yokozawa, T.; Endo, T. J. *Polym. Sci.,*

Part A **1991**, *29*, 1545. (f) Nambu, Y.; Endo, T. *J. Org. Chem.* **1993**, *58*, 1932. (g) Tang, J.; Mohan, T.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 4931. (h) Schwetlick, K.; Noack, R. *J. Chem. Soc., Perkin Trans. 2* **1995**, 395. (i) Weinmann, M.; Walter, O.; Huttner, G.; Lang, H. *J. Organomet. Chem.* **1998**, *561*, 131.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1401–1416
Tetrahedron

Ring expansion of 5- to 6-member zirconacycles by carbenoid insertion

Sally Dixon, Shaun M. Fillery, Aleksandra Kasatkin, David Norton, Emma Thomas and Richard J. Whitby*

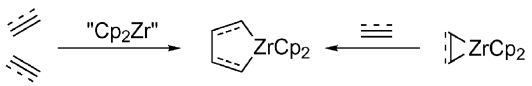
Department of Chemistry, Southampton University, Southampton, Hants SO17 1BJ, UK

Received 7 July 2003; revised 24 September 2003; accepted 24 September 2003

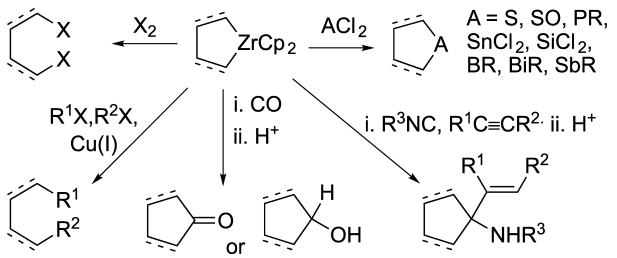
Abstract—A wide range of carbenoids (1-lithio-1-halo species), including those with α-SiR_3, OEt, SPh, SO_2Ph, $P(O)(OEt)_2$, and CN substituents, insert into 5-member zirconacycles (saturated and unsaturated, mono- and bi-cyclic) to afford functionalized 6-member zirconacycles. 1-Lithio-1-haloalkenes insert to afford 6-member zirconacycles with an alkylidene substituent next to the metal. Unexpected double insertion of some carbenoids, and evidence for endocylic β-hydride transfer processes provide additional mechanistic interest.

1. Introduction

Over that past 20 years efficient syntheses of a wide variety of 5-member zirconacycles have been developed. The main routes are by co-cyclisation of 1,*n*-dienes, -diynes and -enynes on a zirconocene ('Cp_2Zr') equivalent,[1] or by trapping zirconocene η^2-alkene, -alkyne, and -benzyne complexes, generated by complexation or by a β-C–H activation process, with alkenes or alkynes (Eq. (1)).[2] The use of unactivated alkenes and alkynes as substrates together with the good diastereocontrol imposed by the metal make these processes particularly attractive for organic synthesis. The ready formation of nitrogen heterocycles,[3] and the use of cleavable silicon tethers[4] are illustrations of the variety of organic structures which may be formed. Many productive means for elaboration of the carbon–zirconium bonds in the 5-member zirconacycles have been developed. Examples include metathesis reactions to form heterocycles;[5] halogenolysis;[6] carbonylation (to yield ketones or alcohols depending on conditions and work-up);[7] tandem insertion of isonitriles and additional π-components;[8] addition to aldehydes;[9] and various copper or nickel induced or catalysed elaborations such as addition of enones, aryl-, allyl-, and alkynyl-halides, and 1,*n*-dihalides; 1,1-addition to acid chlorides, β-haloenones, or propynoates; and 1,2-addition to alkynes (Scheme 1).[10]

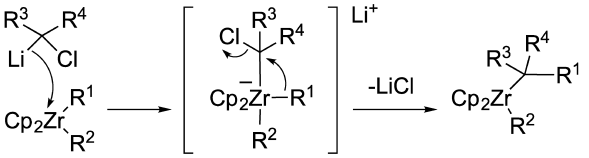


(1)



Scheme 1. Elaboration of 5-member zirconacycles.

A valuable method for the elaboration of carbon-metal bonds is via insertion of 'carbenoids'[11] (1-halo-1-metallo species) since, as the products retain the carbon–metal bond of the starting material, the process is inherently iterative. In 1989 Negishi reported[12] the first insertions of α-halo-organolithium reagents into acyclic zirconocene chlorides. The process is particularly facile as most organozirconocene complexes are electronically unsaturated (16 electron) so the reaction may occur by formation and 1,2-rearrangement of an 18 electron 'ate complex' as shown in Eq. (2). We have developed the insertion of a wide range of carbenoids into organozirconocene chlorides derived by hydrozirconation to provide useful multi-component coupling methods.[13–15]

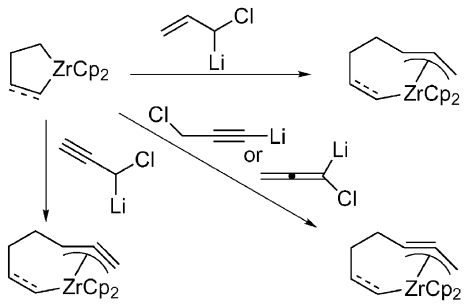


(2)

Homologation of 5- to 6-member zirconacycles through carbenoid insertion potentially provides a rich new class of substrates for the numerous zirconacycle elaborations

Keywords: Zirconium; Carbenoid; Ring expansion; Multi-component; Zirconacycle; Insertion.
* Corresponding author. Tel.: +44-23-80592777; fax: +44-23-80593781; e-mail address: rjw1@soton.ac.uk

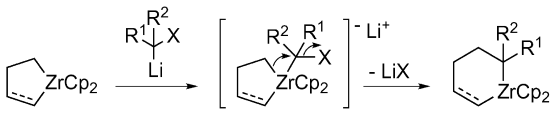
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.056



Scheme 2. Insertion of allyl-, allenyl- and propargyl- carbenoids into zirconacycles.

described above, and hence valuable multi-component coupling methods. Our initial reports concerned the insertion of allyl-, allenyl- or propargyl-carbenoids into zirconacycles (Scheme 2).[16–18] Although the η^1-,η^3- zirconacycles so formed reacted with powerful electrophiles such as aldehyde/$BF_3{\cdot}Et_2O$, they were poor substrates for many of the elaboration methods described above, probably because the metal is electronically saturated (18 electron configuration).

We now report the ring expansion of zirconacyclo-pentanes and -pentenes to afford 6-member zirconacycles by insertion of a wide range of carbenoids (Eq. (3)).[19] Such carbenoid insertions have also been reported for the ring expansion of boracycles and silacycles.[20,21]



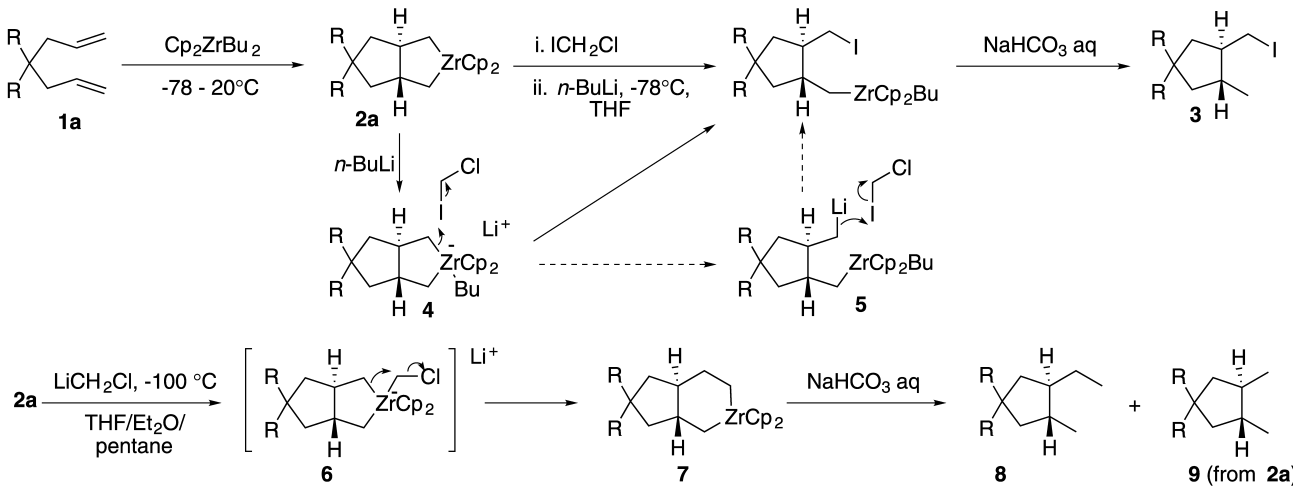
(3)

2. Results and discusion

2.1. Insertion of H-, alkyl-, silyl-, phenylthio-, and ethoxy-substituted carbenoids into zirconacycles

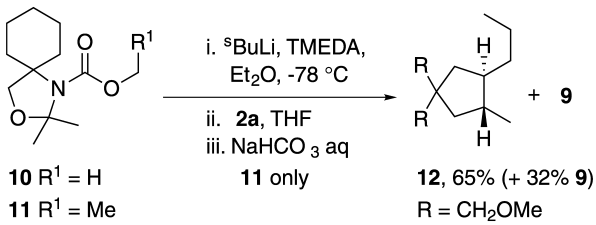
2.1.1. Insertion of methylene carbenoid. Intramolecular co-cyclisation of the 1,6-heptadiene **1a** using zirconocene-(1-butene) (the Negishi reagent),[22] generated in situ from dibutylzirconocene, gave the zirconacyclopentane **2a**. Insertion of a methylene carbenoid ($LiCH_2X$) into **2a** should give the zirconacyclohexane **7** (Scheme 3). The carbenoid $LiCH_2Cl$ is known,[23] but very unstable, so we first tried to generate it in situ by halogen/lithium exchange. However, addition of *n*-BuLi to a mixture of zirconacycle **2a** and ICH_2Cl followed by aqueous work-up gave only the iodide **3**. Presumably *n*-BuLi attacks the zirconium centre to form the zirconate complex **4** which undergoes iodine–metal exchange with ICH_2Cl, either directly, or via the lithium species **5**. Negishi has previously reported a similar ring opening of zirconacyclopentanes with alkyllithium reagents.[24] The fate of the $LiCH_2Cl$ (or $[RZr(Bu)(CH_2Cl)Cp_2]^-\ Li^+$) so formed is not clear, but insertion into the Zr–Bu bond is likely. Although there are a few exceptions[25] we have found that in situ halogen/lithium exchange in the presence of the zirconacycle is not a useful method for generation/insertion of carbenoids. Reaction of ICH_2Cl with *n*-BuLi at −100 °C in a 4:1:1 mixture of THF, diethyl ether and pentane (Trapp solvent)[11b] formed the desired carbenoid $LiCH_2Cl$.[23] Addition of a −78 °C solution of the zirconacycle **2a** in THF via cannula partially formed the desired zirconacyclohexane **7**, and aqueous work-up gave a 2.5:1 mixture of the homologated methylethylcyclopentane **8**, and the dimethylcyclopentane **9** derived from starting zirconacycle **2a** (87% combined yield) (Scheme 3). Complete conversion of **2a** could be achieved by increasing the amount of $LiCH_2Cl$, but this also gave products of further insertion into **7** which were not separable from **8**. Insertion of $LiCH_2Br$[26] generated from CH_2Br_2 and *n*-BuLi gave very similar results to the above.

2.1.2. Carbamate-derived carbenoids. The failure of in situ generation of $LiCH_2X$ by halogen/lithium exchange and the inconveniently low temperatures needed to generate it separately from the zirconacycle prompted us to examine the more stable α-lithiated carbamates $R^1_2NCOOCHLiR^2$ as carbenoids.[27] We have previously shown that for the insertion of allyl carbenoid into zirconacycles, carbamate was a suitable leaving group.[16a] Unfortunately, insertion of the 'methylene carbenoid' derived by lithiation of **10** with *s*-BuLi/tetramethylethylenediamine (TMEDA) was unsuccessful, a problem traced to preferential bis-lithiation of **10**. Lithiation of the ethyl carbamate **11** (1.1 equiv.) using a



Scheme 3. Reaction of zirconacyclopentane **2a** (R=CH_2OMe) with ICH_2Cl+*n*-BuLi.

preformed mixture of *s*-BuLi and TMEDA in ether at −78 °C followed by addition, via cannula, of a solution of zirconacycle **2a** in THF at −78 °C gave, on aqueous quench and chromatography, the product **12** (65%) of insertion as well as **9** (32%) from hydrolysis of the starting zirconacycle (Eq. (4)). Increasing the amount of lithiated carbamate to 5 equiv. surprisingly only increased the ratio of **12** to **9** to 2.7:1 and the yield was lower.



(4)

Attempts to lithiate carbamate **11** in the presence of the zirconacycle failed, so we next examined carbenoids which could be generated in situ by deprotonation with amide bases.

2.1.3. Insertion of α-silyl- and α-stannyl-carbenoids. α-Silyl carbenoids (LiCH(SiR_3)Cl) are remarkably stable,[28] and Negishi,[12] and we[14a] have reported their insertion into acyclic organozirconocenes. Takahashi recently reported their insertion into zirconacyclopentadienes.[29] Although usually generated by deprotonation using an alkyllithium,[28] elimination to form a carbene using LiTMP is known.[30] We were delighted to find that reaction between 1.1 equiv. of chloromethyltrimethylsilane and LDA at −78 °C in the presence of zirconacyclopentane **2b** afforded cleanly a new zirconacyclohexane **13b** upon warming to room temperature (Table 1). It is interesting that Magnus noted[28b] that LDA is not a useful base for deprotonation of Me_3SiCH_2Cl which may indicate the effectiveness of trapping by the zirconacycle in displacing an equilibrium. The ^1H NMR of **13b** showed four equal cyclopentadienyl signals (C_6D_6, δ_H 5.71, 5.63, 5.57 and 5.50 ppm) implying that it was a 1:1 mixture of diastereoisomers. The lack of diastereoselectivity in the carbenoid insertion is consistent with the chiral but racemic zirconacycle reacting with the chiral but racemic carbenoid with clean inversion of configuration at the carbenoid centre. No change in diastereoisomer ratio was observed after heating the mixture of zirconacycles **13b** for 2 days at 80 °C. Protonation of **13b** afforded the trimethylsilyl compound **18b** in good yield (Table 1, entry 1). Zirconacycle **13b** also showed no inclination to insert further carbenoids. For example reaction with 10 equiv. of LiCH($SiMe_3$)Cl gave only the monoinsertion product **18b** on work-up. One explanation for the resistance of **13b** to further carbenoid insertion is that the C–Si bond donates electron density into the empty orbital on the metal (Fig. 1), which is also required for carbenoid insertion (c.f. stabilisation of β-carbenium ions by silicon[31]). We have observed other examples where the presence of electron donation into the empty orbital on the zirconium prevents carbenoid insertion.[32]

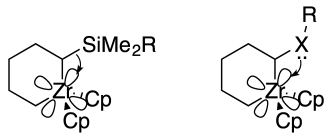
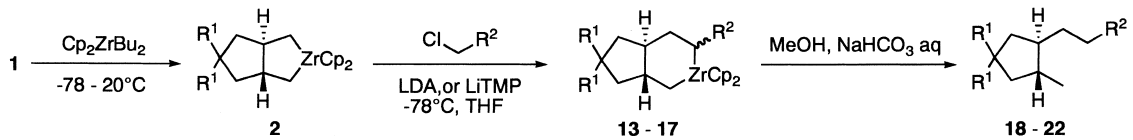


Figure 1. Electron donation to zirconium centre.

In the same way, insertion of the carbenoid derived from in situ lithiation of 1.1 equiv. of (chloromethyl)phenyldimethylsilane into zirconacyclopentanes **2a**,**b** and **c** gave the zirconacyclohexanes **14a**,**b** and **c** and homologated products **19a**,**b** and **c** in good yield (Table 1, entries 2, 3, and 4). For zirconacyclohexane **14b** we confirmed that it was formed as a 1:1 mixture of diastereoisomers, and would not insert further carbenoid. Insertion of the α-tributylstannyl carbenoid[30] LiCH($SnBu_3$)Cl into **2a** occurred in low yield, possibly because of the much faster rate of tin/lithium exchange c.f. silyl/lithium (Table 1, entry 5).

2.1.4. Insertion of S- and O-substituted carbenoids. We next examined insertion of the S- and O-substituted carbenoids PhSCHLiCl and EtOCHLiCl. Before our work[14b] these types of carbenoid were only known as implied intermediates in the formation, and trapping by cyclopropanation, of carbenes[33] which is an indication of how quickly zirconium may trap these exceptionally unstable intermediates. Thus addition of LDA (1.2 equiv.)

Table 1. Insertion of electron rich alkylcarbenoids into zirconacyclopentanes



Entry	Zirconacyclopentane **2**		Carbenoid[a]		Zirconacyclohexane	Product	Yield (%)[b]
	R^1, R^1	**1/2**	R^2	Equiv.			
1	$-CH_2OCMe_2OCH_2-$	**b**	$SiMe_3$	1.1	**13b**	**18b**	78
2	$-CH_2OMe$, $-CH_2OMe$	**a**	$SiMe_2Ph$	1.1	**14a**	**19a**	70
3	$-CH_2OCMe_2OCH_2-$	**b**	$SiMe_2Ph$	1.1	**14b**	**19b**	77
4	H, H	**c**	$SiMe_2Ph$	1.1	**14c**	**19c**	64
5	$-CH_2OMe$, $-CH_2OMe$	**a**	$SnBu_3$	1.0[c]	**15a**	**20a**	11
6	$-CH_2OCMe_2OCH_2-$	**b**	SPh	1.2	**16b**	**21b**	77
7	$-CH_2OCMe_2OCH_2-$	**b**	OEt	1.1	**17b**	**22b**	45

[a] Generated using LDA except.
[b] Isolated yield based on diene **1**.
[c] Used LiTMP.

to a mixture of zirconacycle **2b** and chloromethylphenylsulphide (1.5 equiv.) in THF at −78 °C gave the zirconacycle **16b**. Aqueous work-up gave the phenyl sulphide **21b** in 77% yield (Table 1, entry 6). Attempts to analyse the intermediate zirconacyclohexane **16b** by NMR were thwarted by its low thermal stability. As with the silicon substituted carbenoids, only mono insertion was observed, even with 10 equiv. of PhSCHLiCl, an observation which may be explained by co-ordination of the sulphur lone pair to saturate the zirconium centre (Fig. 1). In a similar way metallation of chloromethylethyl ether (1.1 equiv.) by LDA (1.1 equiv.) in the presence of zirconacycle **2b** at −78 °C afforded the alkyl ethyl ether **22b** in a modest 45% yield after protic quench at −20 °C. (Table 1, entry 7) The intermediate zirconacycle **17b** decomposed above −20 °C.

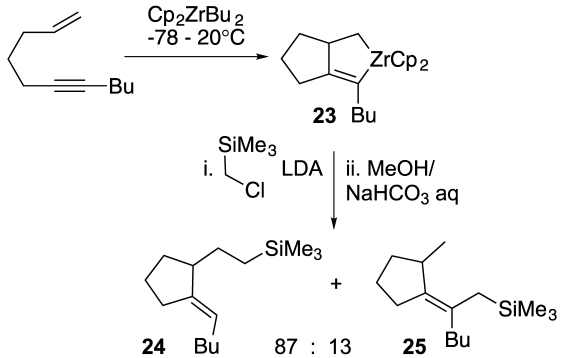
2.1.5. Insertion of electron rich carbenoids into unsaturated zirconacycles. Zirconacyclopentenes are readily formed by the zirconocene mediated intramolecular co-cyclisation of 1,*n*-enynes, for example the formation of **23**.[1] Insertion of electron rich alkyl carbenoids into zirconacyclopentene **23** has so far proved disappointing. Although alkyl-, PhS-, and EtO-substituted carbenoids do insert, the yields are low and the products too messy to properly characterise. The silicon substituted carbenoid $Me_3SiCHLiCl$ inserts efficiently into **23** to give, on aqueous work-up, mostly the expected product **24**, but also a significant amount of the regioisomer **25** derived from insertion into the zirconium–alkenyl bond (Scheme 4). Insertion of many other carbenoids into **23** and related zirconacyclopentenes is exclusively into the zirconium-alkyl bond.[15,16d,e,17,18]

2.2. Insertion of electron poor –PO(OEt)$_2$, –SO$_2$Ph, and –CN substituted carbenoids into zirconacycles

We have previously reported insertion of the readily formed electron poor –PO(OEt)$_2$, –SO$_2$Ph, and –CN substituted carbenoids[34–36] into acyclic organozirconocene chlorides,[14b] and were delighted to find that they inserted with equal facility into zirconacycles.

2.2.1. (EtO)$_2$(O)PCHLiCl. Insertion of (EtO)$_2$(O)PCHLiCl,[35] generated in situ from diethyl chloromethylphosphonate and LDA, into a variety of mono- and bicyclic-zirconacyclopentanes and -zirconacyclopentenes was fast and clean (Table 2, entries 1, 4, 5, 8, and 10). Even using a large excess of the phosphonate substituted carbenoid gave no double insertion. Starting zirconacycles **2a**, **29**, **36**, and **39** were formed by co-cyclisation of the appropriate 1,7-dienes or -enynes using dibutylzirconocene.[1] Zirconacycle **31** was formed by warming dibutylzirconocene in the presence of excess ethylene.[7a,37] The diastereoisomeric mix of **30** was the same as that in the starting zirconacycle.

