Zirconium-Catalyzed Ethylmagnesation of Hydroxylated Terminal Alkenes: A Catalytic and Diastereoselective Carbon–Carbon Bond-Forming Reaction

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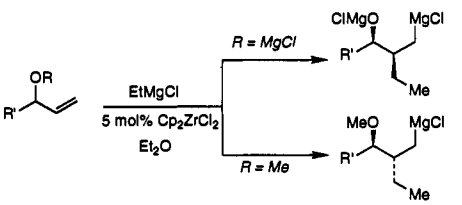
Abstract: Zirconocene dichloride catalyzes the addition of ethylmagnesium halides to chiral allylic and homoallylic alcohols and ethers in an efficient manner. These transformations proceed with high levels of regio- and stereocontrol; with the appropriate choice of the neighboring heteroatom substituent (alcohol vs ether), either of the two diastereotopic faces of a chiral alkene can be selectively functionalized. Experimental data described indicate that the regio- and stereoselective outcomes of catalytic carbomagnesation of acyclic substrates are unique. Simple addition of zirconacyclopropanes to unsaturated alcohols and ethers proceeds without stereoselection and affords the derived metallacyclopentanes either with no regiocontrol or with a completely opposite sense of regiochemistry compared to that obtained under the catalytic conditions. A detailed mechanistic scheme is provided that accounts for all the characteristics of a zirconium-catalyzed ethylmagnesation reaction. The proposed paradigm includes a biszirconocene complex as its centerpiece; intermediacy of the bimetallic complex is supported by rate studies and readily accounts for the observed selectivities. The proposed mechanistic hypothesis rationalizes (i) the requirement for excess EtMgCl, (ii) the necessity for the presence of a Lewis basic heteroatom, and (iii) the reason for the highly regioselective rupture of the intermediate metallacyclopentane.

Introduction

The ability of Cp_2ZrCl_2 to catalyze efficiently the addition of alkylmagnesium halides to alkenes[2] has been the subject of extensive studies in these laboratories.[3] Acyclic olefins in the presence of EtMgCl and 5 mol % of Cp_2ZrCl_2 undergo ethylmagnesation with high levels of regio- and stereoselection and in good yield.[3a,b] These transformations are noteworthy, since functionalization of a monosubstituted terminal olefin is usually not subject to appreciable levels of stereochemical control and because, as shown below, with the appropriate choice of the neighboring heteroatom substituent (alcohol vs ether), either of the two diastereotopic faces of a chiral alkene can be selectively functionalized. The results of our studies on the regio- and diastereocontrolled zirconocene-catalyzed addition of EtMgCl to acyclic allylic and homoallylic alcohols and ethers are presented herein.

An understanding of the mechanism of catalytic carbomagnesation is critical to research directed toward the development of an asymmetric variant of this carbon–carbon bond-forming process. We reasoned that bicyclic disubstituted olefins would



be most suitable as our initial mechanistic probes since their rigid structure would allow for unambiguous examination of heteroatom chelation effects (*exo*- vs *endo*-oxygen).[3c] Our preliminary investigation, which exclusively dealt with preferences in regiochemical control, set the stage for inquiry into the mechanistic details of carbomagnesation of *acyclic* systems. It was to be determined whether the principles afforded by our initial studies are valid in reactions of conformationally nonrigid substrates. At the outset, we expected that the principal focus of our studies would be related to matters of stereocontrol. However, we find that both the regio- and stereoselective outcomes of catalytic carbomagnesation of acyclic substrates are entirely deviant from those observed when unsaturated alcohols and ethers are treated with EtMgCl and stoichiometric amounts of Cp_2ZrCl_2.

Results and Discussion

Stereoselective Ethylmagnesations of Allylic Alcohols and Ethers. As illustrated in Table I, reaction of a variety of allylic alcohols with EtMgCl and 5–10 mol % of Cp_2ZrCl_2 at 25 °C for 8–12 h followed by quenching of the carbomagnesation product with $B(OMe)_3/H_2O_2$ or O_2 at −78 °C results in the stereoselective formation of 1,3-diols. With substrates that contain a β-substituent (entries 4 and 5 of Table I), reaction efficiency suffers when ether is used as solvent; to obtain reasonable conversion, either larger amounts of catalyst (25%, entry 4, Table I) or a change of solvent to THF (entry 5, Table I) is necessary. In

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(2) (a) Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, *32*, 218–220. (b) Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M.; Kukovinets, A. G.; Khalilov, A. M. *Iz. Akad. Nauk SSSR, Ser. Khim.* **1983**, *32*, 2053–2060. (c) Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285*, 43–51 and references cited therein. (d) Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Mulukhov, R. R.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, *38*, 207–208. (e) Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1991**, *40*, 1388–1393.

(3) (a) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079–5080. (b) Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950–8952. (c) Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z. *J. Am. Chem. Soc.* **1992**, *114*, 6692–6697.

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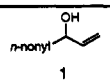
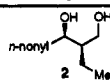
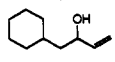
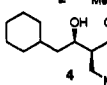
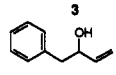
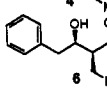
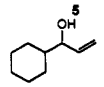
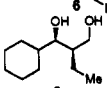
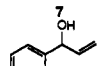
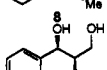
Table I. Diastereocontrol in Catalytic Ethylmagnesation of Allylic Alcohols[a]

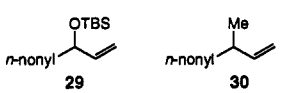
entry	substrate	major product	solvent (% cat.)	ratio (% yield)[b,c]
1	 1	 2	Et_2O (5)	95:5 (70)
			2,5-DMTHF (5)	85:15 (50)
			THF (5)	67:33 (85)
2	 3	 4	Et_2O (5)	95:5 (72)
			2,5-DMTHF (5)	89:11 (80)
			THF (5)	75:25 (80)
3	 5	 6	Et_2O (10)	85:15 (53)
			THF (10)	50:50 (80)
4	 7	 8	Et_2O (25)	75:25 (47)
			THF (25)	67:33 (70)
5	 9	 10	Et_2O (5)	78:22 (15)
			THF (5)	73:27 (60)

[a] Conditions: 4 equiv of EtMgCl, 5 mol % of catalyst, 25 °C, 12 h; O_2 at 0 °C. [b] Isolated yields of purified products after silica gel chromatography. Mass balance ≥90% in all cases. [c] Diastereomeric ratios determined by 300-MHz ^1H NMR or GLC analysis of the derived acetonides or methylene acetals.

general, when reactions are run in Et_2O, diastereoselectivities are higher than when THF is used as solvent. As will be discussed later in detail, this solvent effect is likely due to chelation between the magnesium alkoxide and the transition metal in the reacting alkene–zirconocene complex. With the more Lewis basic THF, metal–heteroatom association is altered and lower levels of stereoselectivity are observed. In accord with this paradigm, when the Lewis basic, but hindered, dimethyltetrahydrofuran (2,5-DMTHF) is used, reaction selectivities diminish (compared to Et_2O) but to a lesser extent than is observed with THF (entries 1 and 2, Table I).