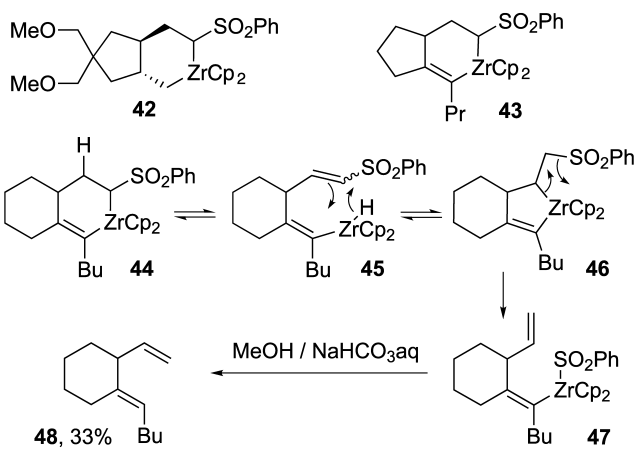
2.2.2. PhSO$_2$CHLiCl. Insertion of PhSO$_2$CHLiCl,[34] generated in situ from chloromethylphenylsulphone and LDA, into saturated zirconacycle **2a** required 4 equiv. of the carbenoid for complete conversion, but was clean (Table 2, entry 2). No double insertion was observed. Insertion into the zirconacyclopentene **33** was also efficient (entry 6). The phenylsulphonyl-substituted zirconacycles **42** and **43** (Scheme 5) derived from **2a** and **33** were stable at room



Scheme 4. Insertion of $Me_3SiCHLiCl$ into a zirconacyclopentene.

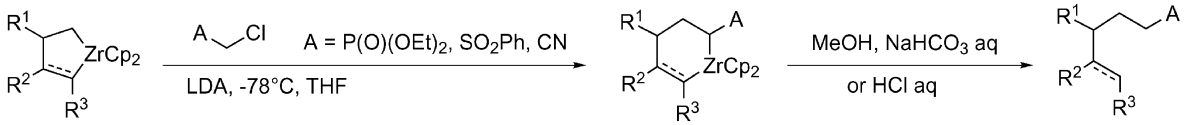
temperature for at least 16 h. In contrast the zirconacyclohexene **44** derived from **36** was thermally unstable, and the reaction needed to be quenched below −40 °C to get a good yield of the expected product **38** (Table 2, entry 9). If zirconacycle **44** was allowed to warm to room temperature before quenching the diene **48** was the major product (Scheme 5). A reasonable explanation for the formation of **48** from **44**, and the markedly contrasting stability of **42** and **43**, is by a β-hydride elimination/re-addition process (Scheme 5). Thus transfer of a β-hydride in **44** to the zirconium gives the zirconium hydride **45**,[38] which can re-add to the alkene to afford the zirconacyclopentene **46**. Irreversible elimination of phenylsulphinate to afford **47** followed by protonolysis gives the diene **48**. The additional conformational constraints provided by the fused 5-member rings in **42** and **43** presumably prevent the orbital alignment needed for the β-hydride transfer. Even though it appears unfavourable the fused 6-member ring in **44** must allow sufficient flexibility for hydride transfer. We have observed similar β-hydride transfers, and dependence on the size (and presence) of a ring fused to the 6-member zirconacycle, in several other systems.[19]

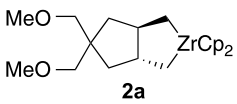
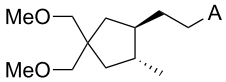
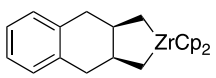
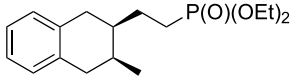
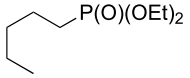
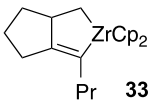
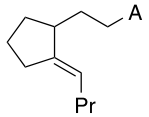
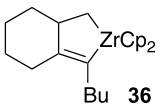
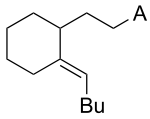
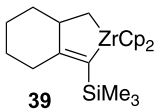
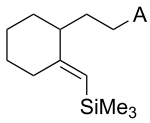
2.2.3. LiClCHCN. Reaction of zirconacyclopentane **2a** with LiClCHCN[36] **49** (1.3 equiv.), generated in situ from chloroacetonitrile and LDA at −78 °C, followed by aqueous work-up gave only a low yield (24%) of the expected insertion product **28** (Table 2, entry 3). The major compound isolated was **50** (45%), the result of bis-insertion of LiClCHCN (Scheme 6). Reducing the amount of carbenoid to 1 equiv. improved the ratio of **28**/**50** to 2:1, but did not improve the yield of **28**. Increasing to 2 equiv. of



Scheme 5. β-Hydride transfer mechanism for elimination.

Table 2. Insertion of electron poor carbenoids into zirconacycles

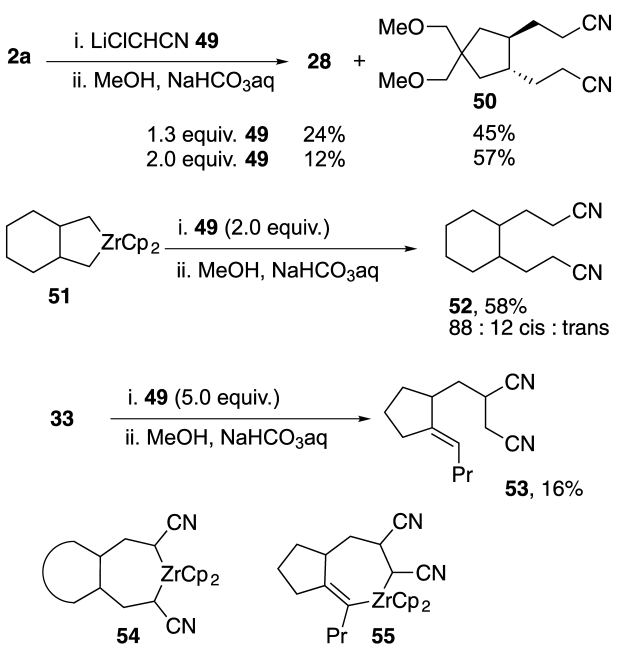


Entry	Zirconacycle[a]	A	Equiv. ACH_2Cl	Product		Yield[b]/%
1		$P(O)(OEt)_2$	1.3		**26**	74
2		SO_2Ph	4.0		**27**	67
3		CN	1.3		**28**	24
4	 **29**	$P(O)(OEt)_2$	1.3	 92 : 8 cis : trans	**30**	63
5	 **31**	$P(O)(OEt)_2$	1.3		**32**	56 (76[c])
6		SO_2Ph	2.0		**34**	84
7	Pr **33**	CN	1.3		**35**	58
8		$P(O)(OEt)_2$	1.3		**37**	81
9	Bu **36**	SO_2Ph	1.3		**38**	60[d]
10		$P(O)(OEt)_2$	1.3		**40**	71
11	**39** $SiMe_3$	CN	1.3		**41**	73

[a] Formed by co-cyclisation of appropriate enyne or diene using Cp_2ZrBu_2 except **31** (from Cp_2ZrBu_2+excess ethene).
[b] Isolated yield based on diene or enyne except **32** which was based on Cp_2ZrCl_2.
[c] NMR yield.
[d] Quenched at −78 °C.

carbenoid gave 57% isolated yield of the bis-insertion product **50**. In a similar way reaction of 2 equiv. of LiClCHCN with zirconacyclopentane **51** gave the bis-inserted product **52** in good isolated yield (Scheme 6). Insertion of 1.3 equiv. of LiClCHCN into the zirconacyclopentenes **33** and **39** gave clean conversion to the mono-inserted products **35** and **41** (Table 2, entries 7 and 11). In an attempt to force double insertion **33** was treated with 5 equiv. of LiClCHCN and gave a low yield of the bis-inserted product **53** as a separable 1:1 mixture of diastereoisomers (Scheme 6). In the formation of **50** and **52** the insertions of LiClCHCN occur on opposite sides of the zirconium to afford the 7-member zirconacycle **54**. In the formation of **53** the second insertion occurs on the same side as the first to afford zirconacycle **55**, presumably because insertion into the alkenyl–metal bond is so unfavourable.

2.2.4. Comparison of $-PO(OEt)_2$, $-SO_2Ph$, and $-CN$ substituted carbenoids. The remarkably different behaviours towards the insertion of a second carbenoid of the phosphonate, sulphone, and nitrile substituted zirconacyclohexanes may be accounted for by donation of electrons from the lone pairs on the sulphone or phosphonate oxygens to the empty orbital on the zirconium (**56**, Fig. 2) which is not possible for the nitrile substituent. It is possible that



Scheme 6. Double insertion of lithiated chloroacetonitrile.

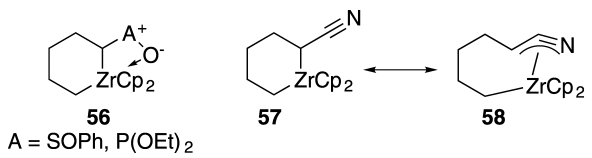


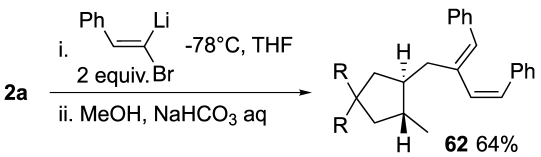
Figure 2. Electron donation to zirconium in sulphone, phosphonate, and nitrile substituted zirconacylohexanes.

the nitrile adopts the 18 electron η^3-co-ordinated structure **58** (Fig. 2) analogous to that displayed by 'propargyl carbenoid' inserted zirconacycles (Scheme 2). However, calculations indicate that the structure **57** is significantly more stable than **58**,[39] and **58** would be expected to be inert to carbenoid attack as the metal has an 18 electron configuration.

2.3. Insertion of 1-lithio-1-haloalkenes

Negishi,[12] and we,[13] have shown that 1-lithio-1-haloalkenes **59** insert readily into acyclic organozirconium species, so we investigated their insertion into zirconacycles (Tables 3 and 4).

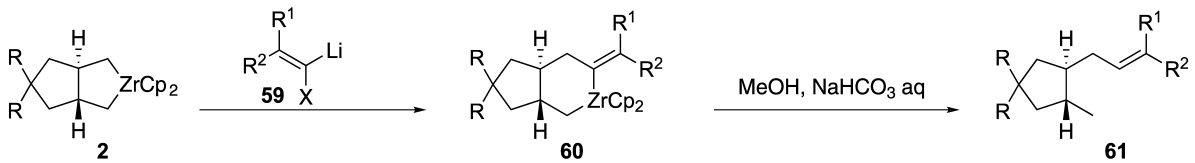
2.3.1. Insertion of 1-lithio-1-haloalkenes into saturated zirconacycles. Addition of lithium tetramethylpiperidide (1.1 equiv.) to a mixture of zirconacyclopentane **2b** and 1-chloro-2-methylprop-1-ene (1.1 equiv.) gave 30% conversion to the zirconacyclohexane **60a**. Increasing to 3 and 5 equiv. of the carbenoid gave 2:1 and 20:1 ratios of the homologated zirconacycle **60a** to starting material **2a**. However, increasing the amount of carbenoid also lead to numerous unidentified side products and the hydrolysed product **61a** was isolated in only 33% yield (Table 3, entry 1). Insertion of the sterically less hindered dienyl-carbenoid **59b**, generated in situ from (*E*)-1,4-dichloro-2-butene and 2 equiv. of LDA,[13] into zirconacyclopentane **2a** gave the diene **61b** in 68% yield as an 87:13 *E*/*Z* mixture after hydrolysis. It was important to use only 1.1 equiv. of the carbenoid as larger amounts gave messy reactions and poor yield. Subsequent results (see below) suggest that multiple insertions of the carbenoid occur to give unstable products. The loss of stereospecificity occurs in the initial elimination of (*E*)-1,4-dichloro-2-butene to give (*Z*)- and (*E*)-1-chloro-1,3-butadiene as an 87:13 mixture.[13] In a similar way (*Z*)-1,4-dichloro-2-butene formed the carbenoid **59c** (>95% *E*) which inserted into **2a** to give the diene **61c** with >95:5 *Z* selectivity, on aqueous work-up. Insertion of the alkynyl-substituted carbenoid **59d**[40] occurred in modest yield (Table 3, entry 4), and there was indication by gas chromatography of double insertion being a problem. The insertion of lithiated β-bromostyrene **59e** into zirconacycle **2a** (Table 3, entry 5) gave the most surprising result in that the expected insertion product **61e** was accompanied by substantial amounts of the bis-insertion product **62**, where the second insertion has taken place into the more hindered side of the zirconacyclohexane (Eq. (5)). Increasing the amount of carbenoid to 2 equiv. gave a good yield of **62**. In the intermediate zirconacyclohexene **63** (Scheme 7) the empty orbital on the metal lies in the plane of the 6-member ring and only attack on the 'CH_2' side seems reasonable to afford the 'ate' complex **64**. We suppose that 1,2-metallate rearrangement of **64** is slower than its isomerisation to a structure such as **65** in which insertion of the carbenoid into the alkenyl–zirconium bond may occur. The isomerisation of **64** into **65** could be via loss/re-addition of cyclopentadienide,[24] or directly via pseudorotation. Modelling of possible ate complex intermediates (**64**, **65**, and others) indicates (if we consider Cp to occupy a single co-ordination site) low energy forms which approximate to both square-pyramidal and trigonal-bipyramidal forms. Since the former is the intermediate in the Berry psuedorotation mechanism[41] for ligand interchange in the latter, it is reasonable that isomerisation of **64** to **65** could be fast.



(5)

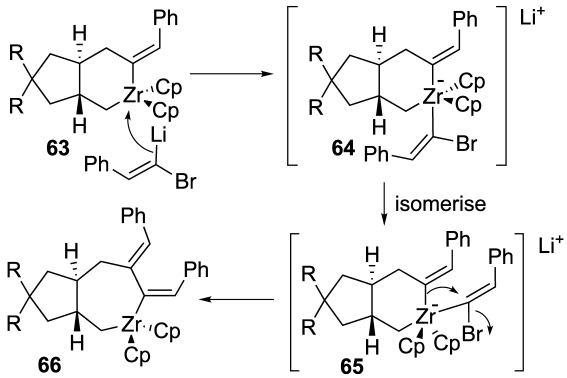
2.3.2. Insertion of 1-lithio-1-haloalkenes into zirconacyclopentenes. A variety of 1-lithio-1-haloalkenes inserted cleanly into unsaturated zirconacyclopentenes (Table 4), including into the monocycle **68**.[42] Worthy of comment is that the carbenoid **59e** derived from β-bromostyrene inserted just once into **67**, even when a large excess

Table 3. Insertion of 1-halo-1-lithioalkenes into saturated zirconacycles

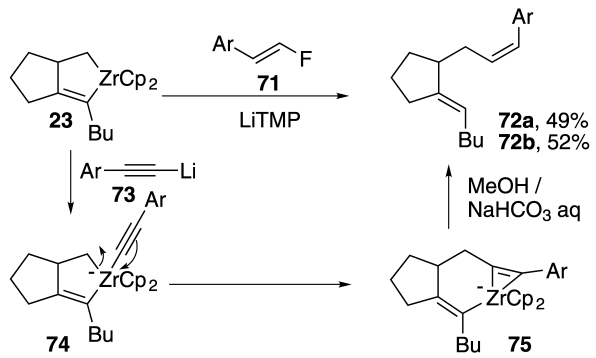


Entry	Zirconacycle[a]		1-Halo-1-lithioalkene[b]				Equiv. of **59**	Product	
	R, R	**2**	R^1	R^2	X	**59**		**61**	Yield[c] **61** (%)
1	$-CH_2OCMe_2OCH_2-$	**b**	Me	Me	Cl	**a**	5	**a**	33
2	$-CH_2OMe$, $-CH_2OMe$	**a**	H	$CH{=}CH_2$	Cl	**b**	1.1	**b**	68
3	$-CH_2OMe$, $-CH_2OMe$	**a**	$CH{=}CH_2$	H	Cl	**c**	3	**c**	87
4	$-CH_2OMe$, $-CH_2OMe$	**a**	$C{\equiv}CBu$	H	Cl	**d**	1.2	**d**	54
5	$-CH_2OMe$, $-CH_2OMe$	**a**	Ph	H	Br	**e**	1.2	**e**	48 (+11% **62**)

[a] Formed by co-cyclisation of **1a** or **1b** using Cp_2ZrBu_2.
[b] Formed by deprotonation of alkenyl halide using LiTMP (**59a**) or LDA (**59b-e**).
[c] Isolated yield based on diene precursor of **2**.



Scheme 7. Possible mechanism for double insertion.



Scheme 8. Attempted insertion of alkenyl fluorides. (a) Ar=Ph, (b) Ar=*p*-PhC_6H_4.

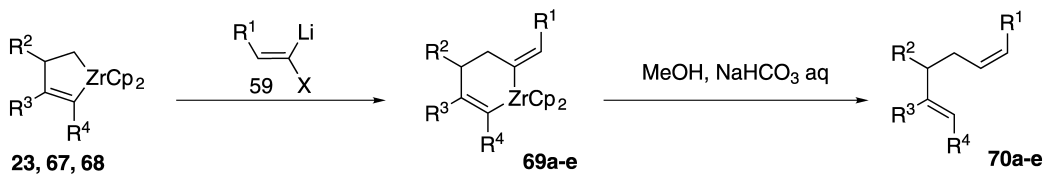
(5 equiv.) was used (c.f. Table 3, entry 5 and Eq. (4)). This observation lends support to the notion that the 'double insertion' product **62** is indeed derived from initial attack on the side of zirconium remote from where it finally inserts (Scheme 7). In the zirconacyclohexene **69b**, from mono-insertion of **59e** into **67**, attack of the carbenoid on the empty orbital on zirconium is blocked from both sides so double insertion does not occur.

2.3.3. Insertions via alkynate complex rearrangement. In an attempt to improve yields we examined insertion of the carbenoids generated by in situ deprotonation of the β-fluorostyrenes **71a** and **b** into zirconacyclopentene **23**. Initial results were promising—reasonable yields of the expected products **72a** and **72b** (Scheme 8). However, further study showed that the products were only arising after the reaction mixture was warmed to room temperature. Quenching at −40 °C gave <5% conversion. It became clear that the mechanism involved very fast elimination of fluoride from **71** to afford the arylalkynes,[43] which lithiated and added to the zirconacycle to afford the ate complex **74**. Slow rearrangement of **74** at room temperature, as has been previously reported by Negishi[44] in monocyclic systems, affords **75** and hence the products **72** on aqueous work-up (Scheme 8). Indeed substituting 1 equiv. of *p*-biphenyl-acetylene for **71a** in the reaction gave 85% conversion to **72b** by gas chromatography, and 65% isolated yield. When **23** was treated with (*E*)-β-chlorostyrene or (*E*)-β-bromo-styrene and LDA (1.5 equiv.) conversion to **72a** was complete in less than 5 min at −78 °C indicating that in these cases the reaction was occurring by direct insertion of the 1-lithio-1-haloalkene.

3. Conclusions

We have demonstrated that a wide range of carbenoids (electron poor and electron rich, alkyl and alkenyl) insert into a range of 5-member zirconacycles (saturated and unsaturated, mono- and bi-cyclic) to afford functionalised 6-member zirconacycles. There is great opportunity for further elaboration of these novel structures to create multi-component coupling reactions of use in organic synthesis. Several mechanistically interesting observations also require further work. The double insertion of lithiated chloroacetonitrile and lithiated β-bromostyrene **59e**, in contrast to the inertness of other systems towards further carbenoid insertion, is an indication of the electronic requirements at the metal for carbenoid insertion to occur which we only partially understand. The suggested facile transfer of a β-hydride from within a zirconacycle ring to the metal in formation of **48** appears unprecedented and orbital alignment seems so bad that further experimental and theoretical investigation is warranted. The remarkable double insertion of lithiated β-bromostyrene into the same side of zirconacycle **2a** to afford **61** confirms earlier results[16e,19b] that show that the regiochemistry of carbenoid

Table 4. Insertion of 1-halo-1-lithioalkenes into unsaturated zirconacycles



Entry	Zirconacycle R^2	R^3	R^4		Carbenoid R^1	X	**59**	Equiv. of **59**	**69/70**	Yield[a] of **70** (%)
1	$CH_2C(CH_2OMe)_2CH_2$		Et	**67**	$CH{=}CH_2$	Cl	**c**	3	**a**	81
2	$CH_2C(CH_2OMe)_2CH_2$		Et	**67**	Ph	Br	**e**	3	**b**	64
3	$-(CH_2)_3-$		Bu	**23**	C≡CBu	Cl	**d**	2	**c**	86
4	H	Pr	Pr	**68**	C≡CBu	Cl	**d**	1.2	**d**	54[b]

[a] Isolated yield based on starting enyne except.
[b] Yield based on 4-octyne.

insertion is not (always) dominated by the direction of initial attack of the carbenoid on the metal. Several mechanisms are possible, and again a combination of experimental and theoretical studies will be needed for clarification.

Overall we believe that as well as providing useful new synthetic methods for organic synthesis our work is uncovering fascinating new aspects of the chemistry of zirconium and provides an exciting field for further research.

4. Experimental

4.1. General

4.1.1. Spectroscopy and analysis. NMR spectra were recorded on Bruker AM300 or DPX400 spectrometers. Unless otherwise stated all spectra were recorded in deuterochloroform at 300 MHz (proton) or 75 MHz (carbon) and are referenced to the residual chloroform peak at 7.27 ppm (^{1}H NMR), and 77.20 ppm (centre peak of triplet, ^{13}C NMR). The NMR spectra of organozirconium compounds were recorded in deuterobenzene (stored over 4 Å molecular sieves) and referenced to residual benzene peak at 7.16 ppm (^{1}H NMR) and 128.0 ppm (centre peak of triplet, ^{13}C NMR). Chemical shifts are reported in parts per million downfield of TMS and the following abbreviations used to denote coupling patterns: s=singlet; d=doublet, t=triplet, q=quartet, br=broad, fs=fine splitting). ^{13}C NMR spectra were proton decoupled and are reported as C, CH, CH_2, CH_3, depending on the number of directly attached protons, this being determined by DEPT experiments. Infrared spectra were recorded for all compounds but are not reported. Mass spectra including accurate mass were recorded on a VG Analytical 70-250-SE double focusing mass spectrometer using Chemical Ionisation (CI) (with ammonia as the reagent gas) or Electron Impact Ionisation (EI) (at 70 eV). LRMS (EI and CI) were also recorded on a ThermoQuest TraceMS GCMS. Atmospheric pressure chemical ionisation (APCI) mass spectra were recorded on a VG Platform spectrometer in acetonitrile. Values of *m*/*z* are reported in atomic mass units (a.m.u.) followed in parentheses by the peak intensity (relative to the base peak of 100%). Elemental analyses were performed by the University College London Microanalysis Service, or at AstraZeneca, Alderley Park.

4.1.2. General procedures. All reactions were carried out under an argon atmosphere using standard Schlenk and syringe techniques. All apparatus was dried in a hot oven (>140 °C, 12 h) before being cooled in a sealed dessicator over silica gel, or assembled while hot and cooled under vacuum (0.1 mm Hg). 'Usual work-up' refers to quenching the reaction with methanol (5 mL) followed by saturated $NaHCO_3$ aq. (5 mL) and stirring at room temperature for 3–16 h before extracting the organic products into ether. The ether solution is then washed with brine, (sometimes preceded by water) dried over $MgSO_4$, the solvents removed in vacuo and the crude product purified by chromatography on silica.

4.1.3. Materials. Unless given below all materials were obtained from commercial sources and if necessary dried and distilled before use. The following compounds were prepared by literature methods, and had spectral properties consistent with those published: 3,3-dimethyl-1-oxa-4-aza-spiro[4.5]decane-4-carboxylic acid methyl (**10**) and ethyl (**11**) esters;[27] tributyl(chloromethyl)stannane;[30] 4,4-bis-(methoxymethyl)hepta-1,6-diene, **1a**;[45,46] 5,5-diallyl-2,2-dimethyl-1,3-dioxane, **1b**;[47] undec-1-en-6-yne;[48] 1,2-diallyl-benzene;[49] dodec-1-en-7-yne;[50] trimethyl(oct-7-en-1-ynyl)-silane;[7c] (*E*)-1-chlorooct-1-en-3-yne;[40] 1-((*E*)-2-fluoro-vinyl)benzene **71a**;[51] 4-(2-fluorovinyl)biphenyl **71b**.[52] The following compounds were prepared by standard procedures, and had the spectral properties given: dec-1-en-6-yne was prepared by alkylation of lithiated pentyne with 5-bromo-1-pentene and had spectral properties: ^{1}H NMR: δ 5.80 (1H, ddt, J=16.9, 10.2, 6.8 Hz), 5.03 (1H, ddt, J=17.1, 3.5, 1.7 Hz), 4.99 (1H, ddt J=10.2, 3.4, 1.1 Hz), 2.21–2.10 (6H, m), 1.63–1.43 (4H, m), 0.97 (3H, t, J=7.4 Hz). ^{13}C NMR: δ 138.28 (CH), 115.07 (CH_2), 80.54 (C), 80.05 (C), 32.97 (CH_2), 28.47 (CH_2), 22.66 (CH_2), 20.90 (CH_2), 18.31 (CH_2), 13.63 (CH_3). LRMS (EI): 136 (M^+, 4%), 121 (M^+-CH_3, 50), 107 ($M^+-C_2H_5$, 80), 93 ($M^+-C_3H_7$, 97). 4,4-Bis(methoxymethyl)non-1-en-6-yne was prepared by ethylation of 4,4-bis(methoxymethyl)hept-1-en-6-yne:[53] ^{1}H NMR: δ 5.80 (1H, ddt, J=16.8, 10.3, 7.7 Hz), 5.90–5.80 (2H, m), 3.32 (6H, s), 3.25 (2H, d, J=9.2 Hz), 3.21 (2H, d, J=9.2 Hz), 2.22–2.10 (6H, m), 1.13 (3H, t, J=7.4 Hz). Petrol refers to the fraction of petroleum ether which boils between 40 and 60 °C, and was distilled before use. THF and ether used in reactions was freshly distilled from sodium/ benzophenone. Pentane was dried over CaH_2 and degassed before use. *n*-Butyllithium (*n*-BuLi) was used as a 2.5 M solution in hexanes (Aldrich) and was stored at 4 °C. Note that batches of *n*-BuLi which have aged at room temperature may give poor results for zirconacycle formation, even though titration for base shows no decline. We suspect that some decomposition to LiH occurs, but as this may be solubilised as part of *n*-BuLi clusters its acts as a competent base. Lithium diisopropylamide (LDA) was either used as purchased from Aldrich as a 2.0 M solution in heptane/ THF/ethybenzene or made freshly from diisopropylamine in THF and *n*-BuLi (2.5 M solution in hexanes). Lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was prepared freshly from 2,2,6,6-tetramethylpiperidine in THF and *n*-BuLi (in hexanes) at a concentration of ≈0.5 M by stirring at 0 °C for 20 min.

4.2. Formation of zirconacycles by intramolecular co-cyclisation of 1,*n*-dienes or -enynes

To a solution of Cp_2ZrCl_2 (0.292 g, 1.00 mmol) in THF (7.0 mL) was added *n*-BuLi (2.00 mmol, 0.80 mL, 2.5 M in hexanes) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then a diene or an enyne (1.00 mmol) in THF (2.0 mL) added and the cooling bath was removed. After stirring at 20 °C for 2 h the resulting solution of the zirconacycle was used directly in the next reaction. With the exception of zirconacycles **29** and **51** the solution could be kept at room temperature overnight without harm. The above procedure is assumed to produce 1.00 mmol of zirconacycle for the purposes of the following experimental.

By the above method the following zirconacycles were

made from the diene or enyne precursors indicated in parenthesis: **2a** (4,4-bis(methoxymethyl)hepta-1,6-diene, **1a**); **2b** (5,5-diallyl-2,2-dimethyl-1,3-dioxane, **1b**); **2c** (1,6-heptadiene); **23** (undec-1-en-6-yne); **29** (1,2-diallylbenzene); **36** (dodec-1-en-7-yne); **39** (trimethyl(oct-7-en-1-ynyl)silane); **33** (dec-1-en-6-yne); **51** (octa-1,7-diene); **67** (4,4-bis(methoxymethyl)non-1-en-6-yne).

4.3. Insertion of electron rich alkyl-substituted carbenoids into zirconacycles

4.3.1. *rac*-(3*R*,4*R*)-3-(Iodomethyl)-1,1-bis(methoxymethyl)-4-methylcyclopentane 3. To a solution of zirconacycle **2a** (1.00 mmol) at −78 °C was added iodochloromethane (1.1 mmol, 176 mg) followed by *n*-BuLi (1.1 mmol) and the reaction was stirred for 30 min at this temperature. The reaction was warmed to room temperature before usual work-up and chromatography (eluent 10% ether in petrol) gave the title compound as a colourless oil (215 mg, 77%). ^{1}H NMR: δ 3.40 (1H, dd, J=3.0, 9.5 Hz), 3.34 (6H, s), 3.20 (4H, s), 3.09 (1H, dd, J=8.0, 9.5 Hz), 1.85 (1H, dd, J=13, 7.3 Hz), 1.84 (1H, dd, J=13, 7.3 Hz), 1.52 (1H, m), 1.38 (1H, m), 1.20 (1H, dd, J=13, 7.2 Hz), 1.17 (1H, dd, J=13, 7.3 Hz), 0.95 (3H, d, J=6.5 Hz) ppm. ^{13}C NMR: δ 77.99 (CH_2), 77.67 (CH_2), 59.39 (2×CH_3), 48.35 (CH), 44.62 (C), 42.06 (CH_2), 40.71 (CH_2), 39.72 (CH), 17.79 (CH_3), 12.58 (CH_2) ppm. LRMS (APCI): 312 (M^+), 297 (M^+-CH_3), 184 (M^+-HI). HRMS (EI): calcd for $C_{11}H_{21}IO_2$ (M^+) 312.0586, found 312.0583.

4.3.2. *rac*-(3*R*,4*R*)-3-Ethyl-1,1-bis(methoxymethyl)-4-methylcyclopentane 8. *n*-BuLi (2.1 mmol,) was added dropwise to a −100 °C solution of iodochloromethane (2.0 mmol, 351 mg) in Trapps solvent (4 mL THF, 1 mL pentane, 1 mL ether). A solution of the zirconacycle **2a** (1.00 mmol) was cooled to −78 °C and slowly added via cannula. The reaction was stirred for 1 h, upon which usual work-up and chromatography (eluent 10% ether/petrol) gave a 2.5:1 mixture of **8** and **9** (171 mg, 87%) from which a pure sample of the title compound could be isolated by careful chromatography (0–10% ether in petrol) and Kugelrohr distillation (70 °C, 1 mm Hg) as a colourless oil. ^{1}H NMR: δ 3.34 (6H, s), 3.19 (4H, m), 1.76 (1H, dd, J=13.0, 7.5 Hz), 1.72 (1H, dd, J=13.0, 7.5 Hz), 1.60–1.30 (2H, m), 1.10–0.95 (4H, m), 0.93 (3H, d, J=6.5 Hz), 0.88 (3H, t, J=7.5 Hz) ppm. ^{13}C NMR: δ 78.14 (CH_2), 77.98 (CH_2), 59.38 (2×CH_3), 48.52 (CH), 45.37 (C), 42.09 (CH_2), 41.50 (CH), 39.19 (CH_2), 26.54 (CH_2), 18.29 (CH_3), 12.79 (CH_3) ppm. LRMS (APCI): 200 (M^+, 30%), 185 (M^+-CH_3, 100). Anal. calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.15; H, 12.04.

4.3.3. *rac*-(3*R*,4*R*)-1,1-Bis(methoxymethyl)-3-methyl-4-propylcyclopentane 12. Ethyl carbamate **11** (1.1 mmol, 265 mg), in ether (3 mL) was cooled to −78 °C and a mixture of TMEDA (1.2 mmol) and *s*-BuLi (1.2 mmol) in ether (2 mL) added dropwise. After 30 min at −78 °C a solution of zirconacycle **2a** (1.00 mmol) at the same temperature was added via cannula. After 30 min the reaction was allowed to warm to room temperature before usual work-up and chromatography (eluent 2–10% ether in petrol) gave the title compound as a colourless oil (74 mg, 35%) together with mixed fractions estimated to contain **12** (65 mg, 30%) and **9** (59 mg, 32%). ^{1}H NMR: δ 3.33 (6H, s), 3.20 (4H, m), 1.76 (1H, dd, J=13.5, 7.5 Hz), 1.72 (1H, dd, J=13.5, 7.5 Hz), 1.60–1.10 (6H, m), 1.00 (2H, m), 0.94 (3H, d, J=6.5 Hz), 0.88 (3H, t, J=7.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.15 (CH_2), 78.00 (CH_2), 59.38 (2×CH_3), 46.44 (CH), 45.28 (C), 41.88 (CH_2), 39.85 (CH), 39.50 (CH_2), 36.20 (CH_2), 21.47 (CH_2), 18.13 (CH_3), 14.50 (CH_3) ppm. LRMS (CI, NH_3): 215 ($M+H^+$, 100%), 182 ($M+H^+-OCH_3$, 44%), 151 ($M+H^+-2(OCH_3)$, 97%). HRMS (EI): calcd for $C_{13}H_{26}O_2$ (M^+) 214.1933, found 214.1932.

4.3.4. *rac*-(2*R*,3*S*)-2,8,8-Trimethyl-3-(2-trimethylsilylethyl)-7,9-dioxaspiro[4.5]decane 18b. To a solution of zirconacycle **2b** (1.00 mmol) at −78 °C, was added chloromethyltrimethylsilane (0.135 g, 1.1 mmol) in THF (1 mL) followed by LDA (1.1 mmol) dropwise over 10 min. After stirring for 30 min at −78 °C, the reaction was allowed to warm to room temperature before usual work-up and chromatography (eluent 10% ether in petrol) gave **18b** (223 mg, 78%) as a colourless oil. ^{1}H NMR: δ 3.56 (4H, m), 1.93 (1H, dd, J=13.0, 7.0 Hz), 1.85 (1H, dd, J=13.0, 8.0 Hz), 1.60 (1H, m), 1.50, (1H, m), 1.41 (6H, s), 1.30 (2H, m), 1.00 (2H, m), 0.94 (3H, d, J=7.0 Hz), 0.54 (1H, ddd, J=14.0, 13.0, 5.0 Hz), 0.38 (1H, ddd, 14.0, 13.0, 5.0 Hz), 0.00 (9H, s) ppm. ^{13}C NMR: δ 97.80 (C), 70.53 (CH_2), 70.48 (CH_2), 49.44 (CH), 42.94 (CH_2), 40.21 (CH_2), 39.50 (CH), 39.06 (C), 27.71 (CH_2), 24.26 (CH_3), 23.81 (CH_3), 18.54 (CH_3), 14.91 (CH_2), −1.57 (CH_3) ppm. LRMS (CI): 285 ($M+H^+$, 100%), 269 (M^+-CH_3, 80), 211 (23), 137 (10), 90 (55), 73 (13). HRMS (CI): calcd for $C_{16}H_{33}O_2Si$ ($M+H^+$) 285.2250, found 285.2221.

By the same method, using appropriate zirconacycle and chloromethyldimethylphenylsilane, the following were prepared.

4.3.5. *rac*-(1*S*,2*R*)-4,4-Dimethoxymethyl-2-methyl-1-(2-phenyldimethylsilylethyl)cyclopentane 19a. Colourless oil. ^{1}H NMR: δ 7.56 (2H, m), 7.41 (3H, m), 3.30 (6H, s), 3.19 (4H, m), 1.80–0.80 (11H, m), 0.72 (1H, ddd, J=14.0, 13.5, 5.5 Hz), 0.27 (6H, s) ppm. ^{13}C NMR: δ 133.71 (CH), 128.90 (C), 128.00 (CH), 127.86 (CH), 78.11 (CH_2), 77.99 (CH_2), 59.39 (2×CH_3), 49.62 (CH), 42.13 (C), 39.42 (CH_2), 39.29 (CH), 27.54 (CH_2), 18.31 (CH_2), 13.98 (CH_2), −2.91 (2×CH_3) ppm. LRMS (CI): 335 ($M+H^+$, 5%), 320 ($M+H^+-CH_3$, 100). HRMS (CI): calculated for $C_{20}H_{35}O_2Si$ ($M+H^+$) 335.2406, found 335.2412.

4.3.6. *rac*-(2*R*,3*S*)-2,8,8-Trimethyl-3-(2-phenyldimethylsilylethyl)-7,9-dioxaspiro[4.5]decane 19b. Colourless oil. ^{1}H NMR: δ 7.40 (2H, m), 7.25 (3H, m), 3.5 (4H, m), 1.85 (1H, dd, J=14.0, 8.0 Hz), 1.78 (1H, dd, J=14.0, 8.0 Hz), 1.50 (1H, m), 1.35 (1H, m), 1.30 (6H, s), 1.20 (2H, m), 1.00 (2H, m), 0.90 (3H, d, J=8.0 Hz), 0.75 (1H, m), 0.55 (1H, ddd, J=15.0, 13.0, 4.0 Hz), 0.20 (6H, s) ppm. ^{13}C NMR: δ 139.61 (C), 133.70 (CH), 128.98 (CH), 127.92 (CH), 97.71 (C), 70.51 (CH_2), 70.44 (CH_2), 49.37 (CH), 42.93 (CH_2), 40.19 (CH_2), 39.57 (C), 39.04 (CH), 27.66 (CH_2), 24.31 (CH_3), 23.85 (CH_3), 18.59 (CH_3), 14.00 (CH_2), −2.87 (2×CH_3) ppm. LRMS (CI): 347 ($M+H^+$, 5%), 332 ($M+H^+-CH_3$, 100). HRMS (CI): calcd for $C_{21}H_{35}O_2Si$ ($M+H^+$) 347.2406, found 347.2381.

NMR data for zirconium complex **14b** as a 1:1 mixture of diastereoisomers, ^{1}H NMR (C_6D_6): δ 7.4 (2H, m), 7.10 (3H, m), 5.70, 5.65, 5.53, 5.50 (10H, 4×s), 3.60 (4H, m), 3.40 (6H, m), 2.27 (1H, m), 2.0–1.0 (10H, m), 0.3–0.1 (12H, 4×s) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ 143.67, 143.58, 133.92, 133.87, 111.53, 110.72, 110.01, 109.97, 97.52, 70.91, 70.71, 59.25, 56.75, 56.31, 52.14, 50.52, 49.91, 48.76, 46.78, 41.34, 39.71, 38.93, 35.04, 34.14, 33.47, 27.22, 25.75, 24.72, 23.72, 1.39, 1.34, −0.47, −1.36 ppm.

4.3.7. *rac*-Dimethyl(2-((1*S*,2*R*)-2-methylcyclopentyl)-ethyl)(phenyl)silane 19c. Colourless oil. ^{1}H NMR: δ 7.56 (2H, m), 7.40 (3H, m), 1.90–1.75 (2H, m), 1.60–1.53 (3H, m), 1.43 (1H, m), 1.30–1.10 (4H, m), 0.974 (3H, d, J=6.6 Hz), 0.853 (1H, ddd, J=14.7, 12.5, 4.4 Hz), 0.727 (1H, ddd, J=14.7, 12.5, 5.5 Hz), 0.12 (6H, s) ppm. ^{13}C NMR: δ 139.94 (C), 133.76 (CH), 128.91 (CH), 127.88 (CH), 50.81 (CH), 40.27 (CH), 35.18 (CH_2), 32.16 (CH), 28.65 (CH_2), 23.66 (CH_2), 19.85 (CH_3), 14.28 (CH_2), −2.78 (CH_3), −2.91 (CH_3) ppm. LRMS (EI): 231 (M^+-CH_3, 4%), 168 ($M-C_6H_6$, 27), 135 ($SiMe_2Ph^+$, 100), 121 (22). HRMS (EI): calcd for $C_{15}H_{23}Si$ (M^+-CH_3) 231.1569, found 231.1568.

4.3.8. Trimethyl(2-((*E*)-2-pentylidenecyclopentyl)ethyl)-silane 24 and trimethyl((*Z*)-2-(2-methylcyclopentyli-dene)hexyl)silane 25. Obtained as a colourless oil and an 87:13 inseparable mixture. ^{1}H NMR: δ 5.15 (1H major, tq, J=7.0, 2.4 Hz), 2.59 (1H minor, pentet, J=6.5 Hz), 2.3–1.1 (15H major+17H minor, m), 0.92 (3H, t, J=7.2 Hz), 0.56 (1H major, ddd, J=14.3, 12.1, 4.4 Hz), 0.462 (1H major, ddd, J=14.3, 12.1, 5.2 Hz), 0.02 (9H minor, s), −0.002 (9H major, s) ppm. ^{13}C NMR: **24**: δ 146.47 (C), 120.17 (CH), 47.22 (CH), 32.38 (CH_2), 32.17 (CH_2), 29.53 (CH_2), 29.31 (CH_2), 28.61 (CH_2), 24.21 (CH_2), 22.50 (CH_2), 14.42 (CH_2), 14.21 (CH_3), −1.55 (CH_3) ppm. **25**: δ 138.51 (C), 127.44 (CH), 36.21 (CH), 34.77 (CH_2), 34.64 (CH_2), 30.46 (CH_2), 29.10 (CH_2), 23.85 (CH_2), 22.92 (CH_2), 22.58 (CH_2), 19.71 (CH_3), 14.31 (CH_3) −0.28 (CH_3) ppm. GCMS (CI): **24**, retention time 9.16 min, 239 ($M+H^+$, 13%), 136 (12), 90 (100), 73 (Me_3Si^+, 48). **25**, retention time 8.66 min, 239 ($M+H^+$. 51%), 122 (22), 90 (94), 73 (Me_3Si^+, 100).

4.3.9. *rac*-(2-((1*S*,2*R*)-4,4-Bis(methoxymethyl)-2-methyl-cyclopentyl)ethyl)tributylstannane 20a. To a solution of zirconacycle **2a** (1.00 mmol) at −78 °C was added chloro-methyltributylstannane (340 mg, 1.00 mmol), followed by the dropwise addition of LiTMP (1.1 mmol) over 15 min. After warming to room temperature usual work-up and chromatography (eluent 3% ether in petrol) gave the title product as a colourless oil (54 mg, 11%). Uninserted product **9** was also isolated (108 mg, 58%). ^{1}H NMR (400 MHz): δ 3.34 (6H, s), 3.22 (2H, d, J=8.5 Hz), 3.18 (2H, d, J=8.5 Hz), 1.81 (1H, dd, J=13.3, 6.8 Hz), 1.72 (1H, dd, J=13.3, 7.3 Hz), 1.70 (1H, m), 1.5–1.4 (7H, m), 1.29 (6H, tq, J=7.5, 7.5 Hz), 1.3–1.2 (2H, m), 1.00 (1H, dd, J=13.3, 5.3 Hz), 0.97 (1H, dd, J=13.3, 5.3 Hz), 0.93 (3H, d, J=6.5 Hz), 0.89 (9H, t, J=7.3 Hz), 0.80 (6H, m), 0.8–0.6 (2H, m) ppm. ^{13}C NMR (100 MHz): δ 78.20 (CH_2), 78.04 (CH_2), 59.39 (CH_3), 59.37 (CH_3), 50.70 (CH), 45.19 (C), 42.15 (CH_2), 39.47 (CH), 39.25 (CH_2), 30.93 (CH_2), 29.45 (CH_2), 27.57 (CH_2), 18.39 (CH_3), 13.87 (CH_3), 8.89 (CH_2), 7.42 (CH_2) ppm. LRMS (EI): 433 (M^+-Bu, 75%), 319 (M^+-3Bu, 6), 235 (Bu_2SnH, 50), 179 $BuSnH_2$ (100). HRMS (EI): calcd for $C_{20}H_{41}O_2{}^{120}Sn$ (M^+-Bu) 433.2129, found 433.2127.

4.3.10. *rac*-(2*R*,3*S*)-2,8,8-Trimethyl-3-(2-phenylsul-phanylethyl)-7,9-dioxaspiro[4.5]decane 21b. To a solution of zirconacycle **2b** (1.00 mmol) at −78 °C (chloro-methyl)phenyl sulphide (1.5 mmol, 238 mg) in THF (1 mL) was added followed by the dropwise addition of LDA (1.2 mmol) over 5 min. After stirring at −78 °C for 1 h the solution was warmed to 0 °C and usual work-up and chromatography (eluent 25% ether in petrol) gave the title compound (246 mg, 77%) as a colourless oil. ^{1}H NMR: δ 7.22 (4H, m), 7.10 (1H, m), 3.50 (4H, m), 2.90 (1H, ddd, J=14.0, 10.0, 7.0 Hz), 2.72 (1H, ddd, J=14.0, 10.0, 7.0 Hz), 1.90 (1H, dd, J=14.0, 7.0 Hz), 1.81 (1H, m), 1.75 (1H, dd, J=14.0, 7.0 Hz), 1.40–1.30 (2H, m), 1.32 (6H, s), 0.90–0.80 (3H, m), 0.85 (3H, d, J=6.5 Hz) ppm. ^{13}C NMR: δ 136.94 (C), 129.10 (CH), 129.01 (CH), 125.91 (CH), 97.80 (C), 70.42 (CH_2), 70.23 (CH_2), 45.77 (CH), 42.50 (CH_2), 40.30 (CH_2), 39.93 (C), 39.55 (CH), 33.58 (CH_2), 32.57 (CH_2), 24.56 (CH_3), 23.49 (CH_3) 18.42 (CH_3) ppm. LRMS (APCI): 320 (M^+, 40%), 305 (M^+-Me, 100). HRMS calcd for $C_{19}H_{28}O_2S$ (M^+) 320.1810, found 320.1807.