Table II summarizes the outcomes of ethylmagnesations of allylic ethers; these carbomagnesations proceed in good yield and stereoselectively. It is noteworthy that the sense of 1,2-asymmetric induction is *opposite* to that of the reactions of magnesium alkoxides. We have proposed that the difference in facial selectivity is due to the absence of heteroatom–transition-metal chelation in the case of allylic ether. This contention is supported by the observation that reaction selectivity is insensitive to Lewis basicity of the solvent employed (entries 1 and 4–6 of Table II). In further contrast to reactions of allylic alcohols, where an increase in the size of the alkyl group results in a decrease in diastereocontrol (entry 1 vs 4 in Table I), ethylmagnesations of allylic ethers can be significantly more selective and equally facile as the size of the alkyl group increases (entry 1 vs 7 in Table II).

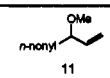
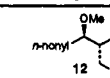
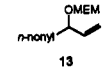
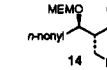
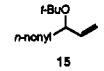
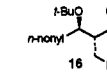
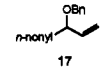
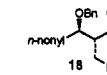
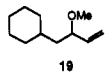
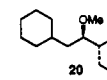
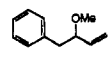
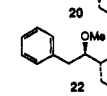
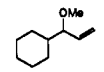
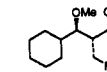
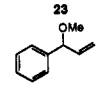
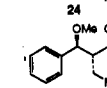
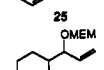
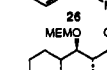
Carbomagnesations of allylic ethers are sensitive to steric effects; as an example, silyl ether **29** is recovered unchanged (>95% mass balance). However, diastereoselection in reactions of allylic ethers and alcohols is not simply the result of interplay of various steric effects: ethylmagnesation of **30** provides an equal mixture of diastereomers.



29 30

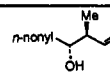
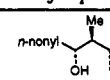
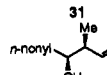
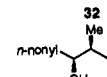
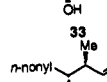
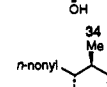
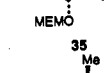
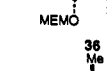
Stereoselective Ethylmagnesations of Homoallylic Alcohols and Ethers. To probe the influence of the internal heteroatom more extensively, we examined catalytic ethylmagnesations of a series of homoallylic alcohols and ethers. Representative data are summarized in Table III. Anti homoallylic alcohol **31** is an excellent substrate for ethylmagnesation. In THF or Et_2O, good yields and high levels of diastereoselection are obtained. The less Lewis basic **35** (compared to **31**) affords **36** in 60% yield and 92:8 diastereoselection; in the presence of a competing ligating solvent

Table II. Diastereocontrol in Catalytic Ethylmagnesation of Allylic Ethers[a]

entry	substrate	major product	solvent (% cat.)	ratio (% yield)[b,c]
1	 11	 12	Et_2O (5)	89:11 (80)
			THF (5)	89:11 (70)
2	 13	 14	Et_2O (5)	90:10 (60)
			THF (5)	83:17 (70)
3	 15	 16	Et_2O (5)	67:33 (85)
4	 17	 18	Et_2O (5)	85:15 (82)
			THF (5)	83:17 (70)
5	 19	 20	Et_2O (5)	83:17 (90)
			THF (5)	80:20 (80)
6	 21	 22	Et_2O (10)	88:12 (90)
			THF (10)	86:14 (80)
7	 23	 24	Et_2O (5)	96:4 (90)
			THF (5)	96:4 (70)
8	 25	 26	Et_2O (1)	87:13 (50)
			THF (10)	87:13 (55)
9	 27	 28	Et_2O (10)	>99:1 (40)
			THF (10)	>99:1 (55)

[a] Conditions: 3 equiv of EtMgCl, 5 mol % of catalyst, 25 °C, 12 h; O_2 at 0 °C. [b] Isolated yields of purified products after silica gel chromatography. Mass balance was ≥90% in all cases. [c] Diastereomeric ratios determined by 300-MHz ^1H NMR or GLC analysis of the derived acetonides or methylene acetals.

Table III. Diastereocontrol in Catalytic Ethylmagnesation of Homoallylic Alcohols and Ethers[a]

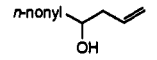
entry	substrate	major product	solvent (% cat.)	ratio (% yield)[b,c]
1	 31	 32	Et_2O (5)	>95:5 (75)
			THF (5)	>95:5 (75)
2	 33	 34	Et_2O (5)	85:15 (55)
			THF (5)	85:15 (55)
3	 35	 36	Et_2O (5)	92:8 (60)
			THF (5)	(<10)
4	 37	 38	Et_2O (5)	50:50 (35)
			THF (5)	(<10)

[a] Conditions: 3 equiv of EtMgCl, 5 mol % of catalyst, 25 °C, 12 h; $B(OMe)_3$, H_2O_2. [b] Isolated yields of purified products after silica gel chromatography. Mass balance ≥90% in all cases. [c] Diastereomeric ratios determined by GLC analysis of the derived lactone (see Experimental Section).

(THF), little reaction occurs. In contrast to ethylmagnesation of **33**, where the anti isomer is produced with 85:15 selectivity (55%), carbomagnesation of derived ether **37** is nonselective and affords **38** in 35% yield. With **37** as substrate, ≤10% of the product is obtained when the Lewis basic THF is used.

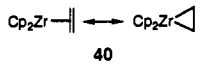
Unlike allylic ethers, homoallylic ethers undergo ethylmagnesation with the same sense of stereoselection as the parent metal alkoxide, indicating that heteroatom–metal chelation is more facile from the homoallylic position than from the allylic site (see below for further discussion). Since the carbon–carbon bond is formed anti to the methyl group, irrespective of the β-oxygen stereochemistry, it can be concluded that the α-stereogenic center is

primarily responsible for stereochemical differentiation. Consistent with this hypothesis, ethylmagnesation of **39** occurs without diastereoselection (80% yield).