4.3.11. *rac*-(2*R*,3*S*)-2-(2-Ethoxyethyl)-3,8,8-trimethyl-7,9-dioxaspiro[4.5]decane 22b. To a solution of zircona-cycle **2b** (1.00 mmol) at −78 °C, chloromethyl ethyl ether (1.1 mmol, 104 mg) in THF (2 mL) followed by LDA (1.1 mmol) were added dropwise. After stirring for 30 min at −78 °C, the reaction was allowed to warm to room temperature over 2 h, then usual work-up and chroma-tography (eluent 10% ether/petrol) gave title product as a colourless oil (115 mg, 45%). A sample for analysis was Kugelrohr distilled (80 °C at 1 mm Hg). ^{1}H NMR: δ 3.55 (4H, m), 3.50–3.30 (4H, m), 1.91 (1H, dd, J=13.5, 6.5 Hz), 1.84 (1H, dd, J=14.0, 7.5 Hz), 1.90–1.80 (1H, m), 1.50–1.20 (3H, m), 1.39 (6H, s), 1.18 (3H, t, J=7.5 Hz), 1.00 (2H, m), 0.95 (3H, d, J=6.0 Hz) ppm. ^{13}C NMR: δ 97.56 (C), 70.25 (CH_2), 70.17 (CH_2), 69.74 (CH_2), 66.08 (CH_2), 43.27 (CH), 42.38 (CH_2), 40.37 (CH_2), 39.80 (C), 39.65 (CH), 33.90 (CH_2), 24.08 (CH_3), 23.59 (CH_3), 18.18 (CH_3), 15.20 (CH_3) ppm. LRMS (APCI): 256 (M^+, 5%), 241 (M^+-Me, 100). Anal. calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.45; H, 11.05.

4.4. Insertion of lithiated diethyl chloromethyl-phosphonate into zirconacycles

4.4.1. General procedure. To a solution of the zirconacycle (1.00 mmol) in THF (10.0 mL) at −90 °C, diethyl chloro-methylphosphonate (0.243 g, 1.30 mmol) was added followed by LDA (1.30 mmol). The mixture was stirred at −90 to −40 °C for 2 h, then quenched with 2 M HCl aq. (5.0 mL) and extracted with ether (3×5 mL). The organic layer was washed with brine (2×10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The products were isolated by column chromatography on silica gel (petrol/EtOAc, 1:1) as colourless to pale yellow oils in the yields given in Table 2. Diethyl pentylphosphonate **32** is a known compound and had data consistent with that previously reported.[54]

4.4.2. Diethyl *rac*-2-((1*R*,2*S*)-4,4-bis(methoxymethyl)-2-methylcyclopentyl)ethylphosphonate 26. ^{1}H NMR: δ 4.12 (4H, m), 3.33 (6H, s), 3.18 (4H, m), 1.95–1.70 (4H, m), 1.60–1.25 (4H, m), 1.35 (6H, t, J=6.5 Hz), 1.02 (2H, m), 0.97 (3H, d, J=6.9 Hz) ppm. ^{13}C NMR (100 MHz): 77.96 (CH_2), 77.52 (CH_2), 61.55 (CH_2, J_{CP}=6.5 Hz), 61.51 (CH_2, J_{CP}=6.5 Hz), 59.35 ($2CH_3$), 47.37 (CH, J_{CP}=17 Hz), 45.27 (C), 41.95 (CH_2), 39.73 (CH), 38.89 (CH_2), 26.35 (CH_2, J_{CP}=5 Hz), 24.60 (CH_2, J_{CP}=140 Hz), 18.15 (CH_3), 16.62 ($2CH_3$, J_{CP}=6 Hz) ppm (also run at 75 MHz to unambiguously distinguish between couplings and chemical shift differences). HRMS (EI): calcd for $C_{16}H_{33}O_5P$ (M^+) 336.2066, found 336.2070.

4.4.3. Diethyl *rac*-2-((2*S*,3*S*)-1,2,3,4-tetrahydro-2-methylnaphthalen-3-yl)ethylphosphonate 30. (containing 6% of *trans*-isomer). ^{1}H NMR: δ 7.1–7.0 (4H, m), 4.15–4.0 (4H, m), 2.92 (1H, dd, J=16.6, 5.5 Hz), 2.79 (1H, dd, J=16.9, 5.1 Hz), 2.60–2.50 (2H, m), 2.10 (1H, m), 1.9–1.5 (5H, m), 1.32 (6H, t, J=7.0 Hz), 0.885 (3H, d, J=6.2 Hz) ppm. ^{13}C NMR: δ 135.59 (C), 135.33 (C), 129.61 (CH), 129.16 (CH), 125.82 (CH), 125.63 (CH), 61.62 (CH_2, d, J_{CP}=6 Hz), 38.37 (CH, d, J_{CP}=16.7 Hz), 37.79 (CH), 31.79 (CH_2), 30.39 (CH_2), 24.47 (CH_2, d, J_{CP}=4.6 Hz), 23.88 (CH_2, d, J_{CP}=140.2 Hz), 16.63 (CH_3, d, J_{CP}=6 Hz), 13.97 (CH_3) ppm. *trans*-Isomer ring Me group visible in ^{1}H NMR: δ 1.03 (3H, d, J=6.2 Hz), and in ^{13}C NMR: δ 19.74 ppm, both confirming stereochemistry. HRMS (EI): calcd for $C_{17}H_{27}O_3P$ (M^+) 310.1698, found 310.1688.

4.4.4. Diethyl 2-((*E*)-2-pentylidenecyclohexyl)ethylphosphonate 37. ^{1}H NMR: δ 5.00 (1H, t, J=7.7 Hz), 4.06 (4H, m), 2.10–1.70 (5H, m), 1.65–1.20 (14H, m), 1.25 (6H, t, J=7.0 Hz), 0.83 (3H, t, J=7 Hz) ppm. ^{13}C NMR: δ 140.25 (C), 122.48 (CH), 61.49 (CH_2, d, J_{CP}=6.3 Hz), 45.51 (CH, d, J_{CP}=17.4 Hz), 33.70 (CH_2), 32.55 (CH_2), 28.15 (CH_2), 26.88 (CH_2), 26.13 (CH_2), 24.55 (CH_2, d, J_{CP}=4.5 Hz), 24.11 (CH_2, d, J_{CP}=140 Hz), 23.39 (CH_2), 22.44 (CH_2), 16.62 (CH_3, d, J_{CP}=5.7 Hz), 14.13 (CH_3) ppm. HRMS (EI): calcd for $C_{17}H_{33}O_3P$ (M^+) 316.2167, found 316.2173.

4.4.5. Diethyl 2-((*E*)-2-((trimethylsilyl)methylene)cyclohexyl)ethylphosphonate 40. ^{1}H NMR: δ 5.06 (1H, s), 4.08 (4H, br s), 2.23 (1H, dt, J=13.2, 7.5 Hz), 2.07 (1H, dt, J=13.2, 6.6 Hz), 2.02 (1H, m), 1.78 (1H, m), 1.7–1.3 (9H, m), 1.32 (6H, t, J=7.0 Hz), 0.08 (9H, s) ppm. ^{13}C NMR: δ 160.71 (C), 120.13 (CH), 61.40 (CH_2), 47.84 (CH, d, J_{CP}= 16.5 Hz), 33.98 (CH_2). 32.88 (CH_2), 28.77 (CH_2), 24.66 (CH_2), 23.99 (CH_2, d, J_{CP}=139.6 Hz), 23.54 (CH_2), 16.17 (CH_3), 0.33 (CH_3) ppm (J_{CP}<6 Hz not resolved). HRMS (EI): calcd for $C_{16}H_{33}O_3PSi$ (M^+) 332.1973, found 332.1979.

4.5. Insertion of lithiated chloromethylphenylsulphone into zirconacycles

4.5.1. *rac*-1-(2-((1*S*,2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl)ethylsulphonyl)benzene 27. To zirconacycle **2a** (1.00 mmol) in THF (5 mL) at −78 °C was added chloromethylphenylsulphone (763 mg, 4.0 mmol) in THF (2 mL), followed by the dropwise addition of LDA (4.0 mmol) over 10 min. The reaction was allowed to warm to room temperature and stirred for 12 h. Usual work-up and chromatography (eluent 40–50% ether in petrol) gave the title compound as a pale yellow oil (228 mg, 67%). ^{1}H NMR: δ 7.86 (2H, d, J=7.0 Hz), 7.60 (1H, t, J=7.0 Hz), 7.53 (2H, t, J=7.0 Hz), 3.26 (6H, s), 3.1–2.9 (6H, m), 2.00 (1H, m), 1.68 (1H, dd, J=12.5, 7.0 Hz), 1.63 (1H, dd, J=12.5, 6.6 Hz), 1.5–1.2 (3H, m), 0.99 (1H, dd, J=12.5, 11.0 Hz), 0.91 (1H, dd, J=12.5, 10.3 Hz), 0.87 (3H, d, J=6.3 Hz) ppm. ^{13}C NMR: δ 139.22 (C), 133.71 (CH), 129.31 (CH), 128.04 (CH), 77.77 (CH_2), 77.73 (CH_2), 59.25 (CH_3), 59.23 (CH_3), 53.38 (CH_2), 45.27 (CH), 45.18 (C), 41.57 (CH_2), 39.84 (CH), 38.81 (CH_2), 26.21 (CH_2), 17.89 (CH_3) ppm. LRMS (EI): 341 ($M+H^+$, 1%), 276 (6), 167 (13), 166 (15), 134 (100). HRMS (EI): calcd for $C_{18}H_{28}O_4S$ (M^+) 340.1708, found 340.1698.

4.5.2. 1-(2-((*E*)-2-butylidenecyclopentyl)ethylsulphonyl)-benzene 34. To a solution of zirconacycle **33** (1.00 mmol) at −78 °C was added chloromethyl phenyl sulphone (0.381 g, 2 mmol) as a solution in THF (1.5 mL) followed by the dropwise addition of LDA (2 mmol). The reaction mixture was warmed to −20 °C over 1 h, kept at −20 °C for 4 h and 0 °C for 2 h before usual work-up and chromatography (30% ether in petrol) gave the title compound as a clear oil (245 mg, 84%). ^{1}H NMR (400 MHz): δ 7.92 (2H, d, J=7 Hz), 7.66 (1H, t, J=7.5 Hz), 7.57 (2H, t, J=7.5 Hz), 5.06 (1H, tq, J=7, 2.5 Hz), 3.17–3.06 (2H, m), 2.35 (1H, septet, J=7 Hz), 2.28–2.23 (1H, broad d, J=16 Hz), 2.11 (1H, dt, J=16, 8 Hz), 2.00–1.89 (3H, m), 1.78 (1H, td, J=12, 7 Hz), 1.72–1.63 (2H, m), 1.57–1.46 (1H, m), 1.33 (2H, pentet, J=7 Hz), 1.22–1.13 (1H, m), 0.87 (3H, t, J=7 Hz) ppm. ^{13}C NMR (100 MHz): δ 144.66 (C), 139.71 (C), 133.98 (CH), 129.65 (CH), 128.45 (CH), 121.85 (CH), 54.93 (CH_2), 43.03 (CH), 32.58 (CH_2), 31.87 (CH_2), 29.21 (CH_2), 26.98 (CH_2), 24.27 (CH_2), 23.09 (CH_2), 14.22 (CH_3) ppm. LRMS (CI): 310 ($M+NH_4^+$, 20%), 293 ($M+H^+$, 15), 150 (M^+-PhSO_2H, 100). HRMS (CI): calcd for $C_{17}H_{25}O_2S$ ($M+H^+$) 293.1575, found 293.1584.

4.5.3. 1-(2-((*E*)-2-Pentylidenecyclohexyl)ethylsulphonyl)benzene 38. To a solution of zirconacycle **36** (1.00 mmol) at −78 °C was added chloromethyl phenyl sulphone (0.248 g, 1.3 mmol) in THF (1.5 mL) followed by the dropwise addition of LiTMP (1.3 mmol) over 10 min. The reaction mixture was kept at −78 °C for 2 h before usual work-up and chromatography (30% ether in petrol) gave the title compound as a yellow oil (0.191 g, 60%). ^{1}H NMR: δ 7.92 (2H, dt, J=7, 2 Hz), 7.66 (1H, tt, J=8, 2 Hz), 7.57 (2H, tt, J=7, 1 Hz), 4.95 (1H, t, J=7 Hz), 3.15–2.94 (2H, m), 2.13–1.84 (6H, m), 1.72–1.19 (11H, m), 0.87 (3H, t, J= 7 Hz) ppm. ^{13}C NMR: δ 139.52 (C), 139.42 (C), 133.73 (CH), 129.40 (CH), 128.17 (CH), 123.10 (CH), 55.11 (CH_2), 43.57 (CH), 33.83 (CH_2), 32.44 (CH_2), 27.96 (CH_2), 26.85 (CH_2), 25.95 (CH_2), 24.62 (CH_2), 23.20 (CH_2), 22.45 (CH_2), 14.16 (CH_3) ppm. LRMS (CI): 338 ($M+NH_4^+$, 100%), 321 ($M+H^+$, 30). HRMS (EI): calcd for $C_{19}H_{28}SO_2$ (M^+) 320.1810, found 320.1812.

4.5.4. (*E*)-1-Pentylidene-2-vinylcyclohexane 48. Method as for the preparation of **38** except that the reaction mixture was stirred at room temperature for 8 h before quenching. The crude product was purified by flash column chromatography in petrol and was subsequently Kugelrohr distilled to yield a clear oil (69 mg, 84% pure by NMR, 33%

estimated yield) the residue being (*E*)-1-methyl-2-pentylidenecyclohexane[55] from quenching of the uninserted zirconacycle. ^{1}H NMR (400 MHz): δ 5.91 (1H, ddd, J=17, 10, 7 Hz), 5.09 (1H, t, J=7 Hz), 5.04–4.98 (2H, m), 2.71 (1H, broad s), 2.39 (1H, m), 2.07–1.91 (3H, m), 1.75–1.70 (2H, m), 1.58 (1H, broad s), 1.5–1.2 (7H, m), 0.91 (3H, t, J=6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.16 (CH), 140.89 (C), 122.31 (CH), 114.43 (CH_2), 48.85 (CH), 34.62 (CH_2), 32.70 (CH_2), 28.42 (CH_2), 28.16 (CH_2), 27.25 (CH_2), 25.24 (CH_2), 22.74 (CH_2), 14.44 (CH_3). GCMS (EI): 178 (M^+, 49%), 163 (M^+-CH_3, 10), 149 ($M^+-C_2H_5$), 136 ($M^+-C_3H_7$, 72), 121 (100).

4.6. Insertion of lithiated 2-chloroacetonitrile into zirconacycles

4.6.1. General procedure. To a solution of the zirconacycle (1.00 mmol) in THF (5 mL) at −90 °C, 2-chloroacetonitrile (0.098 g, 1.30 mmol) was added followed by LDA (1.30 mmol). The mixture was stirred at −90 to −60 °C for 1 h, then quenched with 2 M HCl aq. (5.0 mL) and extracted with ether (3×5 mL). The organic layer was washed with brine (2×10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The products were isolated by column chromatography on silica gel (petrol/EtOAc, 3:1 to 6:1). Products were isolated as colourless to pale yellow oils in the yields given in Table 4. For compounds **50** and **52**, 2 equiv. of the carbenoid were used, and for **53**, 5 equiv.

4.6.2. *rac*-3-((1*R*, 2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl)propanenitrile 28. ^{1}H NMR: δ 3.27 (6H, s), 3.15 (2H, d, J=8.6 Hz), 3.10 (2H, d, J=8.6 Hz), 2.33 (1H, ddd, J=16.9, 7.7, 5.5 Hz), 2.23 (1H, ddd, J=16.9, 8.5, 7.4 Hz), 1.95–1.10 (8H, m), 0.99 (2H, m), 0.90 (3H, d, J=6.3 Hz) ppm. ^{13}C NMR: δ 120.06 (C), 77.95 (CH_2), 77.89 (CH_2), 59.39 (CH_3), 45.77 (CH), 45.41 (C), 41.83 (CH_2), 39.85 (CH), 38.70 (CH_2), 29.68 (CH_2), 18.03 (CH_3), 16.26 (CH_2) ppm. HRMS (CI): calcd for $C_{13}H_{24}O_2N$ ($M+H^+$) 226.1807, found 226.1796.

4.6.3. *rac*-3-((1*R*,2*R*)-2-(2-Cyanoethyl)-4,4-bis(methoxymethyl)cyclopentyl)propanenitrile 50. ^{1}H NMR: δ 3.26 (6H, s), 3.13 (2H, d, J=8.6 Hz), 3.10 (2H, d, J=8.6 Hz), 2.37 (2H, ddd, J=16.9, 7.7, 5.5 Hz), 2.24 (2H, ddd, J=16.9, 8.5, 7.4 Hz), 1.95–1.73 (4H, m), 1.58 (2H, m), 1.37 (2H, m), 1.02 (2H, m) ppm. ^{13}C NMR: δ 119.68 (C), 77.76 (CH_2), 59.40 (CH_3), 45.68 (C), 44.05 (CH), 38.43 (CH_2), 29.16 (CH_2), 16.18 (CH_2) ppm. HRMS (CI): calcd for $C_{15}H_{25}N_2O_2$ ($M+H^+$) 265.1916, found 265.1916.

4.6.4. 3-(2-(2-Cyanoethyl)cyclohexyl)propanenitrile 52. (88:12 mixture of *cis*- and *trans*-isomers). ^{1}H NMR: δ 2.29 (4H, m), 1.95–1.10 (14H, m) ppm. ^{13}C NMR: δ 119.91 (C), 37.80 (CH), 27.4 (CH_2), 25.20 (CH_2), 23.11 (CH_2), 15.37 (CH_2) ppm (*cis*-isomer). δ 119.92 (C), 40.02 (CH), 30.57 (CH_2), 28.88 (CH_2), 25.50 (CH_2), 14.57 (CH_2) ppm (*trans*-isomer). HRMS (CI): calcd for $C_{12}H_{19}N_2$ ($M+H^+$) 191.1548, found 191.1555.

4.6.5. 3-((*E*)-2-((Trimethylsilyl)methylene)cyclohexyl)-propanenitrile 41. ^{1}H NMR: δ 5.11 (1H, s), 2.4–1.3 (13H, m), 0.10 (9H, s) ppm. ^{13}C NMR: δ 159.59 (C), 121.20 (CH), 120.20 (C, CN), 46.15 (CH), 33.92 (CH_2), 32.78 (CH_2), 28.77 (CH_2), 27.82 (CH_2), 23.51 (CH_2), 15.47 (CH_2), 0.45 (3×CH_3) ppm. HRMS (CI): calcd for $C_{13}H_{24}NSi$ ($M+H^+$) 222.1678, found 222.1672.

4.6.6. 3-((*E*)-2-Butylidenecyclopentyl)propanenitrile 35. ^{1}H NMR: δ 5.17 (1H, tq, J=7, 2.5 Hz), 2.43 (1H, dd, J=8, 7 Hz), 2.40–2.27 (3H, m,), 2.20 (1H, broad pentet, J=8 Hz), 1.99–1.84 (4H, m), 1.86–1.80 (1H, m), 1.65–1.50 (2H, m), 1.37 (2H, sextet, J=7 Hz), 1.28–1.19 (1H, m), 0.89 (3H, t, J=7 Hz) ppm. ^{13}C NMR: δ 144.58 (C), 121.62 (CH), 120.29 (C), 43.28 (CH), 32.25 (CH_2), 31.65 (CH_2), 30.01 (CH_2), 28.93 (CH_2), 24.05 (CH_2), 22.89 (CH_2), 15.48 (CH_2), 14.02 (CH_3) ppm. LRMS(CI): 195 ($M+NH_4^+$, 20%), 178 ($M+H^+$, 75), 148 ($M^+-C_2H_5$, 80). HRMS (EI): calcd for $C_{12}H_{19}N$ (M^+) 177.1518, found 177.1518.

4.6.7. 2-(((*E*)-2-Butylidenecyclopentyl)methyl)succinonitrile 53. *Isomer*1. ^{1}H NMR (400 MHz): δ 5.27 (1H, tq, J=7, 2.5 Hz), 3.00 (1H, dq, J=9.5, 6.5 Hz), 2.73 (2H, d, J=6.5 Hz), 2.56 (1H, pentet, J=7 Hz), 2.34–2.17 (2H, m), 2.02–1.90 (3H, m), 1.85–1.59 (4H, m), 1.46–1.35 (3H, m), 0.91 (3H, t, J=7 Hz) ppm. ^{13}C NMR (100 MHz): δ 143.94 (C), 122.77 (CH), 119.27 (C), 115.54 (C), 42.15 (CH), 36.44 (CH_2), 32.63 (CH_2), 31.52 (CH_2), 27.93 (CH_2), 27.06 (CH), 24.00 (CH_2), 23.59 (CH_2), 22.65 (CH_2), 13.83 (CH_3) ppm. LRMS (CI): 234 ($M+NH_4^+$, 16%), 217 ($M+H^+$, 32), 201 (M^+-CH_3, 8), 187 ($M^+-C_2H_5$, 45). *Isomer* 2. ^{1}H NMR (400 MHz): δ 5.19 (1H, tq, J=7, 2.5 Hz), 2.99–2.92 (1H, m), 2.75 (2H, t, J=6 Hz), 2.61 (1H, broad s), 2.38–2.32 (1H, m), 2.21 (1H, dt, J=17, 8.5 Hz), 2.07 (1H, ddd, J=14, 11, 4.5 Hz), 2.01–1.94 (3H, m), 1.83–1.76 (1H, m), 1.65–1.57 (2H, m), 1.38 (2H, pentet, J=7 Hz), 1.28–1.19 (1H, m), 0.91 (3H, t, J=7 Hz) ppm. ^{13}C NMR (100 MHz): δ 144.53 (C), 122.06 (CH), 119.27 (C), 115.97 (C), 41.84 (CH), 37.07 (CH_2), 32.65 (CH_2), 31.91 (CH_2), 29.31 (CH_2), 27.59 (CH), 24.42 (CH_2), 23.06 (CH_2), 22.01 (CH_2), 14.24 (CH_3) ppm. LRMS (CI): 234 ($M+NH_4^+$, 100%), 217 ($M+H^+$, 35), 187 ($M^+-C_2H_5$, 30).

4.7. Insertion of 1-lithio-1-haloalkenes into saturated zirconacycles

4.7.1. *rac*-(2*R*,3*S*)-2,8,8-Trimethyl-3-(3-methylbut-2-enyl)-7,9-dioxaspiro[4.5]decane 61a. To a solution of zirconacycle **2b** (1.00 mmol) at −78 °C was added 1-chloro-2-methyl-1-propene (452 mg, 5 mmol) in THF (2 mL). The solution was then cooled to −90 °C, and LiTMP (5 mmol) was added dropwise over 10 min. After stirring for 30 min at −90 °C usual work-up and chromatography (eluent 25% ether in petrol) gave the title product (83 mg, 33%) as a colourless oil. ^{1}H NMR: δ 5.05 (1H, t septet, J=8.0, 1.5 Hz), 3.56 (4H, m), 2.15 (1H, m), 1.80 (1H, ddd, J=13.2, 7.4, 2.9 Hz), 1.75–1.65 (2H, m), 1.60 (3H, d, J=1.5 Hz), 1.52 (3H, s), 1.45 (1H, m), 1.35 (6H, s), 1.30 (1H, m), 0.97 (2H, m), 0.95 (3H, d, J=7.0 Hz) ppm. ^{13}C NMR: δ 131.77 (C), 123.26 (CH), 97.67 (C), 70.46 (CH_2), 70.39 (CH_2), 46.91 (CH), 42.78 (CH_2), 40.63 (CH_2), 39.67 (C), 39.05 (CH), 31.84 (CH_2), 25.97 CH_3), 24.47 (CH_3), 24.02 (CH_3), 23.95 (CH_3), 18.50 (CH_3) ppm. LRMS (CI): 253 ($M+H^+$, 100%), 237 (12), 195 (99), 177 (56). HRMS (CI) calcd for $C_{16}H_{29}O_2$ ($M+H^+$) 253.2168, found 253.2160. Data consistent with that previously reported.[46]

4.7.2. *rac*-(3*R*,4*R*)-1,1-Bis(methoxymethyl)-3-methyl-4-[(2*E*)-2,4-pentadienyl]cyclopentane 61b. To a solution of zirconacycle **2a** (1.00 mmol) in THF (5 mL) at −90 °C was added (*E*)-1,4-dichloro-2-butene (138 mg, 1.1 mmol) followed by the dropwise addition of LDA (2.2 mmol) over 10 min. After stirring at −90 °C for 1 h usual work-up and chromatography (eluent 10% ether/petrol) gave the title compound as a colourless oil (161 mg, 68%). A sample for analysis was Kugelrohr distilled (80 °C at 1 mm Hg). ^{1}H NMR: δ 6.28 (1H, dt, *J*=17.0, 10.5 Hz), 6.04 (1H, dd, *J*=17.0, 10.5 Hz), 5.69 (1H, ddd, *J*=17.0, 10.5, 9.5 Hz), 5.07 (1H, dd, *J*=17.0, 2.0 Hz), 4.93 (1H, dd, *J*=9.5, 2.0 Hz), 3.32 (6H, s), 3.20 (4H, m), 2.34 (1H, ddd, *J*=10.5, 6.5, 2.9 Hz), 2.0–0.9 (10H, m) ppm. ^{13}C NMR: δ 137.29 (CH), 134.21 (CH), 131.58 (CH), 114.69 (CH_2), 77.90 (CH_2), 77.78 (CH_2), 59.22 (CH_3), 59.00 (CH_3), 46.57 (CH), 45.06 (C), 41.94 (CH), 41.34 (CH_2), 39.23 (CH_2), 36.57 (CH_2), 17.77 (CH_3) ppm. LRMS (APCI): 238 (M^+, 100%). Anal. calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.48; H, 10.85.

4.7.3. *rac*-(3*R*,4*R*)-1,1-Bis(methoxymethyl)-3-methyl-4-[(2*Z*)-2,4-pentadienyl]cyclopentane 61c. To a solution of zirconacycle **2a** (1.00 mmol) in THF (5 mL) at −90 °C was added (*Z*)-1,4-dichlorobut-2-ene (125 mg, 1.00 mmol), followed by LDA (1.0 mmol) dropwise over 15 min. The reaction was stirred at −90 °C for 35 min before usual work-up and chromatography ($AgNO_3$ doped silica, eluent 4–50% ether in petrol) gave the title compound as a colourless oil (143 mg, 60%) and non-inserted product **9** (43 mg, 23%). A sample of **61c** for analysis was Kugelrohr distilled (80 °C at 1 mm Hg). ^{1}H NMR (400 MHz): δ 6.64 (1H, dt, *J*=16.6, 10.5 Hz), 6.00 (1H, t, *J*=10.5 Hz), 5.46 (1H, dt, *J*=10.5, 7.5 Hz), 5.17 (1H, d, *J*=16.6 Hz), 5.07 (1H, d, *J*=10.5 Hz), 3.33 (3H, s), 3.32 (3H, s), 3.20–3.15 (4H, m), 2.42 (1H, m), 1.98 (1H, dt, *J*=14.1, 7.5 Hz), 1.74 (2H, dd, *J*=13.1, 7.0 Hz), 1.54 (1H, m), 1.41 (1H, m), 1.04 (1H, dd, *J*=13.1, 11.0 Hz), 1.02 (1H, dd, *J*=13.1, 2.0 Hz), 0.96 (3H, d, *J*=6.5 Hz) ppm. ^{13}C NMR (100 MHz): δ 131.46 (CH), 130.68 (CH), 128.67 (CH), 115.91 (CH_2), 77.07 (CH_2), 76.97 (CH_2), 58.36 (CH_3), 45.94 (CH), 44.24 (C), 40.83 (CH_2), 38.55 (CH), 38.31 (CH_2), 30.48 (CH_2), 17.25 (CH_3) ppm. LRMS (APCI): 238 (M^+, 100%). Anal. calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.68; H, 11.05.

4.7.4. *rac*-(3*R*,4*R*)-1,1-Bis(Methoxymethyl)-3-methyl-4-((*Z*)-non-2-en-4-ynyl)cyclopentane 61d. To zirconacycle **2a** (1.00 mmol) in THF (5 mL) at −78 °C was added (*E*)-1-chloro-oct-1-en-3-yne (171 mg, 1.00 mmol), followed by LDA (1.0 mmol) dropwise over 15 min. The reaction was stirred at −78 °C for 40 min before usual work-up and chromatography (eluent 3% ether in petrol) gave the title compound as a colourless oil (158 mg, 54%). ^{1}H NMR (400 MHz): δ 5.824 (1H, dt, *J*=10.7, 7.5 Hz), 5.434 (1H, dtt, *J*=10.7, 2.1, 1.4 Hz), 3.329 (3H, s), 3.324 (3H, s), 3.2 (4H, m), 2.524 (1H, dddd, *J*=14.1, 7.5, 4.3, 1.5 Hz), 2.337 (2H, dt, *J*=2.3, 6.9 Hz), 2.087 (1H, dddd, *J*=14.1, 8.8, 7.5, 1.3 Hz), 1.756 (1H, dd, *J*=7.0, 3.5 Hz), 1.731 (1H, dd, *J*=7.0, 3.8 Hz), 1.6–1.4 (6H, m), 1.097 (1H, dd, *J*=13.3, 10.8 Hz), 1.001 (1H, dd, *J*=13.0, 11.0 Hz), 0.975 (3H, d, *J*=6.3 Hz), 0.923 (3H, t, *J*=7.3 Hz). ^{13}C NMR (100 MHz): δ 141.02 (CH), 109.79 (CH), 94.46 (C), 77.88 (CH_2), 77.77 (CH), 77.45 (C), 59.18 (CH_3), 46.38 (CH), 45.16 (C), 41.62 (CH_2), 39.44 (CH), 39.06 (CH_2), 33.69 (CH_2), 30.93 (CH_2), 21.92 (CH_2), 19.18 (CH_2), 18.08 (CH_3), 13.56 (CH_3) ppm. LRMS (EI): 292 (M^+, 1%), 260 (M^+−MeOH, 12), 247 (8), 215 (35), 107 (65), 91 (72). HRMS (EI): calcd for $C_{19}H_{32}O_2$ (M^+) 292.2402, found 292.2403.

4.7.5. *rac*-1-((*Z*)-3-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl)prop-1-enyl)benzene 61e. To zirconacycle **2a** (1.00 mmol) at −78 °C was added (*E*)-β-bromostyrene (183 mg, 1.00 mmol) followed by LDA (1.0 mmol) dropwise over 20 min. The reaction was stirred at −78 °C for 5 min before usual work-up and chromatography (eluent 4% ether in petrol) gave the title compound as a colourless oil (138 mg, 48%) together with bis-inserted product **62** (43 mg, 11%). ^{1}H NMR (400 MHz): δ 7.32 (2H, t, *J*=7.5 Hz), 7.27 (2H, d, *J*=7.5 Hz), 7.21 (1H, t, *J*=7.5 Hz), 6.41 (1H, d, *J*=11.5 Hz), 5.68 (1H, dt, *J*=11.5 7.3 Hz), 3.34 (3H, s), 3.31 (3H, s), 3.21 (1H, d, *J*=9.0 Hz), 3.19 (1H, d, *J*=9.0 Hz), 3.18 (1H, d, *J*=9.0 Hz), 3.16 (1H, d, *J*=9.0 Hz), 2.61 (1H, m), 2.08 (1H, ddd, *J*=15.0, 7.5, 7.5 Hz), 1.82 (1H, dd, *J*=13.0, 7.0 Hz), 1.74 (1H, dd, *J*=13.0, 7.0 Hz), 1.6–1.5 (1H, m), 1.5–1.4 (1H, m), 1.05 (1H, dd, *J*=10.1, 7.0 Hz), 1.02 (1H, dd, *J*=10.1, 7.0 Hz), 0.95 (3H, d, *J*=6.0 Hz) ppm. ^{13}C NMR (100 MHz): δ 137.97 (C), 132.05 (CH), 129.18 (CH), 128.97 (CH), 128.21 (CH), 126.53 (CH), 78.10 (CH_2) 77.98 (CH_2), 59.39 (CH_3), 59.37 (CH_3), 47.27 (CH), 45.33 (C), 41.87 (CH_2), 39.78 (CH), 39.47 (CH_2), 32.55 (CH_2), 18.52 (CH_3) ppm. LRMS (EI): 288 (M^+, 12%), 256 (M^+−MeOH, 30), 211 (M^+−Ph, 38), 137 (70). HRMS (EI): calcd for $C_{19}H_{28}O_2$ (M^+) 288.2089, found 288.2092.

4.7.6. *rac*-(1*E*,3*Z*)-2-(((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl)methyl)-1,4-diphenylbuta-1,3-diene 62. Method as for **61** except that 2 equiv. of (*E*)-β-bromostyrene and LDA were used to afford **62** as a colourless oil (250 mg, 64%). ^{1}H NMR (400 MHz): δ 7.56 (2H, d, *J*=7.5 Hz), 7.45–7.35 (4H, m,), 7.35–7.25 (4H, m), 6.67 (1H, s), 6.56 (1H, d, *J*=12.2 Hz), 6.35 (1H, d, *J*=12.2 Hz), 3.42 (3H, s), 3.39 (3H, s), 3.27 (1H, d, *J*=8.5 Hz), 3.23 (1H, d, *J*=8.5 Hz), 3.23 (1H, d, *J*=9.0 Hz), 3.20 (1H, d, *J*=9.0 Hz), 2.79 (1H, dd, *J*=13.6, 3.5 Hz), 2.23 (1H, dd, *J*=13.6, 10.0 Hz), 1.86 (1H, dd, *J*=13.1, 7.0 Hz), 1.78 (1H, dd, *J*=13.1, 7.3 Hz), 1.68 (1H, m), 1.50 (1H, m, 1.08 (1H, dd, *J*=13.1, 10.5 Hz), 1.05 (1H, dd, *J*=13.1, 10.5 Hz), 0.91 (3H, d, *J*=6.0 Hz) ppm. ^{13}C NMR (100 MHz): δ 139.27 (C), 138.00 (C), 137.92 (C), 134.03 (CH), 130.38 (CH), 129.43 (CH), 129.04* (CH), 129.01* (CH), 128.20* (CH), 78.03 (CH_2), 77.90 (CH_2), 59.36 (CH_3), 59.32 (CH_3), 45.80 (CH), 45.30 (C), 41.69 (CH_2), 40.23 (CH), 39.77 (CH_2), 34.90 (CH_2), 18.01 (CH_3) ppm (*—contain overlapping peaks). LRMS (EI): 390 (M^+, 8%), 358 (M^+−MeOH, 6), 326 (M^+−2MeOH, 5), 218 (55), 129 (100). HRMS (EI): calcd for $C_{27}H_{34}O_2$ (M^+) 390.2559, found 390.2553.

4.8. Insertion of 1-halo-1-lithioalkenes into unsaturated zirconacycles

4.8.1. (4*E*)-1,1-Bis(methoxymethyl)-3-((*Z*)-penta-2,4-dienyl)-4-propylidenecyclopentane 70a. To zirconacycle **67** (1.00 mmol) in THF (5 mL) at −90 °C was added (*Z*)-1,4-dichloro-2-butene (375 mg, 3.0 mmol), followed by LDA (6.0 mmol) dropwise over 25 min. The reaction was

stirred at −90 °C for 30 min before usual work-up and chromatography ($AgNO_3$ doped silica, eluent 3–50% ether in petrol) gave the title compound as a pale yellow oil (213 mg, 81%). ^{1}H NMR (400 MHz): δ 6.61 (1H, dt, *J*=17.1, 10.5 Hz), 6.03 (1H, t, *J*=10.5 Hz), 5.47 (1H, dt, *J*=10.5, 7.5 Hz), 5.19 (1H, m), 5.17 (1H, d, *J*=17.1 Hz), 5.08 (1H, d, *J*=10.5 Hz), 3.34 (3H, s), 3.32 (3H, s), 3.28 (1H, d, *J*=8.7 Hz), 3.24 (1H, d, *J*=8.7 Hz), 3.19 (2H, s), 2.58–2.47 (2H, m), 2.20 (1H, d, *J*=16.6 Hz), 2.12 (1H, d, *J*=16.6 Hz), 2.12 (1H, m), 1.98 (2H, dq, *J*=7.5, 7.5 Hz), 1.83 (1H, dd, *J*=13.1, 7.5 Hz), 1.11 (1H, dd, *J*=13.1, 10.5 Hz), 0.94 (3H, t, *J*=7.5 Hz) ppm. ^{13}C NMR: δ 143.52 (C), 132.58 (CH), 131.35 (CH), 129.95 (CH), 123.14 (CH), 117.00 (CH_2), 77.70 (CH_2), 75.35 (CH_2), 59.43 (CH_3), 59.42 (CH_3), 45.81 (C), 41.81 (CH), 37.75 (CH_2), 35.86 (CH_2), 32.64 (CH_2), 22.67 (CH_2), 14.44 (CH_3) ppm. LRMS (EI): 264 (M^+, 2%), 232 (M^+−MeOH, 23), 187 (26), 165 (40), 133 (44), 105 (45), 91 (100). HRMS (EI): calcd for $C_{16}H_{24}O$ (M^+−MeOH) 232.1827, found 232.1830

4.8.2. 1-((1*Z*)-3-((*E*)-4,4-Bis(methoxymethyl)-2-propylidenecyclopentyl)prop-1-enyl)benzene 70b. To zirconacycle **67** (1.00 mmol) in THF (5 mL) at −78 °C was added (*E*)-β-bromostyrene (200 mg, 1.1 mmol) followed by LDA (1.1 mmol) dropwise over 15 min. The reaction was stirred at −78 °C for 30 min before usual work-up and chromatography (eluent 4% ether in petrol) gave the title compound as a colourless oil (200 mg, 64%). ^{1}H NMR (400 MHz): δ 7.29 (2H, dd, *J*=7.5, 7.5 Hz), 7.24 (2H, d, *J*=7.5 Hz), 7.18 (1H, t, *J*=7.5 Hz), 6.41 (1H, d, *J*=11.6 Hz), 5.66 (1H, dt, *J*=11.6, 7.0 Hz), 5.19 (1H, t, *J*=7.0 Hz), 3.30 (3H, s), 3.28 (3H, s), 3.23 (1H, d, *J*=9.0 Hz), 3.19 (1H, d, *J*=9.0 Hz), 3.18 (2H, s), 2.66 (1H,ddd, *J*=14.0, 7.0, 7.0 Hz), 2.57 (1H, m), 2.24 (1H, ddd, *J*=14.0, 7.0, 7.0 Hz), 2.18 (1H, d, *J*=16.8 Hz), 2.06 (1H, d, *J*=16.8 Hz), 1.94 (2H, dq, *J*=7.5, 7.5 Hz), 1.86 (1H, dd, *J*=12.8, 8.0 Hz), 1.10 (1H, dd, *J*=12.8, 10.5 Hz), 0.90 (3H, t, *J*=7.5 Hz) ppm. ^{13}C NMR (100 MHz): δ 143.58 (C), 137.96 (C), 131.57 (CH), 129.57 (CH), 128.94 (CH), 128.23 (CH), 126.55 (CH), 123.21 (CH), 77.71 (CH_2), 75.46 (CH_2), 59.42 (CH_3), 59.39 (CH_3), 45.90 (C), 42.22 (CH), 37.85 (CH_2), 35.88 (CH_2), 33.50 (CH_2), 22.67 (CH_2), 14.33 (CH_3) ppm. LRMS (EI): 282 (M^+−MeOH, 10%), 237 (M^+−Ph, 5), 197 (M^+−PhCHCHCH$_2$, 10), 165 (32), 133 (31), 117 (35), 91 (100). HRMS (EI): calcd for $C_{21}H_{30}O_2$ (M^+) 314.2246, found 314.2245.

4.8.3. (2*E*)-1-((2*Z*)-2-Nonen-4-ynyl)-2-pentylidenecyclopentane 70c. To a stirred solution zirconacycle **23** (1.00 mmol) in THF (5.0 mL) at −78 °C was added (*E*)-1-chloro-1-octen-3-yne (0.2 mL, 2.0 mmol) followed by LiTMP (2.0 mmol). The mixture continued to stir at −78 °C for 20 min then at room temperature overnight before usual work-up and Kugelrohr distillation (110 °C, 15 mm Hg) gave the title compound as a pale yellow oil (223 mg, 86%). ^{1}H NMR (400 MHz): δ 5.77 (1H, dt, *J*=10.6, 7.4 Hz), 5.40 (1H br d, *J*=10.6 Hz), 5.13 (1H t, *J*=6.8 Hz), 2.44 (1H, dt, *J*=13.3, 6.8 Hz), 2.33 (1H, m), 2.30–2.15 (4H, m), 1.91 (2H, m), 1.75–1.60 (2H, m), 1.44 (2H, sextet, *J*=6.8 Hz), 1.36 (3H, m), 1.25 (5H, m), 0.85 (6H, m) ppm. ^{13}C NMR (100 MHz): δ 145.66 (C), 141.38 (CH), 120.65 (CH), 110.09 (CH), 94.49 (C), 77.72 (C), 43.90 (CH), 34.95 (CH_2), 32.47 (CH_2), 32.07 (CH_2), 31.11 (CH_2), 29.33 (CH_2), 29.27 (CH_2), 24.19 (CH_2), 22.54 (CH_2), 22.09 (CH_2), 19.37 (CH_2), 14.21 (CH_3), 13.75 (CH_3) ppm. LRMS (CI): 259 (M+H^+, 90%), 137 (100). HRMS (EI): calcd for $C_{19}H_{30}$ (M^+) 258.2348, found 258.2338.

4.8.4. (4*E*,8*Z*)-5-Propylpentadeca-4,8-dien-10-yne 70d. To zirconocene dichloride (292 mg, 1.00 mmol) in THF (5 mL) at −78 °C under argon was added *n*-BuLi (2.0 mmol) and stirred for 20 min before the reaction was placed under an ethene atmosphere. The reaction was warmed to room temperature and 4-octyne (110 mg, 1.00 mmol) was added and the reaction stirred for 3 h to form zirconacycle **68**. The solution was then cooled to −78 °C and 1-chloro-oct-1-en-3-yne (157 mg, 1.1 mmol) added, followed by LDA (1.1 mmol) dropwise over 15 min. The reaction was stirred at −78 °C for 45 min before usual work-up and chromatography (eluent petrol) gave the title compound as a colourless oil (134 mg, 54%). ^{1}H NMR (400 MHz): δ 5.81 (1H, dt, *J*=10.5, 7.5 Hz), 5.42 (1H, dt, *J*=10.5, 2.0 Hz), 5.16 (1H, t, *J*=7.0 Hz), 2.39 (2H, dt, *J*=7.5 Hz), 2.34 (2H, td, *J*=7.0, 2.0 Hz), 2.07 (2H, t, *J*=7.5 Hz), 2.04–1.94 (4H, m), 1.53 (2H, m), 1.45–1.30 (6H, m), 0.92 (3H, t, *J*=7.5 Hz), 0.90 (6H, t, *J*=7.5 Hz) ppm. ^{13}C NMR: δ 142.48 (CH), 138.59 (C), 125.56 (CH), 109.44 (CH), 94.70 (C), 77.47 (C), 36.08 (CH_2), 32.18 (CH_2), 31.11 (CH_2), 29.96 (CH_2), 29.02 (CH_2), 23.38 (CH_2), 22.11 (CH_2), 21.71 (CH_2), 19.37 (CH_2), 14.35 (CH_3), 14.02 (CH_3), 13.78 (CH_3) ppm. LRMS (EI): 246 (M^+, 15%), 217 (M^+−C_2H_5, 18), 203 (M^+−C_3H_7, 95), 189 (M^+−C_4H_9, 25), 161 (50), 147 (53). HRMS (EI): calcd for $C_{18}H_{30}$ (M^+) 246.2348, found 246.2346.