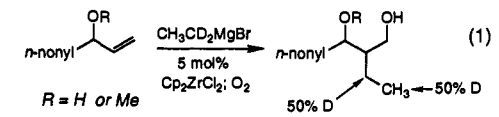
39

Deuterium-Labeling Experiments. In our previous studies,[3] metal–alkene complex **40**, the product of reaction of EtMgCl with Cp_2ZrCl_2,[4] was found to be the likely alkylating agent.[5]

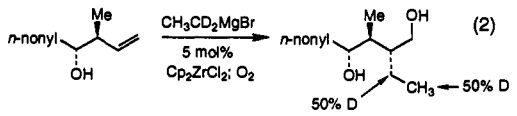


40

This possibility was corroborated by the observation that ethylmagnesation of a number of representative substrates with CH_3CD_2MgBr (5 mol % of Cp_2ZrCl_2) results in complete scrambling of deuterium between the two carbons of the ethyl group (eqs 1 and 2).



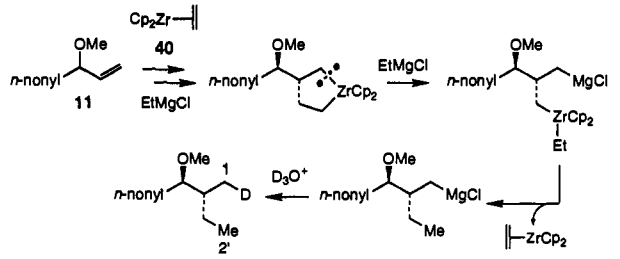
(1)



(2)

The pathway illustrated in Scheme I provides a plausible and general mechanistic scheme for the catalytic ethylmagnesation process. Addition of **40** to the olefinic substrate leads to the formation of the derived zirconacyclopentane. Subsequent site-selective cleavage would then result in the ethylmagnesation product (see Scheme I). That the intermediate zirconacyclopentane reacts with the EtMgCl to effect rupture of the metallacycle with high site-selectivity was ascertained by deuterium-labeling experiments. For example, as shown in Scheme I, when reactions of **11** (in Et_2O and THF) are quenched with D_2SO_4/D_2O, >95% deuterium is incorporated at C1, whereas <5% labeling is detected at C2′ (^{13}C NMR). This type of labeling pattern, where only the C1 carbon is deuterated, was also observed, with similarly high levels of selectivity, for allylic alcohols (in Et_2O and THF) and homoallylic alcohols and ethers.

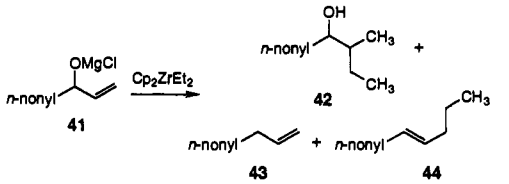
Scheme I[a]



[a] >95% D at C1; <5% D at C2′.

Within this general mechanistic construct (Scheme I), factors which give rise to the observed trends and degrees of regio-

Table IV. Reaction of Allylic Magnesium Alkoxide **41** with Diethylzirconocene[a]



equiv of Cp_2ZrEt_2	% conv	% of **42**	% of **43**	% of **44**[b]
1.0	36	19	7	10
2.0	53	25	11	17
3.0	82	33	23	25
4.0	95	40	28	27

[a] Reactions were performed in a 4:1 Et_2O/THF mixture at 25 °C for 4 h. All values were determined by GLC analysis of the unpurified reaction mixture. [b] In all cases, an equal mixture of syn and anti isomers was formed.

(formation of a primary vs a secondary C–Zr bond) and stereoselectivity and the origin of the site-selective cleavage of the intermediate metallacyclopentane remained to be established. In our initial studies, differences in reactivity and selectivity patterns of catalytic and stoichiometric additions of **40** to chiral alkenes proved to be instrumental in our understanding of some of the underpinning aspects of the catalytic process.[3c] Accordingly, we undertook a comprehensive study of the noncatalytic (in zirconium) reaction of **40** and a select number of aforementioned acyclic substrates.

Stoichiometric Reactions of Zirconacyclopropane 40 with Chiral Alkenes. As illustrated in Table IV, treatment of **41** with 1 equiv of Cp_2ZrEt_2 (precursor to **40**) results in 36% overall conversion (4:1 Et_2O:THF). Along with ethylmagnesation product **42**, which is formed as an *equal mixture of stereoisomers* and constitutes ~20% of the resulting mixture, 7% of 1-dodecene (**43**) and 10% of 4-tetradecene (**44**, mixture of cis and trans) are produced (GLC analysis of unpurified reaction mixture). The data in Table IV indicate that as the amount of Cp_2ZrEt_2 is increased, higher conversion is achieved but **42** is never formed stereoselectively and the ratio of the three products, **42–44**, remains approximately the same. In contrast, with 5 mol % of Cp_2ZrCl_2 and 3 equiv of EtMgCl, **42** is obtained with 88:12 diastereoselectivity (syn:anti, in 4:1 Et_2O:THF) and ~5% of **43** and <5% of **44** are detected. With Et_2O as solvent, the stoichiometric process provides syn **42** with 75:25 selectivity; in contrast, under the catalytic conditions (5 mol % of Cp_2ZrCl_2), 95:5 syn:anti diastereoselection is obtained.

When similar experiments are performed with methyl ether **11** (in THF), **44** is generated as the major constituent (~60%) along with 10–15% of **43**. *No carbomagnesation product is detected according to ^1H NMR (300 MHz) and GLC analysis of the unpurified reaction mixture.* Addition of excess diethylzirconocene does not lead to the formation of the carbometalation product, only more **43** and **44** are formed; with 4.0 equiv of Cp_2ZrEt_2, 33% of **43** and 67% of **44** are observed (>95% conversion). In contrast, when catalytic conditions are used, **11** affords **12** in 70% purified yield and 89:11 anti:syn selectivity, with only ~5% of 4-tetradecene (**44**) and <5% of 1-dodecene (**43**) formed as byproducts (GLC).

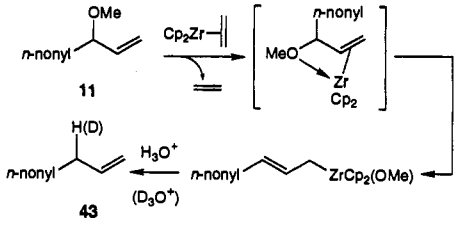
The terminal alkene (**43**) generated in the above experiments most likely arises from ligand exchange between **40** and the reacting olefin (Scheme II).[6] Elimination of the α-heteroatom leads to the allylic zirconocene system which exists as the primary allylmetal.[7] Therefore, the degree of which **43** is formed in stoichiometric reactions serves as an indication of the extent to

(4) (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544–2546. (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*, 3336–3346. (c) Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1989**, *111*, 4495–4496.