4.9. Insertions via rearrangement of alkynate complexes

4.9.1. 1-((1*Z*)-3-((*E*)-2-Pentylidenecyclopentyl)-1-propenyl)benzene 72a. To a stirred solution of zirconacycle **23** (0.5 mmol) in THF (5 mL) at −78 °C was added 1-[(*E*)-2-fluoro-1-ethenyl]benzene (0.06 mL, 0.5 mmol) followed by LiTMP (0.5 mmol). The mixture was warmed slowly to room temperature then stirred for 12 h before usual work-up and chromatography (eluted with petrol) yielded the title compound as a colourless oil (63 mg, 49.5%). ^{1}H NMR (400 MHz): δ 7.30 (5H, m), 6.46 (1H, br d, *J*=11.8 Hz), 5.73 (1H, dt, *J*=11.8, 7.0 Hz), 5.21 (1H, tq, *J*=7.0, 2.0 Hz), 2.60 (1H, dddd, *J*=14.7, 10.3, 4.5, 1.5 Hz), 2.45 (1H, m), 2.35–2.15 (3H, m), 1.98 (2H, apparent q, *J*=5.9 Hz), 1.86 (1H, m), 1.70 (1H, m), 1.50–1.40 (2H, m), 1.35–1.21 (4H, m), 0.90 (3H, t, *J*=6.8 Hz) ppm. ^{13}C NMR (100 MHz): δ 145.65 (C), 138.03 (C), 132.07 (CH), 129.36 (CH), 128.93 (CH), 128.25 (CH), 126.53 (CH), 120.76 (CH), 44.60 (CH), 33.33 (CH_2), 32.75 (CH_2), 32.05 (CH_2), 29.34 (CH_2), 29.32 (CH_2), 24.17 (CH_2), 22.57 (CH_2), 14.23 (CH_3) ppm. LRMS (EI): 254 (M^+, 42%), 197 (M^+−C_4H_9, 11), 137 (100), 117 (PhCH=CHCH_2^+, 91), 115 (100). HRMS (EI): calcd for $C_{19}H_{26}$ (M^+) 254.2035, found 254.2047. By the same method 4-[3-(2-butylidene-cyclopentyl)-propenyl]-biphenyl **72b** was formed from 4-(2-fluorovinyl)biphenyl in 52% yield.

4.9.2. 4-[3-(2-Butylidene-cyclopentyl)-propenyl]-biphenyl 72b. To a stirred solution of zirconacycle **23** (1.00 mmol) at −78 °C was added 4-ethynyl-biphenyl (178 mg, 1.00 mmol) followed by LiTMP (1.0 mmol). The

solution was then warmed to room temperature and stirred for 12 h before usual work-up and chromatography (petrol) gave the title compound as a colourless oil (210 mg, 64%). ^{1}H NMR: δ 7.65–7.57 (4H, m), 7.50–7.31 (5H, m), 6.50 (1H, d, J=11.8 Hz), 5.77 (1H, dt, J=11.8, 7.0 Hz), 5.25 (1H, tq, J=7.4, 2.0 Hz), 2.68 (1H, dddd, J=14.3, 7.0, 4.8, 1.8 Hz), 2.49 (1H, m), 2.42–2.20 (3H, m), 2.00 (2H, br d, J=7.0 Hz), 1.90 (1H, ddt, J=11.8, 4.8, 6.6 Hz), 1.74 (1H, m), 1.56 (1H, m), 1.40–1.26 (5H, m), 0.91 (3H, t, J= 7.0 Hz) ppm. ^{13}C NMR: δ 145.66 (C), 141.03 (C), 139.27 (C), 137.10 (C), 132.72 (CH), 132.37 (CH), 129.39 (CH), 129.04 (CH), 127.90 (CH), 127.35 (CH), 127.14 (CH), 126.97 (CH), 120.82 (CH), 44.63 (CH), 33.52 (CH_2), 32.80 (CH_2), 32.07 (CH_2), 30.18 (CH_2), 29.38 (CH_2), 24.22 (CH_2), 22.60 (CH_2), 14.26 (CH_3) ppm. LRMS (EI): 330 (M^+, 32%), 249 (9), 193 (p-$PhC_6H_4CH{=}CHCH_2^+$, 100), 178 (88). HRMS (EI): calcd for $C_{25}H_{30}$ (M^+) 330.2348, found 330.2352.

Acknowledgements

We thank the Engineering and Physical Sciences Research Council (EPSRC) for a postdoctoral award (GR/N00647) to A. K. and studentships to S. D., S. M. F., D. N. and E. T. We thank our industrial partners for collaborating on this work through the CASE scheme: Julian Blagg (Pfizer, Sandwich) and Ed Griffen (AstraZeneca, Alderley Park). R. J. W. thanks Pfizer for generous uncommitted support during the course of this work.

References and notes

1. (a) Negishi, E. Zirconium-promoted Bicyclization of Enyne. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 1163. (b) Broene, R. D. Transition Metal Alkyl Complexes: Reductive Dimerization of Alkenes and Alkynes; *Comprehensive Organometallic Chemistry II: A Review of the Literature 1982–1994*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 323–348.
2. (a) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266–6268. (b) Takahashi, T.; Xi, Z. F.; Rousset, C. J.; Suzuki, N. *Chem. Lett.* **1993**, 1001–1004. (c) Buchwald, S. L.; Broene, R. D. Transition Metal Alkyne Complexes: Zirconium–Benzyne Complexes; *Comprehensive Organometallic Chemistry II: A Review of the Literature 1982–1994*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 771–784.
3. (a) Kemp, M. I.; Whitby, R. J.; Coote, S. J. *Synthesis* **1998**, 552–556, see also pp 557–568. (b) Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633–5642. (c) Mori, M.; Uesaka, N.; Saitoh, F.; Shibasaki, M. *J. Org. Chem.* **1994**, *59*, 5643–5649.
4. Probert, G. D.; Harding, R.; Whitby, R. J.; Coote, S. J. *Synlett* **1997**, 1371–1374.
5. (a) Fagan, P. J.; Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 1880–1889. (b) Spence, R. E. V.; Hsu, D. P.; Buchwald, S. L. *Organometallics* **1992**, *11*, 3492–3493. (c) Buchwald, S. L.; Fisher, R. A.; Foxman, B. M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 771–772. (d) Ura, Y.; Li, Y. Z.; Xi, Z. F.; Takahashi, T. *Tetrahedron Lett.* **1998**, *39*, 2787–2790. (e) Buchwald, S. L.; Qun, F. *J. Org. Chem.* **1989**, *54*, 2793–2797.
6. (a) Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 6435–6437. (b) Xi, C. J.; Huo, S. Q.; Afifi, T. H.; Hara, R.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 4099–4102. (c) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870–2874. (d) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797–11810. (e) Nishihara, Y.; Aoyagi, K.; Hara, R.; Suzuki, N.; Takahashi, T. *Inorg. Chim. Acta* **1996**, *252*, 91–99. (f) Aoyagi, K.; Kasai, K.; Kondakov, D. Y.; Hara, R.; Suzuki, N.; Takahashi, T. *Inorg. Chim. Acta* **1994**, *220*, 319–326. (g) Ubayama, H.; Xi, Z. F.; Takahashi, T. *Chem. Lett.* **1998**, 517–518.
7. (a) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521–3523. (b) Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5105–5108. (c) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336–3346. (d) Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N.; Nakajima, K. *Organometallics* **1994**, *13*, 4183–4185. (e) Takahashi, T.; Huo, S. Q.; Hara, R.; Noguchi, Y.; Nakajima, K.; Sun, W. H. *J. Am. Chem. Soc.* **1999**, *121*, 1094–1095. (f) Barluenga, J.; Sanz, R.; Fananas, F. J. *Chemistry* **1997**, *3*, 1324–1336. (g) Takahashi, T.; Xi, Z. F.; Nishihara, Y.; Huo, S. Q.; Kasai, K.; Aoyagi, K.; Denisov, V.; Negishi, E. *Tetrahedron* **1997**, *53*, 9123–9134.
8. (a) Davis, J. M.; Whitby, R. J.; Jaxa-Chamiec, A. *Tetrahedron Lett.* **1992**, *33*, 5655–5658. (b) Davis, J. M.; Whitby, R. J.; Jaxa-Chamiec, A. *Tetrahedron Lett.* **1994**, *35*, 1445–1448. (c) Davis, J. M.; Whitby, R. J.; Jaxa-Chamiec, A. *Synlett* **1994**, 110–112. (d) Probert, G. D.; Whitby, R. J.; Coote, S. J. *Tetrahedron Lett.* **1995**, *36*, 4113–4116.
9. (a) Copéret, C.; Negishi, E.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 695–698. (b) Li, P. X.; Xi, Z. F.; Takahashi, T. *Chin. J. Chem.* **2001**, *19*, 45–51.
10. (a) Kotora, M.; Xi, Z. F.; Takahashi, T. *J. Synth. Org. Chem. Jpn* **1997**, *55*, 958–969. (b) Takahashi, T.; Kotora, M.; Hara, R.; Xi, Z. *Bull. Chem. Soc. Jpn* **1999**, *72*, 1591–2602. (c) Xi, Z. F.; Li, Z. P.; Umeda, C.; Guan, H. R.; Li, P. X.; Kotora, M.; Takahashi, T. *Tetrahedron* **2002**, *58*, 1107–1117. (d) Liu, Y. H.; Shen, B. J.; Kotora, M.; Takahashi, T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 949–952. (e) Takahashi, T.; Sun, W. H.; Liu, Y. H.; Nakajima, K.; Kotora, M. *Organometallics* **1998**, *17*, 3841. (f) Lipshutz, B. H.; Segi, M. *Tetrahedron* **1995**, *51*, 4407–4420. (g) Takahashi, T.; Sun, W. H.; Xi, C. J.; Ubayama, H.; Xi, Z. F. *Tetrahedron* **1998**, *54*, 715–726. (h) Takahashi, T.; Li, Y. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2003; pp 50–85.
11. (a) Closs, G. L.; Moss, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 4042–4053. (b) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 41–52.
12. Negishi, E.; Akiyoshi, K.; O'Connor, B.; Takagi, K.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 3089–3091.
13. (a) Kasatkin, A.; Whitby, R. J. *Tetrahedron Lett.* **1997**, *38*, 4857–4860. (b) Kasatkin, A.; Whitby, *J. Am. Chem. Soc.* **1999**, *121*, 7039–7049.
14. (a) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **1999**, *40*, 9353–9357. (b) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 6211–6216.

15. (a) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 6201–6205. (b) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron* **2003**, *59*, 9857–9864.
16. (a) Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1994**, *35*, 9465–9468. (b) Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1994**, *35*, 785–788. (c) Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1996**, *37*, 7661–7664. (d) Gordon, G. J.; Whitby, R. J. *Synlett* **1995**, 77–78. (e) Gordon, G. J.; Luker, T.; Tuckett, M. W.; Whitby, R. J. *Tetrahedron* **2000**, *56*, 2113–2129. (f) Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1995**, *36*, 4109–4112. (g) Tuckett, M. W.; Watkins, W. J.; Whitby, R. J. *Tetrahedron Lett.* **1998**, *39*, 123–126.
17. Gordon, G. J.; Whitby, R. J. *Chem. Commun.* **1997**, 1045–1046.
18. Gordon, G. J.; Whitby, R. J. *Chem. Commun.* **1997**, 1321–1322.
19. (a) Fillery, S. M.; Gordon, G. J.; Luker, T.; Whitby, R. J. *Pure Appl. Chem.* **1997**, *69*, 633–638. (b) Dixon, S.; Whitby, R. J. Elaboration of Zirconium Species by Insertion of Carbenoids; In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2003; pp 86–109.
20. Matsumoto, K.; Aoki, Y.; Oshima, K.; Utimoto, K.; Rahman, N. A. *Tetrahedron* **1993**, *49*, 8487–8502.
21. (a) Brown, H. C.; Jayaraman, S. *Tetrahedron Lett.* **1993**, *34*, 3997–4000. (b) Brown, H. C.; Phadke, A. S.; Rangaishenvi, M. V. *J. Am. Chem. Soc.* **1988**, *110*, 6263–6264.
22. Negishi, E.; Cederbaum, F.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829–2832.
23. (a) Barluenga, J.; Liavona, L.; Concellon, J. M.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 297–300. (b) Kobrich, G.; Fischer, R. H. *Tetrahedron* **1968**, *24*, 4343–4346.
24. Kondakov, D.; Negishi, E. I. *Chem. Commun.* **1996**, 963–964.
25. Modest yields (<30%) of insertion products are obtained when zirconacyclopentanes or -pentenes are mixed with 1, 1-dibromoalkanes or 1,1-dibromoalkenes and *t*-BuLi added at −100 °C. Whitby, R. J.; Vicart, N. Unpublished work.
26. Villieras, J.; Rambaud, M. *Synthesis* **1980**, 644–646.
27. Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422–1424.
28. (a) Villieras, J.; Rambaud, M.; Kirschleger, B.; Tarhouni, T. *J. Organomet. Chem.* **1980**, *190*, C31–C35. (b) Burford, C.; Cooke, F.; Roy, G.; Magnus, P. *Tetrahedron* **1983**, *39*, 867–876.
29. Xi, Z. F.; Huo, S. Q.; Noguchi, Y.; Takahashi, T. *Chem. Lett.* **2000**, 218–219.
30. (a) Olofson, R. A.; Hoskin, D. H.; Lotts, K. D. *Tetrahedron Lett.* **1978**, 1677–1680. (b) Seitz, D. E.; Carroll, J. J.; Cartaya, C. P.; Lee, S.-H.; Zapata, A. *Synth. Commun.* **1983**, *13*, 129–134.
31. Colvin, E. *Silicon in Organic Synthesis*; Butterworths: London, 1981; pp 15–20.
32. For example we have found that $Cp_2Zr(OMe)R$ and 1-aza-2-zirconacyclopentanes are inert towards carbenoid insertion whereas $Cp_2Zr(Cl)R$ and zirconacyclopentanes react well, the difference in behavior being postulated to be due to donation of the O or N lone pair into the available orbital on the formally 16 electron metal centres.
33. (a) Olofson, R. A.; Lotts, K. D.; Barber, G. N. *Tetrahedron Lett.* **1976**, 3779–3782. (b) Truce, W. E.; Badiger, V. V. *J. Org. Chem.* **1964**, *29*, 3277–3280. (c) Schollkopf, U. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 588–598.
34. (a) Durst, T.; Tin, K.-C.; de Reinach-Hirtzbach, F.; Decesare, J. M.; Ryan, M. D. *Can. J. Chem.* **1979**, *57*, 258. (b) Arai, S.; Shioiri, T. *Tetrahedron* **2002**, *58*, 1407–1413.
35. (a) Perriot, P.; Villieras, J.; Normant, J. F. *Synthesis* **1978**, 33–34. (b) Coutrot, P.; Savignac, P. *Synthesis* **1978**, 34–36.
36. Svoboda, J.; Kocfeldova, Z.; Palecek, J. *Coll. Czech. Chem. Commun.* **1988**, *53*, 822–832.
37. Takahashi, T.; Suzuki, N.; Hasegawa, M.; Nitto, Y.; Aoyagi, K.; Saburi, M. *Chem. Lett.* **1992**, 331–334.
38. The hydrozirconation of internal alkenes to afford terminal zirconium species is an example of fast β-hydride elimination/re-addition to change the position of the zirconium (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333–340. Endocyclic β-hydride transfer to the metal in bis(aryloxy)titanacyclopentanes has been postulated as part of a catalytic cycle: (b) Okamoto, S.; Livinghouse, T. *J. Am. Chem. Soc.* **2000**, *122*, 1223–1224.
39. Calculations were carried out using semi empirical method with MNDO-PM3(tm) parameter set, which covers transition metals, as implemented in the Spartan02 program (Wavefunction inc.).[56] The calculations indicate the form **65** to be around 2.5 kcal/mol more stable than **64**, though energies from semiempirical calculations, even comparing conformers, are unreliable.
40. Alami, M.; Crousse, B.; Linstrumelle, G. *Tetrahedron Lett.* **1995**, *36*, 3687–3690.
41. (a) Berry, R. S. *J. Chem. Phys.* **1960**, *32*, 933. (b) Lauterbur, P. C.; Ramirez, F. *J. Am. Chem. Soc.* **1968**, *90*, 6722–6726.
42. Xi, Z. F.; Hara, R.; Takahashi, T. *J. Org. Chem.* **1995**, *60*, 4444–4448.
43. Kataoka, K.; Tsuboi, S. *Synthesis* **1999**, 452–456.
44. Dumond, Y.; Negishi, E. *J. Am. Chem. Soc.* **1999**, *121*, 11223–11224.
45. Luker, T.; Whitby, R. J.; Webster, M. *J. Organomet. Chem.* **1995**, *492*, 53–57.
46. Luker, T. J. PhD Thesis, Southampton University, 1995.
47. Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 6435–6437.
48. Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S.; Van Pelt, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 7199–7207.
49. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557–1565.
50. Krafft, M. E.; Bonaga, L. V. R.; Hirosawa, C. *J. Org. Chem.* **2001**, *66*, 3004–3020.
51. Cox, D. G.; Gurusamy, N.; Burton, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 2811–2812.
52. Uno, H.; Sakamoto, K.; Semba, F.; Suzuki, H. *Bull. Chem. Soc. Jpn* **1992**, *65*, 210–217.
53. Ojima, I.; Vu, A. T.; Lee, S.-Y.; McCullagh, J. V.; Moralee, A. C.; Fujiwara, M.; Hoang, T. H. *J. Am. Chem. Soc.* **2002**, *124*, 9164–9174.
54. Patois, C.; Savignac, P. *Bull. Soc. Chim. Fr.* **1993**, *130*, 630.
55. Montchamp, J. L.; Negishi, E. *J. Am. Chem. Soc.* **1998**, *120*, 5345–5346.
56. Kong, J.; White, C. A.; Krylov, A. I.; Sherrill, D.; Adamson, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwaltney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y. H.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W. M.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; Van Voorhis, T.; Oumi, M.; Hirata, S.; Hsu, C. P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W.; Head-Gordon, M.; Pople, J. A. *J. Comp. Chem.* **2000**, *21*, 1532–1548.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 1417–1424

Reaction of oxazirconacycloheptenes with aldehydes mediated by CuCl: one-pot synthesis of tetrahydrofuran derivatives from four different components involving two molecules of the same or different aldehydes, an ethylene and an alkyne☆

Changjia Zhao,[a] Jiang Lu,[a] Zhiping Li[a] and Zhenfeng Xi[a,b,*]

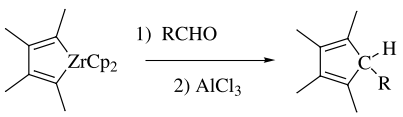
[a]*Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

Received 4 October 2003; accepted 19 October 2003

Abstract—Reaction of zirconacyclopentenes with 2 equiv. of the same aldehydes in the presence of 1 equiv. of CuCl from −78 °C to room temperature afforded tetrahydrofuran derivatives in good isolated yields upon hydrolysis with aqueous 3 N HCl. Oxazirconacycloheptenes, generated in situ from zirconacyclopentenes with one aldehyde was found to be the reactive intermediate. When treated with a second aldehyde and CuCl, an oxazirconacycloheptene gave a tetrahydrofuran derivative comprised of four different components involving an alkyne, an ethylene and two different aldehydes, thus providing the first one-pot synthesis of important tetrahydrofuran derivatives from four components. When bulky aldehydes were used, hydrolysis of the above reaction mixtures afforded 2-hexen-1,6-diols, which could be quantitatively transformed to their corresponding tetrahydrofuran derivatives when treated with stronger aqueous acid (12 N HCl).

1. Introduction

Zirconacyclopentadienes **1** and zirconacyclopentenes **2** can be readily prepared via cross-coupling of two alkynes or pair-selective coupling of an alkyne with an ethylene on low valent zirconocene species, respectively.[1,2] In order to develop synthetically useful methods by combining the transition-metal-mediated C–C bond forming reaction with the Lewis acids-mediated organic transformation reaction,[3–10] we studied Lewis acids-mediated reaction of these readily available zirconacycles with unsaturated organic substrates such as aldehydes.[11,12] In the presence of classical Lewis acids such as $AlCl_3$ and BF_3, reaction of zirconacyclopentadienes **1** with a wide variety of aldehydes afforded multiply substituted cyclopentadienes, via a novel deoxygenation of the C=O double bond of aldehydes (Eq. 1).[11] When a zirconacyclopentene **2** was treated with two molecules of an aldehyde, Oppenauer-type oxidation took place to give homoallylketones **3** and alcohols (Eq. 2).[12] Only one of the two aldehydes was incorporated into the product. The second molecule of aldehyde was reduced to an alcohol. Interestingly, as shown in Eq. 3, when the Lewis acid was changed from $AlCl_3$ to CuCl, tetrahydrofuran derivatives (THF derivatives for short) **4** were obtained in good yields from the reaction of zirconacyclopentenes with two molecules of aldehydes.[13] Both of the two molecules of aldehydes were incorporated into the products. In this paper, we report a full investigation of this useful preparation of THF derivatives,[14–20] including (1) preparation of THF derivatives from an alkyne, an ethylene, and two molecules of the same aldehydes, (2) preparation of THF derivatives from an alkyne, an ethylene, and two different aldehydes (Scheme 1), and (3) mechanistic aspects.



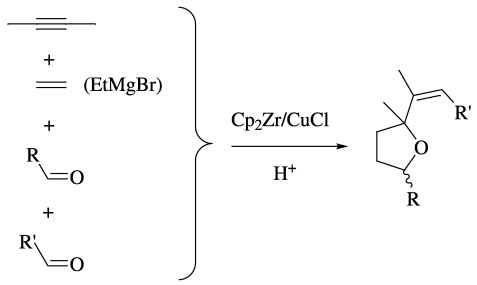
1 (1)

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2003.10.095

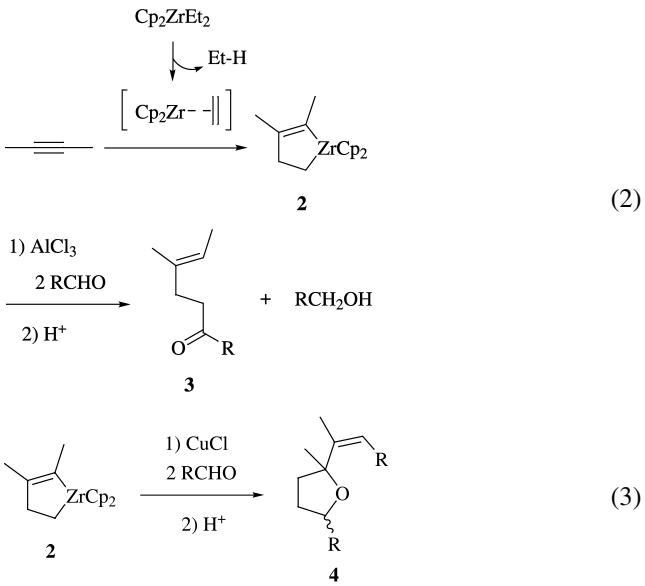
Keywords: Aldehydes; Alkynes; Ethylene; Four-component synthesis; Tetrahydrofuran derivatives; Zirconacyclopentenes; Oxazirconacycloheptenes; CuCl.

* Corresponding author at present address: Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China. Tel.: +86-10-6275-9728; fax: +86-10-6275-1708; e-mail address: zfxi@pku.edu.cn

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.10.095



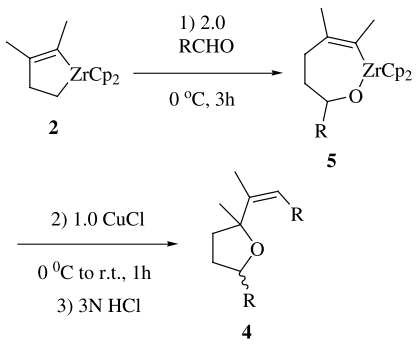
Scheme 1. One-pot synthesis of THF derivatives from four different components.



2. Results and discussion

2.1. Preparation of 1-alkenyl tetrahydrofuran derivatives from an alkyne, an ethylene and two of the same aldehydes

Reaction of Cp_2ZrEt_2 with an alkyne from −78 to 0 °C forms a zirconacyclopentene **2** in high yields via a pair-selective coupling of the alkyne with the in situ generated zirconocene–ethylene complex, as developed by Takahashi and co-workers.[1,2] When a zirconacyclopentene is treated with aldehydes, insertion of an aldehyde into the Zr-sp3 C bond takes place to afford the corresponding seven-membered oxazirconacycloheptene **5**.[21] Hydrolysis of the reaction mixtures of oxazirconacycloheptenes with 3 N HCl gave the corresponding alcohols.[21] It is noteworthy that oxazirconacycloheptenes do not react with the second molecule of aldehydes. However, interestingly, our preliminary results have demonstrated that, in the presence of 1 equiv. of CuCl, oxazirconacycloheptenes do react with a second molecule of aldehyde, leading to the unexpected THF derivatives upon hydrolysis of the reaction mixture with either aqueous 3 N HCl or saturated aqueous $NaHCO_3$ (Scheme 2).[13] Several ways of adding aldehydes and CuCl to zirconacyclopentenes have been tested, and THF derivatives can be obtained in most cases. Scheme 2 shows the best reaction condition (including addition order of aldehydes and CuCl) for the formation of THF



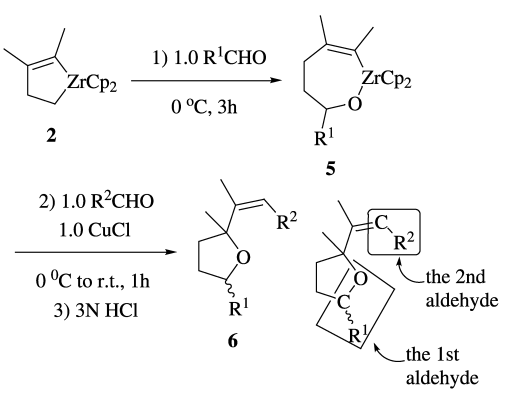
Scheme 2.

derivatives. Representative results are given in Table 1. The stereochemistry of the vinyl moiety in **4e** was determined by NOE measurement. NOESY cross-peaks were observed between the vinyl hydrogen and the methyl hydrogen, thereby establishing the trisubstituted olefin geometry (see Supporting Information). Aromatic aldehydes could generally afford THF derivatives in good yields. When aliphatic aldehydes were used, although the corresponding oxazirconacycloheptenes **5** could be formed cleanly,[21] the next reaction step involving CuCl was messy.

2.2. Preparation of 1-alkenyl tetrahydrofuran derivatives from an alkyne, an ethylene and two different aldehydes

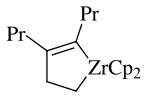
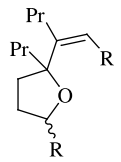
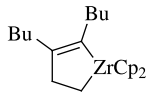
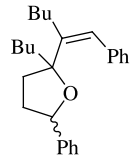
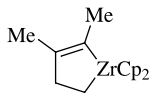
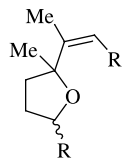
Since oxazirconacycloheptenes **5** were formed in situ from zirconacyclopentenes with an aldehyde and were the reactive intermediates for the formation of THF derivatives (Scheme 2), we assumed a different aldehyde could be used as the second aldehyde to react with oxazirconacycloheptenes **5**, thus affording THF derivatives from two different aldehydes. As given in Scheme 3 and Table 2, THF derivatives could be prepared highly chemoselectively from two different aldehydes; the first aldehyde was highly regioselectively incorporated into the α-position of the THF skeletons, while the second aldehyde was perfectly transformed to be the alkenyl moiety in the product.

Interestingly, when bulky aldehydes were used, 2-hexen-1,6-diols **7** were obtained as the only products after the reaction mixtures were hydrolyzed with aqueous 3 N HCl. Particularly interesting, when two different bulky aldehydes were added step by step, the first aldehyde was incorporated



Scheme 3.

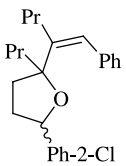
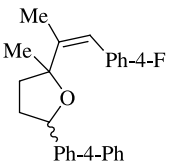
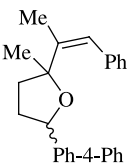
Table 1. Formation of THF derivatives from two molecules of the same aldehydes, one alkyne and one ethylene

Entry	Zircona-cyclopentene	Aldehyde	Product **4**		Yield of **4** (%)[a]
1		RCHO		**4a**[b]	71 (44)
2				**4b**[c]	(42)
3				**4c**[d]	(54)
4		PhCHO		**4d**[e]	(48)
5		RCHO		**4e**[f]	(56)
6				**4f**[g]	(55)

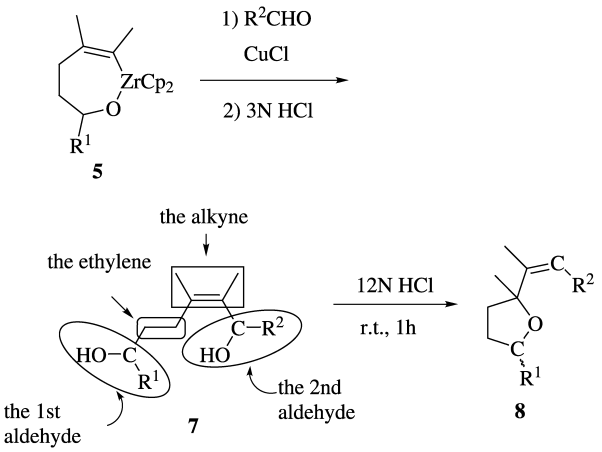
[a] Combined GC yields. Combined isolated yields are given in parentheses.
[b] R=phenyl, two isomers in 2:1.
[c] R=4-methylphenyl, two isomers in 1:1.
[d] R=4-F-phenyl, two isomers in 2:1.
[e] Two isomers in 7:5.
[f] R=phenyl, two isomers in 3:2.
[g] R=2,4,6-trimethylphenyl, two isomers in 1:1.

in the diols **7** at the 6 position, while the second aldehyde made a C–C bond with the alkenyl carbon to form an allylic alcohol moiety (Scheme 4). Representative results are given in Table 3. The structure of **7c** was determined by single crystal X-ray analysis (see Supporting Information). These diols **7** could be quantitatively transformed to THF derivatives **8a**–**c** when treated with aqueous 12 N HCl at room temperature for 1 h (Fig. 1). Similarly, these THF

Table 2. Formation of THF derivatives from two different aldehydes, one alkyne and one ethylene

Alkyne	First aldehyde	Second aldehyde	Product **6**		Yield of **6** (%)[a]
Pr—≡—Pr	2-Cl–PhCHO	PhCHO		**6a**[b]	55
Me—≡—Me	4-Ph–PhCHO	4-F–PhCHO		**6b**[c]	56
Me—≡—Me	4-Ph–PhCHO	PhCHO		**6c**[d]	52

[a] Combined isolated yield.
[b] Two isomers in 5:4.
[c] Two isomers in 2:1.
[d] Two isomers in 3:2.

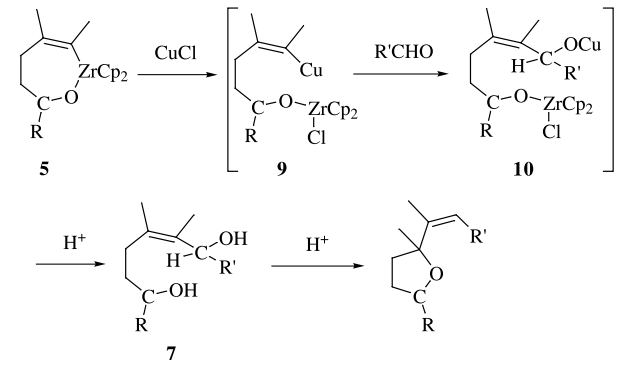


Scheme 4.

derivatives **8a–c** were obtained also as a mixture of two isomers.

2.3. Mechanistic aspects

Two pathways are proposed for the formation of THF derivatives from the CuCl-mediated reaction of oxazirconacycloheptenes **5** with aldehyde. Transmetallation of the Zr–C bond in oxazirconacycloheptenes **5** is assumed to be the first step to form cuparate **9** (Scheme 5).[22] This organocopper compound adds to the carbonyl C=O bond of aldehyde,[23] which upon hydrolysis gives 2-hexen-1,6-diols. Cyclization is then accomplished in acidic media with allylic inversion to afford the final THF derivatives.



Scheme 5.

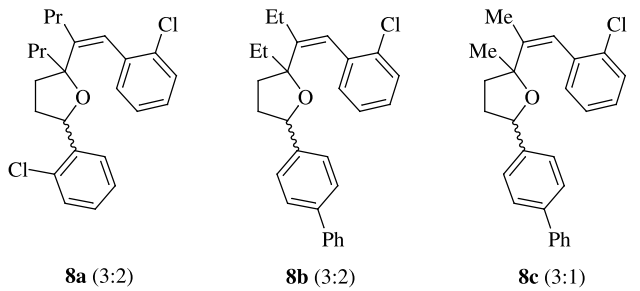
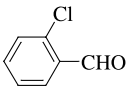
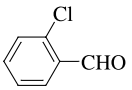
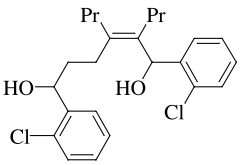
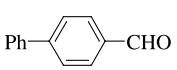
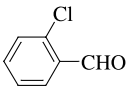
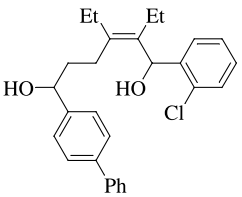
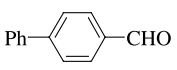
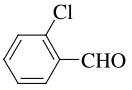
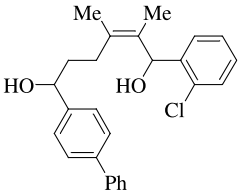


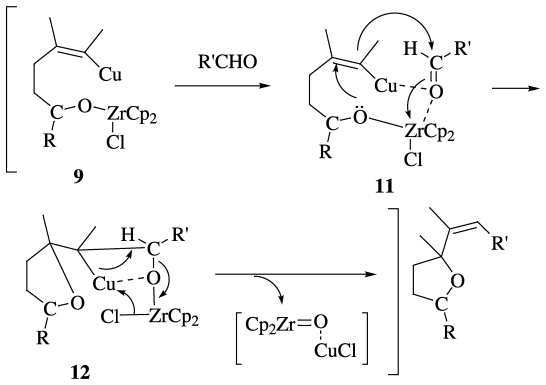
Figure 1.

Although the above pathway seems more likely, the following mechanism cannot be ruled out, since formation of THF derivative **4a** was observed in the reaction mixture by NMR without hydrolysis. A concerted addition and sequential release of $Cp_2Zr{=}O{\cdot}CuCl$ is proposed (Scheme 6). Intramolecular nucleophilic attack by an oxygen atom on

Table 3. Isolation of diols by hydrolysis of the reaction mixtures of oxazirconacycles with aldehydes in the presence of CuCl

Alkyne	First aldehyde	Second aldehyde	Product **7**		Yield of **7** (%)[a]
Pr—≡—Pr				**7a**[b]	56
Et—≡—Et				**7b**[c]	47
Me—≡—Me				**7c**[d]	48

[a] Combined isolated yield.
[b] Two isomers in 5:1.
[c] Two isomers in 4:3.
[d] Two isomers in 1:1.



Scheme 6.

a suitable activated carbon center has been a common approach.

3. Conclusions

Development of synthetically useful methods for the preparation of THF derivatives is of great interest since tetrahydrofuran skeletons are frequently found in important natural products. In this paper, we report the first example of one-pot four-component synthesis of THF derivatives via a novel CuCl-mediated reaction of oxazirconacycloheptenes with aldehydes. When four different components involving one alkyne, one ethylene, and two different aldehydes, THF derivatives could be also formed highly selectively.

4. Experimental

4.1. General methods

All reactions were conducted under a slightly positive pressure of dry, prepurified nitrogen using standard Schlenk line techniques when appropriate. Unless otherwise noted, all starting materials were commercially available and were used without further purification. Tetrahydrofuran (THF) was refluxed and distilled from sodium/benzophenone under a nitrogen atmosphere. EtMgBr and *n*-BuLi were obtained from Kanto Chemicals Co. Ltd.

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.4 MHz, respectively, in $CDCl_3$ unless stated otherwise. GC yields were determined using suitable hydrocarbons as internal standards.

4.2. Typical procedure for preparation of 1-alkenyl tetrahedron derivatives from an alkyne, an ethylene and two of the same aldehydes (4a–4f)

A 50-mL Schlenk tube under dried nitrogen was charged with Cp_2ZrCl_2 (0.59 g, 2 mmol) and THF (20 mL). To this mixture was added ethylmagnesium bromide (1.0 M THF solution, 4 mmol, 4 mL) at −78 °C. After 1 h of stirring, alkyne (2 mmol) was added and the reaction mixture was stirred at 0 °C for 3 h. Then to the reaction mixture was added aldehyde (4 mmol), the reaction mixture was continued to stir at 0 °C for 3 h, and CuCl (200 mg, 2 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 1 h. The above reaction mixture was then quenched with 3 N HCl and extracted with ether. The extract was washed with sat. $NaHCO_3$, water and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a light yellow liquid. The liquid was subjected to silica gel column using petroleum ether and dichloromethane (3:1) as the eluent. The final product was obtained as a colorless liquid.

4.2.1. THF derivative (4a). Light yellow liquid, GC yield 71%, isolated yield 44% (293 mg), mixture of isomers (2:1). ^{1}H NMR (TMS, $CDCl_3$) δ=0.88 (t, J=7.5 Hz, 3H), 0.95 (t, J=7.5 Hz, 3H), 1.18–2.33 (m, 8H), 4.96–5.03 (m, 1H), 6.68 (s) 6.75 (s) (total 1H), 7.16–7.44 (m, 10H); ^{13}C NMR (TMS, $CDCl_3$) δ=14.51, 14.60, 14.75, 14.82, 17.74, 22.62, 22.73, 31.38, 31.67, 34.10, 35.22, 36.54, 36.70, 41.41, 42.53, 80.26, 80.39, 89.24, 89.39, 123.82, 125.03, 125.82, 126.01, 126.28, 127.12, 127.14, 128.13, 128.15, 128.23, 128.29, 128.58, 138.64, 138.76, 143.22, 143.67, 145.82, 146.10; HRMS calcd for $C_{24}H_{30}O$: 334.2297, found: 334.2296.

4.2.2. THF derivative (4b). Light yellow liquid, isolated yield 42% (306 mg), mixture of isomers (1:1). ^{1}H NMR (TMS, $CDCl_3$) δ=0.86–0.98 (m, 6H), 1.26–1.52 (m, 4H), 1.69–2.28 (m, 8H), 2.32 (s, 3H), 2.33 (s, 3H), 4.91–4.96 (m, 1H), 6.62 (s) 6.69 (s) (total 1H), 7.10–7.32 (m, 8H); ^{13}C NMR (TMS, $CDCl_3$) δ=14.52, 14.60, 14.76, 14.81, 17.74, 21.11, 22.60, 22.71, 31.44, 31.73, 34.15, 35.18, 36.54, 36.72, 41.53, 42.63, 80.13, 80.37, 89.21, 89.31, 123.64, 124.86, 125.84, 126.33, 128.51, 128.85, 128.87, 128.90, 128.96, 135.54, 135.57, 135.72, 135.83, 136.69, 136.70, 140.27, 140.73, 145.21, 145.50; HRMS calcd for $C_{26}H_{34}O$: 362.2610, found: 362.2603.

4.2.3. THF derivative (4c). Light yellow liquid, isolated yield 54% (400 mg), mixture of isomers (2:1). ^{1}H NMR ($CDCl_3$, TMS) δ=0.84–0.97 (m, 6H), 1.27–1.59 (m, 4H), 1.67–1.87 (m,3H), 1.94–2.0 (m, 1H), 2.10–2.32 (m, 4H), 4.92–5.00 (m, 1H), 6.62 (s) 6.66 (s), (total 1H), 6.97–7.05 (m, 4H), 7.17–7.25 (m, 2H), 7.32–7.39 (m, 2H); ^{13}C NMR δ=14.48, 14.57, 14.73, 14.79, 17.74, 22.54, 22.66, 31.26, 31.56, 34.04, 35.25, 36.53, 36.63, 41.37, 42.55, 79.72, 79.77, 89.28, 89.40, 115.01 (d, J=21.0 Hz, J_2CF), 115.09 (d, J=21.0 Hz, J_2CF), 122.84, 124.05, 127.40 (d, J=8.0 Hz, J_3CF), 127.88 (d, J=7.5 Hz, J_3CF), 130.00, 130.10, 134.63, 134.67, 134.71, 138.92, 138.96, 139.28, 139.31, 145.70, 145.72, 146.07, 161.28 (d, J=242.9 Hz, JCF), 162.09 (d, J=242.9 Hz, JCF); HRMS calcd. for $C_{24}H_{28}OF_2$: 370.2108, found: 370.2113.

4.2.4. THF derivative (4d). Light yellow liquid, isolated yield 48% (346 mg), mixture of isomers (7:5). ^{1}H NMR (TMS, $CDCl_3$) δ=0.82–0.95 (m, 6H), 1.20–1.53 (m, 8H), 1.73–2.05 (m, 1H), 4.97–5.04 (m, 1H), 6.67 (s) 6.75 (s) (total 1H), 7.18–7.44 (m, 10H); ^{13}C NMR (TMS, $CDCl_3$) δ=13.76, 14.18, 23.17, 23.20, 23.37, 23.38, 26.60, 26.63, 28.84, 29.14, 31.33, 31.48, 34.13, 35.21, 36.66, 36.82, 38.10, 39.90, 80.29, 80.37, 89.25, 89.44, 123.80, 124.94, 125.85, 126.01, 126.31, 127.13, 127.16, 128.12, 128.13, 128.23, 128.30, 128.64, 128.66, 138.67, 138.78, 143.22, 143.70, 145.84, 146.21; HRMS calcd. for $C_{26}H_{34}O$: 362.2610, found: 362.2609.

4.2.5. THF derivative (4e). Light yellow liquid, isolated yield 56% (311 mg), mixture of isomers (3:2). ^{1}H NMR (TMS, $CDCl_3$) δ=1.52 (s), 1.58 (s) (total 3H), 1.91–2.41 (m, 7H), 5.08 (t, J=7.2 Hz,) 5.14 (t, J=6.9 Hz) (total 1H), 6.77 (s) 6.81 (s) (total 1H), 7.17–7.59 (m, 14H); ^{13}C NMR (TMS, $CDCl_3$) δ=14.97, 15.97, 26.63, 27.09, 34.38, 35.04, 36.82, 37.08, 80.21, 80.41, 86.38, 86.77, 122.29, 123.20, 126.02, 126.30, 126.67, 127.05, 127.08, 127.10, 127.14, 128.03, 128.73, 129.06, 129.09, 138.53, 138.57, 140.18, 140.21, 141.04, 141.11, 142.01, 142.18, 142.61, 142.66; HRMS calcd for $C_{20}H_{22}O$: 278.1676, found: 278.1671.

4.2.6. THF derivative (4f). Light yellow liquid, isolated yield 55% (400 mg), mixture of isomers (1:1). ^{1}H NMR (TMS, $CDCl_3$) δ=1.47–1.58 (m, 6H), 1.98–2.47 (m, 22H), 5.36 (t, J=7.5 Hz), 5.50 (t, J=8.1 Hz) (total 1H), 6.49 (s, 1H), 6.80–6.86 (m, 4H); ^{13}C NMR (TMS, $CDCl_3$) δ=13.60, 14.60, 20.08, 20.75, 20.89, 20.97, 25.15, 26.90, 30.49, 30.91, 30.94, 36.20, 36.94, 75.20, 75.99, 85.66, 85.81, 120.86, 121.51, 127.87, 130.01, 130.14, 133.70, 133.99, 134.61, 134.80, 135.53, 135.62, 136.56, 136.57, 136.61, 136.66, 141.68, 142.72; HRMS calcd. for $C_{26}H_{34}O$: 362.2610, found: 362.2595.