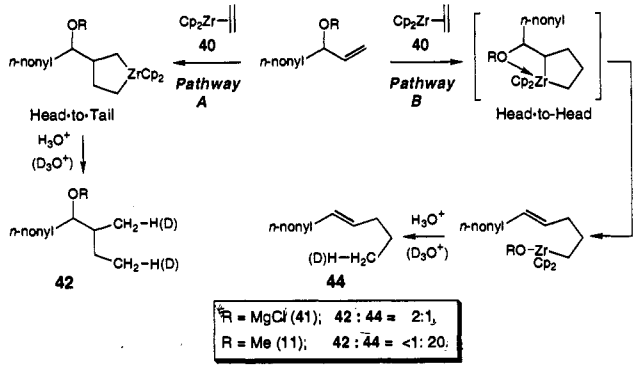
(5) Zirconacycles have been shown to be intermediates in the carbomagnesation reaction. See: (a) References 3a and 3c. (b) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266–6268. (c) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268–6270. (d) Lewis, D. P.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *32*, 6797–6800.

(6) (a) Ito, H.; Taguchi, T.; Hanazawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295–1298. (b) Ito, H.; Taguchi, T.; Hanazawa, Y. *Tetrahedron Lett.* **1992**, *33*, 7873–7876.

Scheme II



Scheme III[a]



[a] R = MgCl (**41**); **42**:**44** = 2:1. R = Me (**11**); **42**:**44** = <1:20.

which ligand exchange involving **40** and the reacting olefin takes place.

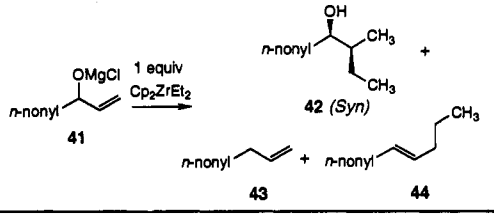
4-Tetradecene (**44**) is likely the result of head-to-head addition of **40** to an allylic magnesium alkoxide or ether. As shown in Scheme III, reaction of zirconacyclopropane **40** according to pathway B leads to the formation of the internal olefin and the primary C–Zr bond. When the products derived from **41** and **11** are treated with D_3O^+, >95% deuterium incorporation at the terminal carbon is observed (^2H and ^{13}C NMR). The extent to which 4-tetradecene is formed can be viewed as an indication of the levels of regiochemical control present in the addition of the zirconacyclopropane to the olefinic substrate.

It is important to note that the reactivity pattern observed for **41** and **11** is in contrast to that observed for 1-decene, which reacts readily with **40** under stoichiometric conditions to afford efficiently the head-to-tail metallacyclopentane (>80%).[2,5b-d] It is plausible that allylic alkoxides and ethers are *inherently* less reactive than 1-decene, since the α-oxygen substituent renders the addition process energetically less favorable due to steric reasons (similar to the lack of reactivity observed for **30**). Thus, it must be that the low reactivity of allylic ethers and alcohols (to afford the head-to-tail zirconacyclopentane) under the stoichiometric conditions is overcome when reactions are run catalytically (see below). The outcomes of stoichiometric reactions involving **40** suggest that, en route to the intermediate zirconacyclopentane, although formation of the primary C–Zr bond may be favored on steric grounds, the electron-withdrawing ability of the α-oxygen substituent perhaps results in placement of the transition metal at the secondary carbon.[8] Such effects are likely due to the stabilization of electron density at the carbon atom of the C–Zr bond. This type of inductive effect has been invoked to explain the regiochemical preferences of other

(7) Upon addition of H_3O^+, **43** is formed exclusively. Analysis of a ^1H NMR spectrum indicates the complete absence of the corresponding disubstituted olefin isomer (no doublet for vinyl CH_3 detected). Quenching with D_3O^+ affords only the terminal olefin with >95% labeling at the allylic site (^2H NMR and ^{13}C NMR analysis). When the derived deuterated ether is used ($ROCD_3$, H_3O^+ quench) or when $Cp_2Zr(C_2D_5)$ is used (H_3O^+ quench), **43** is formed with <5% deuterium incorporation.

(8) It is unlikely that formation of the head-to-head metallacyclopentane is due to association of the incoming zirconacyclopropane with the alkene substrate, since (i) the more Lewis basic **41** affords less head-to-head isomer and (ii) such interaction would preempt chelation of the empty transition-metal orbital with the reacting π-system.

Table V. Effects of Excess EtMgCl on the Reaction of Allylic Magnesium Alkoxide **41** with Diethylzirconocene[a]



% excess EtMgCl	% conv	% of **42**	(syn:anti)[b]	% of **43**	% of **44**
0	36	19	(50:50)	7	10
100	97	88	(80:20)	7	2
200	99	94	(82:18)	4	1
300	99	94	(88:12)	4	1

[a] Reactions were performed in a 4:1 Et_2O/THF mixture at 25 °C for 4 h. All values were determined by GLC analysis of the unpurified reaction mixture. [b] Diastereoselectivities were determined by analysis of ^1H NMR spectra (300 MHz).

zirconocene-mediated coupling reactions that involve styrene (including carbomagnesation).[9]

Regardless, as summarized in Scheme III, these data indicate that *in contrast to the catalytic ethylmagnesation, **41** reacts with **40** without regiochemical control*[10] *and that addition of zirconacyclopropane to ether **11** proceeds with the regiochemistry opposite to that observed under the catalytic conditions (92% regiocontrol).*[11] The discrepancy between the outcomes of catalytic and stoichiometric conditions is not limited to allylic alcohols and ethers. Treatment of the magnesium salt of homoallylic alcohol **31** with 1 equiv of Cp_2ZrEt_2 (in THF at 25 °C) results in complete recovery of the starting material.

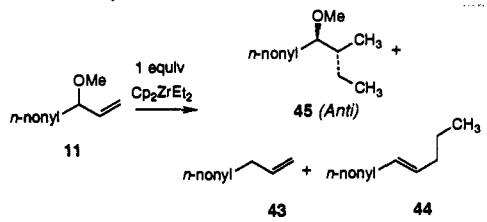
Such stark contrast in the reaction efficiency and the regio- and stereochemical outcomes of stoichiometric and catalytic processes is the result of absence of excess EtMgCl in the latter protocol. Table V illustrates that as the amount of excess Grignard reagent is increased, significantly less 4-tetradecene and 1-dodecene is formed and levels of stereoselectivity approach and reach those obtained under the catalytic conditions. The data in Table VI

(9) Takahashi, T.; Suzuki, N.; Hasegawa, M.; Nitto, Y.; Aoyagi, K.; Saburi, M. *Chem. Lett.* **1992**, 331–334.