4.3. Typical procedure for preparation of 1-alkenyl tetrahedron derivatives from an alkyne, an ethylene and two of the different aldehydes (6a–6c)

A 50-mL Schlenk tube under dried nitrogen was charged with Cp_2ZrCl_2 (0.59 g, 2 mmol) and THF (20 mL). To this mixture was added ethylmagnesium bromide (1.0 M THF solution, 4 mmol, 4 mL) at −78 °C. After 1 h of stirring, the alkyne (2 mmol) was added and the reaction mixture was stirred at 0 °C for 3 h. Then to the reaction mixture was added the first aldehyde (2 mmol), the reaction mixture was continued to stir at 0 °C for 3 h, and CuCl (200 mg, 2 mmol) and the second aldehyde (2 mmol) were added and the reaction mixture was warmed to room temperature and stirred for 1 h. The above reaction mixture was then quenched with 3 N HCl and extracted with ether. The extract was washed with sat. $NaHCO_3$, water and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a light yellow liquid. The liquid was subjected to silica gel column using petroleum ether and dichloromethane (3:1) as the eluent. The final product was obtained as a colorless liquid.

4.3.1. THF derivative (6a). Light yellow liquid, isolated yield 55% (405 mg), mixture of isomers (5:4). ^{1}H NMR (TMS, $CDCl_3$) δ=0.87–1.00 (m, 6H), 1.26–2.61 (m, 12H), 5.29–5.38 (m, 1H), 6.67 (s), 6.79 (s) (total 1H), 7.12–7.36 (m, 8H), 7.68–7.74 (m, 1H); ^{13}C NMR (TMS, $CDCl_3$) δ=14.48, 14.63, 14.74, 14.80, 17.69, 17.92, 22.62, 22.80, 31.33, 31.66, 32.78, 33.28, 35.98, 36.15, 40.48, 42.37, 76.75, 77.08, 89.33, 89.69, 124.33, 125.00, 126.07, 126.12, 126.71, 126.79, 126.81, 127.04, 127.94, 128.17, 128.19, 128.60, 128.63, 129.15, 129.19, 131.63, 131.66, 138.57, 138.64, 141.52, 141.65, 145.10, 145.86; HRMS calcd for $C_{24}H_{29}OCl$: 368.1907, found: 368.1912.

4.3.2. THF derivative (6b). Light yellow liquid, isolated yield 56% (416 mg), mixture of isomers (2:1). ^{1}H NMR ($CDCl_3$, TMS) δ=1.51 (s), 1.58 (s) (total, 1H) 1.89–2.41 (m, 7H), 5.07 (t, J=6.9 Hz), 5.14 (t, J=6.9 Hz) (total, 1H), 6.73 (s) 6.76 (s) (total 1H), 6.98–7.60 (m, 13H); ^{13}C NMR δ=14.91, 15.25, 26.59, 27.08, 34.29, 35.05, 36.85, 37.05, 80.18, 80.49, 86.29, 86.69, 114.86 (J=21.1 Hz, J_2CF) 121.19, 122.15, 126.29, 126.66, 126.72, 126.95, 127.08 (d, J=1.8 Hz, J_3CF), 127.14, 128.73, 129.49, 130.48 (d, J=2.5 Hz, J_4CF), 130.58 (d, J=2.5 Hz, J_4CF), 134.45, 134.50, 140.22, 140.25, 141.00, 141.07, 141.92, 142.16, 142.50, 142.61, 161.20 (J=244.6 Hz, JCF); HRMS calcd for $C_{26}H_{25}OF$: 372.1889, found: 372.1896.

4.3.3. THF derivative (6c). Light yellow liquid, isolated yield 52% (368 mg), mixture of isomers (3:2). ^{1}H NMR ($CDCl_3$, TMS) δ=1.52 (s) 1.58 (s) (total 3H), 1.91–2.41 (m, 7H), 5.08 (t, J=7.2 Hz) 5.14 (t, J=6.9 Hz) (total 1H), 6.77 (s), 6.81 (s) (total 1H), 7.17–7.59 (m, 14H); ^{13}C NMR δ=14.97, 15.31, 26.63, 27.09, 34.38, 35.04, 36.82, 37.08, 80.21, 80.41, 86.38, 86.77, 122.29, 123.20, 126.02, 128.03, 128.73, 129.06, 129.09, 138.53, 138.57, 142.61, 142.66; HRMS calcd for $C_{26}H_{26}O$: 354.1984, found: 354.1974.

4.4. Typical procedure for preparation of 2-hexen-1.6-diol derivatives (7a–7c)

A 50-mL Schlenk tube under dried nitrogen was charged with Cp_2ZrCl_2 (0.59 g, 2 mmol) and THF (20 mL). To this mixture was added ethylmagnesium bromide (1.0 M THF solution, 4 mmol, 4 mL) at −78 °C. After 1 h of stirring, the alkyne (2 mmol) was added and the reaction mixture was stirred at 0 °C for 3 h. Then to the reaction mixture was added the first aldehyde (2 mmol), the reaction mixture was continued to stir at 0 °C for 3 h, and CuCl (200 mg, 2 mmol) and the second aldehyde (2 mmol) were added and the reaction mixture was warmed to room temperature and stirred for 1 h. The above reaction mixture was then quenched with 3 N HCl and extracted with ether. The extract was washed with sat. $NaHCO_3$, water and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a light yellow solid. The solid was subjected to silica gel column using petroleum ether and ether (1:1) as the eluent. The final product was obtained as a colorless solid.

4.4.1. 2-Hexen-1.6-diol derivative (7a). Colorless solid, isolated yield 55% (405 mg), mixture of isomers (5:1). For the major, ^{1}H NMR ($CDCl_3$, TMS) δ=0.65 (t, J=7.2 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H), 1.26–2.21 (m, 9H), 2.96–3.11 (m, 1H), 4.03 (s, br 1H) 4.23 (s, br 1H), 5.00–5.12 (m, 1H), 5.86 (s) 6.03 (s) (total 1H), 7.08–7.28 (m, 6H), 7.42 (d, J=7.5 Hz) 7.42 (d, J=7.5 Hz) (total 1H), 7.62 (d, J=7.5 Hz) 7.63 (d, J=7.5 Hz) (total 1H); ^{13}C NMR ($CDCl_3$, TMS) δ=14.23, 14.53, 21.49, 23.52, 25.62, 30.53, 32.59, 35.37, 68.59, 70.24, 126.41, 126.96, 127.03, 127.75, 127.96, 128.14, 129.06, 129.23, 131.41, 132.30, 134.06, 138.64, 140.72, 142.36. Elemental analysis calcd for $C_{24}H_{30}O_2Cl_2$: C 68.40, H 7.13, found: C 68.40, H7.17.

4.4.2. 2-Hexen-1.6-diol derivative (7b). Colorless solid, isolated yield 47% (409 mg), mixture of isomers (4:3). ^{1}H NMR (TMS, $CDCl_3$) δ=0.55 (t, J=7.5 Hz) 0.82 (t, J=7.5 Hz) (total 3H), 0.94 (t, J=7.5 Hz) 0.99 (t, J=7.5 Hz) (total 3H), 1.65–2.08 (m, 5H), 2.19–2.31 (m, 2H), 2.93–3.04 (m, 1H), 3.60–4.20 (s, br, 2H), 4.58–4.71 (m, 1H), 5.97 (s) 6.00 (s) (total 1H)), 7.07–7.62 (m,

13H); ^{13}C NMR (TMS, $CDCl_3$) δ=7.95, 13.18, 13.69, 14.63, 20.89, 21.27, 23.59, 25.40, 33.60, 33.67, 36.54, 37.15, 69.81, 71.79, 75.09, 78.60, 126.19, 126.20, 126.41, 126.48, 126.96, 126.98, 127.03, 127.11, 127.14, 127.20, 127.83, 127.85, 127.87, 127.90, 128.69, 128.73, 128.88, 128.97, 132.27, 132.34, 134.83, 134.94, 139.27, 139.35, 140.03, 140.25, 140.51, 140.54, 140.76, 140.80, 143.73, 143.72; FAB-MS: $C_{28}H_{31}O_2^{35}Cl$ 441(M+Li). Elemental analysis calcd for $C_{28}H_{31}O_2Cl$: C 77.33, H 7.19, found: C 77.07, H 7.24.

4.4.3. 2-Hexen-1.6-diol derivative (7c), (1*R*,6*R*) and (1*S*,6*S*). Colorless solid, mp 99–102 °C, isolated yield 24% (193 mg); ^{1}H NMR (TMS, $CDCl_3$) δ=1.35 (s, 3H), 1.70 (s, 3H), 1.84–1.94 (m, 2H), 2.01–2.13 (m, 1H), 3.07–3.17 (m, 1H), 3.74 (s, br, 1H), 4.09 (s, br, 1H), 4.57–4.66 (m, 1H), 6.04 (s, 1H), 7.09–7.60 (m, 13H). ^{13}C NMR (TMS, $CDCl_3$) δ=13.51, 18.20, 29.21, 36.06, 69.38, 71.51, 126.13, 126.28, 126.91, 126.94, 127.10, 127.74, 128.02, 128.65, 128.98, 129.20, 131.69, 132.50, 139.99, 140.36, 140.70, 143.72; FAB-MS: $C_{26}H_{27}O_2^{35}Cl$ 413 (M+Li). Elemental analysis calcd for $C_{26}H_{27}O_2^{35}Cl$: C 76.70, H 6.69, found: C 76.20, H 7.04.

4.4.4. 2-Hexen-1.6-diol derivative (7c), (1*S*,6*R*) and (1*R*,6*S*). Colorless solid, mp 82–85 °C, isolated yield 24% (197 mg). ^{1}H NMR (TMS, $CDCl_3$) δ=1.39 (s, 3H), 1.67 (s, 3H), 1.87–1.94 (m, 2H), 2.12–2.22 (m, 1H), 2.71–2.78 (m, 1H), 3.21 (s, br, 2H), 4.69 (t, J=6.3 Hz, 1H), 5.93 (s, 1H), 7.11–7.64 (m, 13H); ^{13}C NMR (TMS, $CDCl_3$) δ=13.71, 18.97, 30.98, 37.43, 69.87, 74.88, 126.19, 126.45, 126.99, 127.13, 127.19, 127.98, 128.22, 128.70, 129.17, 131.94, 134.00, 140.31, 140.55, 140.73, 143.67; FAB-MS $C_{26}H_{27}O_2^{35}Cl$ 413 (M+Li). Elemental analysis calcd for $C_{26}H_{27}O_2^{35}Cl$: C 76.70, H 6.69, found: C 76.21, H 7.09.

4.5. Typical procedure for preparation of compounds 8a–8c

2-Hexen-1.6-diol derivative (1 mmol) was dissolved in 10 mL THF, to the solution was added 10 mL conc. HCl dropwise at 0 °C in 10 min, then the mixture was warmed to room temperature and stirred for 1 h, and the mixture was extracted with ether, the combined extract was washed with sat. $NaHCO_3$, water and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a light yellow liquid.

4.5.1. THF derivative (8a). Light yellow liquid, mixture of isomers (3:2). ^{1}H NMR (TMS, $CDCl_3$) δ=0.72–1.02 (m, 6H), 1.27–2.60 (m, 12H), 5.34–5.42 (m, 1H), 6.66 (s) 6.80 (s) (total 1H), 7.15–7.40 (m, 7H), 7.69 (d, J=7.5 Hz), 7.81 (d, J=7.8 Hz) (total 1H); ^{13}C NMR (TMS, $CDCl_3$), 14.54, 14.69, 14.77, 17.70, 17.97, 22.56, 22.65, 30.97, 31.45, 32.76, 33.14, 35.65, 36.01, 40.62, 42.21, 76.93, 89.09, 89.54, 122.81, 122.96, 126.27, 126.30, 126.70, 126.74, 126.80, 127.23, 127.59, 127.65, 127.88, 127.93, 129.07, 129.16, 129.21, 130.03, 130.14, 131.57, 133.74, 133.78, 137.54, 137.59, 141.41, 141.78, 146.15, 146.93; HRMS calcd for $C_{24}H_{28}OCl_2$: 402.1517, found: 402.1515.

4.5.2. THF derivative (8b). Light yellow liquid, mixture of isomers (3:2). ^{1}H NMR (TMS, $CDCl_3$) δ=0.91 (t, J=7.5 Hz), 0.92 (t, J=7.5 Hz) (total 3H), 1.00 (t, J=7.5 Hz), 1.07 (t, J=7.5 Hz) (total 3H), 1.54–2.55 (m, 8H), 5.04–5.11 (m, 1H), 6.68 (s), 6.76 (s) (total 1H), 7.14–7.60 (m, 13H); ^{13}C NMR (TMS, $CDCl_3$) δ=8.86, 8.92, 13.88, 13.97, 21.42, 21.81, 31.47, 32.59, 34.10, 34.94, 35.99, 36.18, 79.93, 80.21, 89.29, 89.43, 122.25, 123.10, 126.19, 126.24, 126.61, 126.41, 126.69, 126.79, 126.82, 126.89, 126.96, 127.04, 127.15, 127.24, 127.35, 127.53, 128.63, 129.10, 130.09, 130.17, 133.60, 133.63, 137.51, 137.63, 139.95, 139.97, 140.94, 140.97, 142.15, 142.68, 147.75, 147.99; HRMS calcd for $C_{28}H_{29}OCl$: 416.1907; found: 416.1883.

4.5.3. THF derivative (8c). Light yellow liquid, mixture of isomers (3:1). ^{1}H NMR (TMS, $CDCl_3$) δ=1.51 (s) 1.58 (s) (total 3H), 1.74 (s) 1.79 (s) (total 3H), 1.82–2.00 (m, 2H), 2.11–2.40 (m, 2H), 5.09–5.16 (m, 1H),6.78 (s), 6.86 (s) (total 1H), 7.07–7.57 (m, 14H); ^{13}C NMR (TMS, $CDCl_3$) δ=14.58, 15.13, 26.59, 26.88, 34.28, 34.73, 36.51, 37.06, 80.32, 86.10, 86.52, 120.24, 120.86, 126.09, 126.11, 126.26, 126.94, 126.99, 127.07, 127.53, 128.64, 128.68, 128.74, 129.16, 130.70, 130.76, 133.85, 133.89, 136.87, 136.89, 140.03, 140.04, 140.90, 140.94, 141.81, 142.61, 143.71, 144.20; HRMS calcd. for $C_{26}H_{25}OCl$: 388.1594, found: 388.1610.

Acknowledgements

This work was partially supported by the Natural Science Foundation of China (29825105, 20172003, 20232010), the Major State Basic Research Development Program (G2000077502-D) and Dow Corning Corporation. Cheung Kong Scholars Programme and Qiu Shi Science & Technologies Foundation are gratefully acknowledged.

References and notes

1. For recent reviews on preparation and reaction chemistry of zirconacyclopentenes and zirconacyclopentadienes, see: (a) Takahashi, T.; Kotora, M.; Hara, R.; Xi, Z. *Bull. Chem. Soc. Jpn* **1999**, *72*, 2591. (b) Takahashi, T.; Xi, Z. *Recent Res. Dev. Pure Appl. Chem.* **1998**, *2*, 515. (c) Kotora, M.; Xi, Z.; Takahashi, T. *J. Synth. Org. Chem. Jpn* **1997**, *55*, 958. (d) Kotora, M.; Xi, Z.; Takahashi, T. *J. Synth. Org. Chem. Jpn* **1997**, *55*, 958.
2. (a) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 687. (b) Xi, Z.; Hara, R.; Takahashi, T. *J. Org. Chem.* **1995**, *60*, 4444. (c) Takahashi, T.; Xi, C.; Xi, Z.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. *J. Org. Chem.* **1998**, *63*, 6802.
3. (a) Santelli, M.; Pons, J. M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC: Tokyo, 1996. (b) In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000. (c) *Tetrahedron*; Maruoka, K., Ed.; 2001; 57, p 805.
4. (a) Jiang, B.; Tilley, T. D. *J. Am. Chem. Soc.* **1999**, *121*, 9744. (b) Suh, M. C.; Jiang, B.; Tilley, T. D. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2870. (c) Nakamoto, M.; Tilley, T. D. *Organometallics* **2001**, *20*, 5515.
5. (a) Negishi, E.; Okukado, N.; King, A. O.; van Horn, D. E.;

Spiegel, *J. Am. Chem. Soc.* **1978**, *100*, 2254. (b) van Horn, D. E.; Valente, L. F.; Idacavage, M. J.; Negishi, E. *J. Organomet. Chem.* **1978**, *156*, C20. (c) Negishi, E.; Takahashi, T.; Baba, S.; van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393.

6. Takahashi, T.; Li, Y.; Ito, T.; Xu, F.; Nakajima, K.; Liu, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1144.
7. (a) Suzuki, K. *Pure Appl. Chem.* **1994**, *66*, 1557. (b) Suzuki, K.; Hasegawa, T.; Imai, T.; Maeta, H.; Ohba, S. *Tetrahedron* **1995**, *51*, 4483.
8. (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Hitchcock, S. A.; Mayhugh, D. R.; Gregory, G. S. *Tetrahedron Lett.* **1995**, *36*, 9085. (c) Kamikawa, T.; Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 3161. (d) Gordon, G. J.; Luker, T.; Tuckett, M. W.; Whitby, R. J. *Tetrahedron* **2000**, *56*, 2113.
9. (a) Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995**, *60*, 3278. See also: (b) Deloux, L.; Srebnik, M. *J. Org. Chem.* **1994**, *59*, 6871.
10. (a) Deng, G.; Tian, X.; Qu, Z.; Wang, J. *Angew. Chem., Int. End. Engl.* **2002**, *41*, 2773. (b) Yao, W.; Wang, J. *Org. Lett.* **2003**, *5*, 1527. (c) Yao, W.; Liao, M.; Zhang, X.; Xu, H.; Wang, J. *Eur. J. Org. Chem.* **2003**, 1784.
11. (a) Xi, Z.; Li, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2950. (b) Zhao, C.; Li, P.; Cao, X.; Xi, Z. *Chem. Eur. J.* **2002**, *8*, 4292.
12. (a) Zhao, C.; Yu, T.; Xi, Z. *Chem. Commun.* **2002**, 142. (b) Zhao, C.; Yan, J.; Xi, Z. *J. Org. Chem.* **2003**, *68*, 4355.
13. Preliminary results have been reported: Zhao, C.; Lu, J.; Yan, J.; Xi, Z. *Tetrahedron Lett.* **2003**, *44*, 6895.
14. For reviews on tetrahydrofuran subunits in natural products, see: (a) Garson, M. J. *Chem. Rev.* **1993**, *93*, 1699. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. See also: (c) Alali, F. Q.; Liu, X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (d) Collum, D. B.; McDonald, J. H.; Still, C. W. *J. Am. Chem. Soc.* **1980**, *102*, 2117. see also pp 2118 and 2120. (e) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304. (f) Gesson, J. P.; Jacquesy, J. C. *Tetrahedron Lett.* **1987**, *28*, 69.
15. For recent reviews on tetrahydrofuran synthesis, see: (a) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631. (b) Alvarez, E.; Candenas, M. L.; Perez, R.; Ravelo, J. L.; Martin, J. D. *Chem. Rev.* **1995**, *95*, 1953. (c) Koert, U. *Synthesis* **1995**, 115. (d) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10794.
16. For examples on metal-mediated synthesis of tetrahydrofuran derivatives, see: (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Ajamian, A.; Gleason, J. L. *Org. Lett.* **2001**, *3*, 4161. (c) Shim, J. G.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 3067. (d) Sekido, M.; Aoyagi, K.; Nakamura, H.; Kabuto, C.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 7142.
17. For Rh(VII) promoted tandem oxidative polycyclization of polyene alcohols affording poly-THF, see: (a) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 1447. (b) Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C.; Sinha, S. C. *Pure Appl. Chem.* **1997**, *69*, 423. (c) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem Soc.* **1997**, *119*, 12014. (d) Towne, B. T.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022. (e) Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076.
18. Monocyclization of bis-homoallylic alcohols affording THF derivatives, see: (a) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 3729. see also pp 5299 and 5303. (b) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett.* **1994**, *35*, 5133.
19. A three-component coupling leading to THF derivatives mediated by Pd(II), see: Liu, G. S.; Lu, X. Y. *Tetrahedron Lett.* **2003**, *44*, 467.
20. For acid-promoted formation of oxacycles from 1,6-diols. See: (a) Lorenzo, E.; Alonso, F.; Yus, M. *Tetrahedron Lett.* **2000**, *41*, 1661. (b) Gil, J. F.; Ramon, D. J.; Yus, M. *Tetrahedron* **1994**, *50*, 7307. See also: (c) Patient, L.; Berry, M. B.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1015. (d) Karikomi, M.; Watanabe, S.; Kimura, Y.; Uyehara, T. *Tetrahedron Lett.* **2002**, *43*, 1495. (e) Nakada, M.; Iwata, Y.; Takano, M. *Tetrahedron Lett.* **1999**, *40*, 9077.
21. For insertion of aldehydes into zirconacyclopentenes, see: (a) Coperet, C.; Negishi, E.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 695. (b) Li, P.; Xi, Z.; Takahashi, T. *Chin. J. Chem.* **2001**, *19*, 45.
22. For CuCl-mediated reactions of zirconacyclopentenes, see: (a) Xi, C.; Huo, S.; Afifi, T. H.; Hara, R.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 4099. (b) Takahashi, T.; Xi, Z.; Kotora, M.; Xi, C.; Nakajima, K. *Tetrahedron Lett.* **1996**, *37*, 7521. (c) Kasai, K.; Kotora, M.; Suzuki, N.; Takahashi, T. *J. Chem. Soc., Chem. Commun.* **1995**, 109. (d) Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Tetrahedron Lett.* **1994**, *35*, 5685. (e) Ura, Y.; Li, Y.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1998**, *39*, 2787. (f) Lipshutz, B. H.; Segi, M. *Tetrahedron* **1995**, *51*, 4407. (g) Xi, C.; Kotora, M.; Takahashi, T. *Tetrahedron Lett.* **1999**, *40*, 2357. (h) Takahashi, T.; Shen, B.; Nakajima, K.; Xi, Z. *J. Org. Chem.* **1999**, *64*, 8706.
23. Lipshutz, B. H. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 1. 107.