(10) Unlike stoichiometric addition of **40** to ether **11**, in related reactions that involve allylic magnesium alkoxide **41**, a 2:1 mixture of regioisomeric metallacyclopentanes is generated (in favor of the head-to-tail isomer). This variation in regiocontrol in the addition process does not arise from head-to-tail to head-to-head interconversion in the case of allylic ethers. Control experiments indicate that the selectivities shown in Scheme III represent inherent kinetic regiochemical preferences in the formation of the metallacyclopentane. Treatment of **41** with 1 equiv of Cp_2ZrEt_2 affords ~20% of the carbomagnesation product (**42**) after 24 h at 25 °C (20% of **42** is isolated after 4 h as well). Quenching with D_2O/D_2SO_4 results in >75% double-deuteration (**42**-d_2), indicating the presence of the head-to-tail zirconacyclopentane after an extended reaction time. Although unlikely, it may also be argued that rapid Zr–Mg exchange leads to the dimagnesium derivative of **42**, which then is quenched with D_3O^+. Regardless, this experiment illustrates the kinetic selectivity of C–C bond formation. The control experiment also indicates that **43** does not arrive from decomposition of zirconacyclopentanes (to give the precursor to **43**, Scheme II), since in such a case, after 24 h, little **42** would be recovered. For reports on group IV metallacyclopentane equilibria, see: (a) McDermott, J. X.; Wilson, M. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 6529–6536. (b) Yasuda, H.; Tatsumi, K.; Nakamura, K. *Acc. Chem. Res.* **1985**, *18*, 120–126. (c) Erker, G.; Dorf, U.; Rheingold, A. *Organometallics* **1988**, *7*, 138–143. (d) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521–3523. (e) Takahashi, T.; Hasegawa, M.; Suzuki, N.; Saburi, M.; Rousset, C. J.; Fanwick, P. E.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 8564–8566.

(11) This difference in regioselectivity could be partly attributed to the weaker electron-withdrawing ability of the heteroatom substituent (ClMgO vs MeO). However, the discrepancy in regiochemical control (>95% for **11** in favor of a secondary C–Zr bond vs a 1:2 mixture of regioisomers for **41**) appears too significant to arise only from differences in the electronic properties of the α-heteroatom. It is tenable that in the stoichiometric reactions involving **41**, participation of the alkoxy *magnesium* chloride and the intermediacy of a magnesium–zirconium bimetallic system are responsible for the formation of the head-to-tail zirconacycle. Experiments designed to elucidate the role of the neighboring magnesium halide on the zirconacyclopropane addition are in progress.

Table VI. Effects of Excess EtMgCl on the Reaction of Allylic Ether **11** with Diethylzirconocene[a]



% excess EtMgCl	% conv	% of **45**	(anti:syn)[b]	% of **43**	% of **44**
0	62	00		19	43
100	78	00		23	55
200	100	83	(89:11)	3	14
300	100	92	(89:11)	1	7

[a] Reactions were performed in THF at 25 °C for 4 h. All values were determined by GLC analysis of the unpurified reaction mixture. [b] Diastereoselectivities were determined by analysis of ^{1}H NMR spectra (300 MHz).

demonstrate that similar trends hold, even more impressively, for allylic ether **11**. Whereas in the absence of additional EtMgCl, >60% of **44** and <5% of **45** are detected, in the presence of 2 equiv of EtMgCl, **45** is obtained as the principal product (>80%, GLC analysis) and only ~15% of **44** is formed. As additional amounts of EtMgCl are added, more **45** and less of the elimination products **43** and **44** are generated. Similarly, when the magnesium salt of homoallylic alcohol **31** is treated with diethylzirconocene in the presence of 1 equiv of EtMgCl, ~50% of carbometalation product is observed; with 2 equiv of Grignard reagent, the reaction proceeds to completion. Diastereochemical control in reactions involving **31** is uniformly >95:5 anti:syn in favor of **32**. Experiments designed to elucidate the origin of the difference between the outcome of the catalytic and stoichiometric reactions are discussed below.

Regioselectivity in Formation of Head-to-Tail Zirconacyclopentane. The above data collectively indicate that under *catalytic* conditions, formation of the head-to-tail metallacyclopentane from an allylic or homoallylic alcohol and ether does not arise from simple addition of the zirconacyclopropane to the olefinic substrate. However, it is plausible that the metal-coordinated olefin (not the "naked" alkene) is the reactive species. In contrast to the unbound π-system, the olefin–metal complex may undergo reaction to afford the head-to-tail adduct efficiently and with regiocontrol. The proposal that alkene substrates react through their derived olefin–transition-metal complexes is particularly attractive, since our previous studies on bicyclic substrates and the stereochemical and reactivity trends shown in Tables I–III suggest some type of *internal* heteroatom–metal interaction.

Experimental data indicate that the metal which is associated with the π-system and is involved in the internal chelation is not magnesium. In stoichiometric reactions of allylic and homoallylic magnesium alkoxides, where both bound magnesium halide and ample external $MgCl_2$ (from reaction of Cp_2ZrCl_2 with EtMgCl) are available, either no reaction occurs (with **31**) or there is little or no stereo- (1:1) or regioselectivity (2:1) in favor of the head-to-tail metallacycle (with **41**). It is, however, plausible that the metal which associates with the olefin is zirconium. Although under stoichiometric conditions formation of the zirconocene of the reacting alkene occurs to a limited extent (generation of **43** supports this claim, see Scheme II), such a complex may not be in its active form. It is tenable that the derived *zirconate*[12] (e.g., **46** in Scheme IV) is responsible for the facile and selective formation of the head-to-tail adduct. Involvement of metal complexes such as **46** accounts for our findings that additional

(12) Alkyl zirconates of this type have been reported to be involved in zirconocene-catalyzed hydrogenations. See: Takahashi, T.; Suzuki, N.; Kageyama, M.; Nitto, Y.; Saburi, M.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 1579–1582.

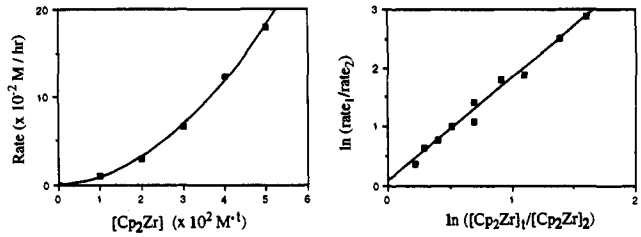
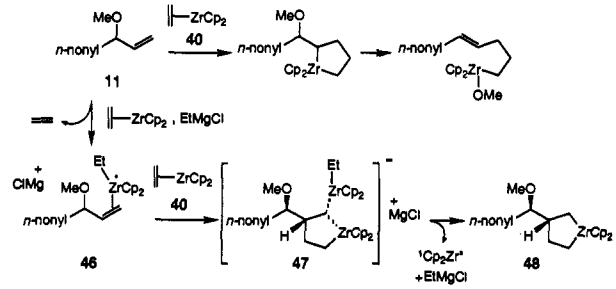


Figure 1. Dependence of initial rate of ethylmagnesation of **11** on concentration of Cp_2ZrCl_2. Changes in the concentration of carbomagnesation product (up to 10% conversion) were monitored by GLC analysis with hexadecane as an internal reference. The slope of ln of ratio of reaction rates vs ln of ratio of zirconium concentration is 1.8 ± 10%.

Scheme IV



EtMgCl is required for efficient and regioselective formation of the head-to-tail zirconacyclopentane.[13] Association and subsequent addition of **40** to electron-rich **46** then selectively affords zirconacyclopentane **48**,[14] via the bimetallic complex **47**.[15] The biszirconocene system (e.g., **47**) is formed preferentially at the terminal carbon due to steric requirements, resulting in the *primary* C–Zr bond and nearly complete turnover in regiochemistry of addition.[16]

Measurements of reaction rate under varying concentrations of Cp_2ZrCl_2 in ethylmagnesations of allylic substrates support the contention that two zirconium species are involved in the catalytic reaction. As an example, a set of data, obtained for ethylmagnesation of **11**, is shown in Figure 1. The rate of ethylmagnesation is not linearly dependent on the concentration of zirconocene and, within experimental error (±10%), is second order in zirconium. Since our studies illustrate that direct addition of **40** to the olefin substrate is most likely not operative under the catalytic conditions, it cannot be argued that addition and cleavage events equally contribute to the overall rate. Moreover, our data indicate that rupture of the metallacyclopentane is probably not the catalyst turnover-limiting step. When **11** is treated with 1 equiv of Cp_2ZrEt_2 and 60 equiv of EtMgCl in THF (to emulate catalytic conditions when 5 mol % catalyst and 3 equiv of EtMgCl is used) and various aliquots from the reaction mixture are

(13) It is unlikely that the zirconate derived from addition of EtMgCl to **40**, rather than zirconocene–alkene complex **40**, is the "alkylating agent", since the available ligation site (in **40**) is most likely required for the addition to occur. Preassociation of the reacting alkene probably precedes the generation of the zirconacyclopentane.

(14) The Cp_2Zr thus released will subsequently associate with another alkene substrate to eventually regenerate **46**.

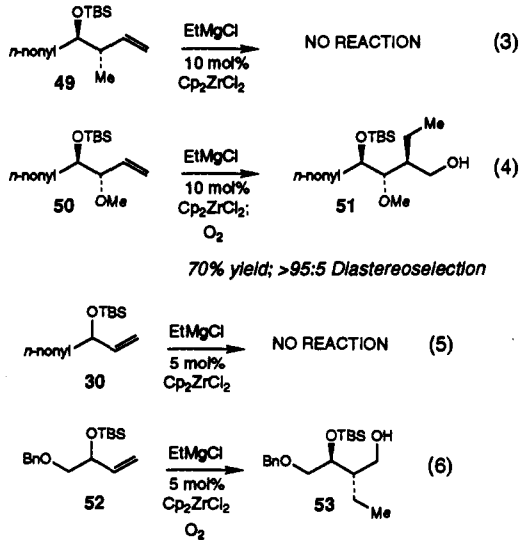
(15) A recent observation that underlines the significance of bimetallic systems in controlling reaction selectivity is the regioselective hydrozirconation of alkenylzinc halides by $Cp_2ZrH(Cl)$. This transformation proceeds with excellent regiocontrol via the terminal zinc–zirconium complex. See: Tucker, C. E.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 9888–9890.

(16) For a recent report on crystallographic and spectroscopic studies of a dizirconocene complex, where one transition metal is an ethyl zirconate, see: (a) Binger, P.; Langhauser, F.; Gabor, B.; Herrmann, A. T.; Kruger, C. *J. Chem. Soc., Chem. Commun.* **1992**, 505–506. Trigonal bipyramidal methyl groups that are bridged by two zirconocene groups have been reported. See: (b) Waymouth, R. M.; Santarsiero, B. D.; Grubbs, R. H. *J. Am. Chem. Soc.* **1984**, *106*, 4050–4051. (c) Waymouth, R. M.; Santarsiero, B. D.; Coots, R. J.; Bronikowski, M. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 1427–1441. (d) Buchwald, S. L.; Lucas, E. A.; Davis, W. M. *J. Am. Chem. Soc.* **1989**, *111*, 397–398. (e) Horton, A. D.; Orpen, A. G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 876–878.

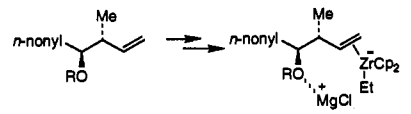
deuterated (D_2O/D_2SO_4) and analyzed (^{13}C NMR), at 45%, 65%, and 90% conversion (GLC), >95% of the monodeuterated species is detected (monodeuterated product indicates cleaved zirconacyclopentane, see Schemes I and IX for detail). These data indicate that the opening of **48** (see Scheme I) is significantly faster than the addition process and that the formation of the metallacyclopentane could well be turnover-limiting.

Two factors can account for the proposal that zirconate of the reacting alkene is a better substrate for carbomagnesation than the parent (uncomplexed) olefin. (1) The highly Lewis basic, electron-rich metal–alkene complex is better able to associate with the incoming zirconacyclopropane (donation to vacant $1a_1$ orbital of transition metal in **40**). (2) Upon formation of the C–C bond, electron density at the carbon of the incipient C–Zr bond can be shared with empty orbitals on two coordinating transition metals. The intermediacy of the bimetallic complex (e.g., **47**, Scheme IV) provides a rational explanation for the striking reversal of regiochemical outcomes between the stoichiometric and catalytic carbomagnesations of allylic substrates **41** and **11** (see Tables IV–VI).

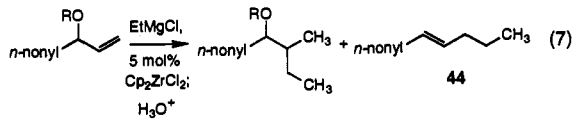
Influence of an Internal Heteroatom on the Efficiency of Head-to-Tail Zirconacyclopentane Formation. A variety of observations indicate that a Lewis basic heteroatom substituent is needed to override the inherent lack of reactivity of allylic and homoallylic alcohols and ethers, so that head-to-tail metallacyclopropane addition proceeds efficiently. (1) In contrast to homoallylic alcohols **31** and **33** which undergo ethylmagnesation with reasonable facility (Table III), **30** (see above) affords 15% of the carbometalation product. (2) In reactions of syn and anti homoallylic alcohols and ethers (Table III), the Lewis basicity of the internal heteroatom is directly linked to the efficiency of ethylmagnesation. Homoallylic magnesium alkoxides afford significantly higher yields than the corresponding ethers. (3) Silyl ether **49** is completely resistant to carbomagnesation, whereas **50** affords the desired ethylmagnesation product with excellent diastereocontrol in 70% yield after silica gel chromatography (eqs 3 and 4). (4) In contrast to silyl ether **30** which is unreactive under catalytic ethylmagnesation conditions, β-benzyloxy α-silyl ether **52** undergoes smooth ethylmagnesation stereoselectively to afford **53**; as expected, in THF there is significantly less reaction. It is important to note that since homoallylic as well as allylic oxygen-containing functional groups are capable of enhancing reactivity, the electron-withdrawing property of the heteroatom cannot be the central factor that leads to the enhancement of reaction efficiency under the *catalytic* conditions.



The significance of a heteroatom to the overall reaction efficiency may be readily rationalized through involvement of the zirconate of the reacting olefin in the catalytic ethylmagnesation. The dependence of substrate reactivity on an internal Lewis base is most likely related to a coordination process that includes such functionality.[17] Formation of the requisite zirconate should be more favorable in the presence of an oxygen substituent, since, as shown below, chelation between the magnesium ion and the Lewis base should stabilize the metal–olefin complex. An olefin substrate which contains a Lewis basic functionality may be viewed as a strongly chelating bidentate ligand: the π-cloud associates with the transition metal, and the heteroatom interacts with the magnesium counterion.[18]



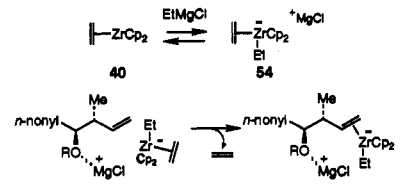
If zirconate formation is assisted by a heteroatom in the alkene substrate and the zirconocene complex of the reacting olefin is responsible for the turnover in regioselectivity (via the bimetallic complex), then in the presence of an inferior internal Lewis base, lesser amounts of the head-to-tail metallacycle should form. The data presented in eq 7 indicate that as the Lewis basicity of the α-heteroatom is diminished, lower ratios of carbomagnesation product:4-tetradecene are indeed observed. (As shown in Scheme III, intermediacy of the head-to-head zirconacycle would result in the formation of an internal disubstituted alkene, such as **44**). It is unlikely that differences in the electron-withdrawing ability of the oxygen substituent are solely responsible for the significant variations observed in regiocontrol in the addition of the zirconacyclopropane to the alkene.



R = MgCl	>35 : 1	
R = Me	12 : 1	*(Solvent: Et_2O)*
R = MEM	2 : 1	

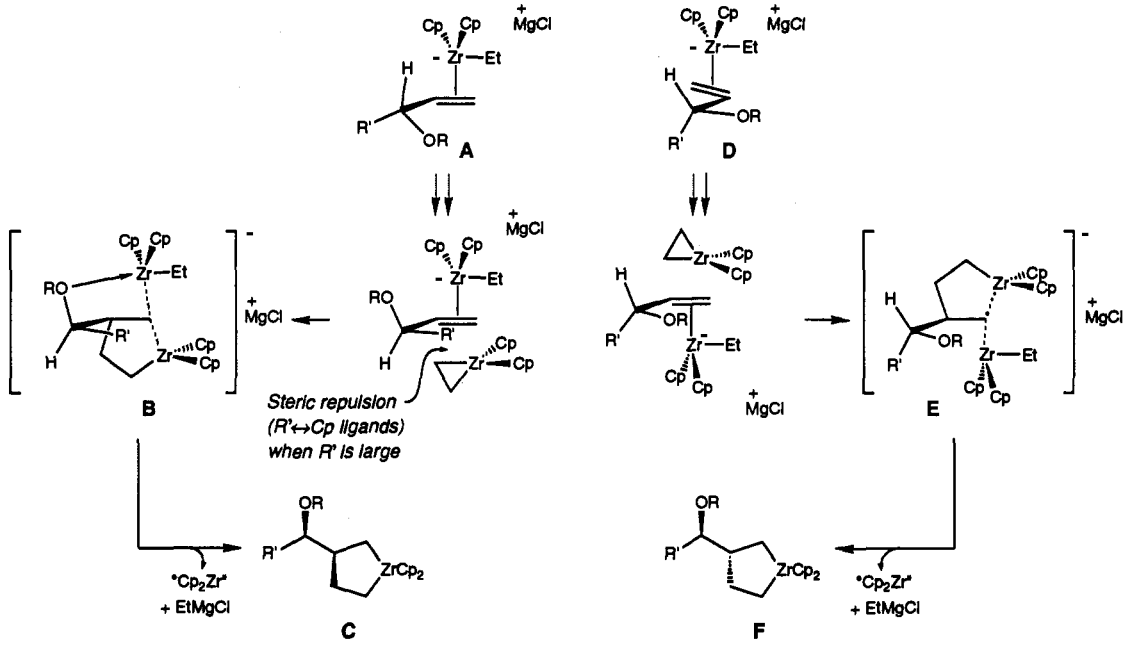
Origin of Stereocontrol in C–C Bond Formation. Terminal alkenes are not generally subject to strict conformational control, and hence, functionalization of these substrates with levels of selectivity ≥90%, particularly in reactions which occur intermolecularly, is uncommon. Any proposed mechanistic model for stereoselective catalytic ethylmagnesations described above must offer a rationale for (1) the stereochemical trends observed

(17) With stoichiometric amounts of **40**, ligand exchange between the zirconacyclopropane and **11** or **41** occurs to a certain extent (~15% dodecene is formed; 1-dodecene is derived from the zirconocene complex of the reacting olefin, see Scheme II). With 5–10% **40** without excess EtMgCl, the amount of ligand exchange would likely be less. However, when excess EtMgCl is present, it is plausible that ligand exchange is more favored, since internal chelation between **54** and the heteroatom, as shown below, could facilitate such a process.



(18) Whereas THF does not alter reactivity in reactions of allylic ethers, it does so when homoallylic ethers are employed as substrates (compare entries 2 and 3 in Tables II and III). It is reasonable that internal chelation between the heteroatom and zirconate magnesium can be altered by the chelating solvent when the Lewis base is at the homoallylic site but not when the donor oxygen resides at the more proximal allylic position.

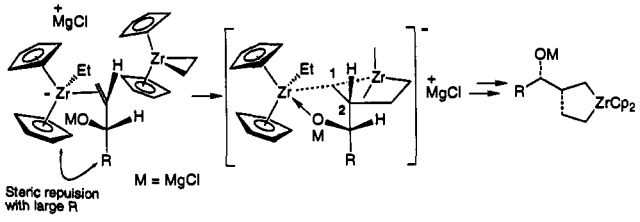
Scheme V



with allylic and homoallylic substrates and (2) the reversal of stereoselectivity in reactions of allylic alcohols vs ethers.

The hypothesis that the zirconocene complex of the reacting alkene is involved in the catalytic carbomagnesation may account for the stereochemical outcomes of reactions illustrated in Tables I–III. The main topological feature of the reaction, anti addition of the zirconacyclopropane to the zirconate of the reacting alkene, is consistent with the mechanistic formulations proposed by us for the regioselective carbomagnesations of bicyclic homoallylic alcohols and ethers.[3c] There are two steps which could be stereochemistry-determining in the catalytic cycle: the metal–alkene complexation and the addition process. It is unlikely that significant π-facial selectivity occurs at the ligand-exchange step. As illustrated in Scheme V, there should be little difference in energy between diastereomeric complexes **A** and **D**.[19] The trends and levels of stereoselection can best be explained if the addition reaction (**A** → **B** or **D** → **E**) is assumed to be the stereochemistry-determining step in the catalytic cycle. It is plausible that addition of the bulky zirconacyclopropane would occur syn to the smallest α-substituent, H (Scheme V, **A** → **B** and **D** → **E**). With an allylic magnesium alkoxide as substrate, addition of **40** proceeds so that as the carbon–carbon bond is being formed at C2 and C2–Zr interaction is weakened, the Lewis basic heteroatom can interact with the transition metal.[20] Only in **B**, which leads to the syn ethylmagnesation product, is the heteroatom properly aligned for such association (proper overlap of Lewis base with the available orbital on the transition metal).[21]

However, to minimize unfavorable steric repulsions, it is best to position the alkyl group (rather than the oxygen substituent) anti to the incoming zirconacyclopropane; such mode of approach would result in **E**, wherein internal chelation would be minimal (orthogonal alignment of oxygen lone pairs and the Zr $1a_1$ orbital). For further clarification, the related steric and stereoelectronic issues are illustrated below. It is evident from the transition-state structure shown that formation of the C–C bond is favored to occur syn to the small (H) group, so as to avoid unfavorable eclipsing interactions with the protruding α-substituent.



Heteroatom interaction with the transition metal should become more costly as the size of the R group is increased; oxygen–metal association positions the alkyl substituent oriented toward the Cp ligand of the bound zirconocene (see above figure). Indeed, data in Table I indicate that with larger substituents (R′ = *n*-nonyl vs cyclohexyl, entries 1 and 4), stereocontrol decreases noticeably (95:5 and 75:25, respectively). When α-alkyl groups are more cumbersome, addition through **B** is rendered less favorable, whereas reaction via **E** becomes more likely, leading to lower ratios of syn:anti isomers. When the reaction is performed in THF, internal chelation (in **B**) is significantly altered, since a solvent molecule may serve as the donor, and the sterically more favorable pathway that leads to the eventual formation of the anti metallacyclopentane **F** becomes competitive.

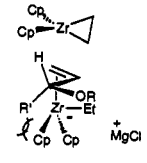
With the less Lewis basic methyl ethers, compared to the parent metal alkoxide, there is diminished tendency for the heteroatom to interact with zirconocene. Thus, addition through **E** becomes predominant (due to minimization of unfavorable steric interactions), leading to the formation of the anti ethylmagnesation product (Scheme V). Intermediacy of **E** allows **40** to add syn to the small H and anti to the larger alkyl substituent, leaving the medium-sized OMe to adopt the inside position.[22] When a methyl

(19) In general, with terminal alkenes, where any significant allylic strain ($A^{1,2}$ or $A^{1,3}$) is absent, little stereocontrol is achieved. For an excellent review on allylic strain, see: Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

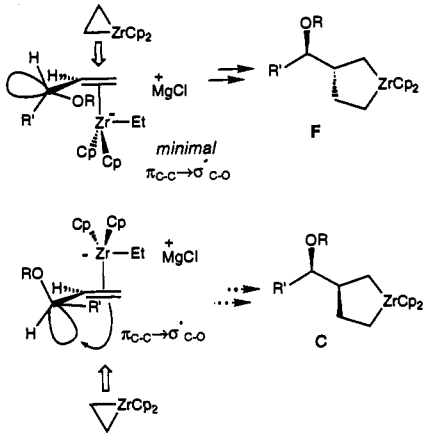
(20) If the addition step is indeed the turnover-limiting step, then formation of zirconacyclopentane should involve a late transition state, where zirconocene is largely dissociated from the reacting alkene, allowing the resident heteroatom to interact with available empty orbitals of the departing transition metal.

(21) Lauher, J. W.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1729–1742.

(22) Reaction through the alkene–metal complex conformation shown below should be unfavored due to inherent steric interactions.



Scheme VI

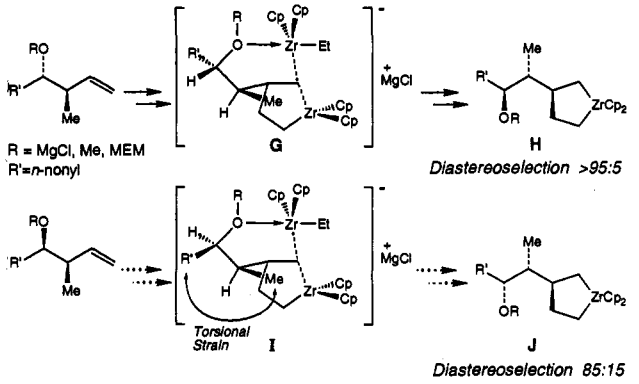


ether substrate has a relatively small alkyl group (e.g., R′ = *n*-nonyl), some reaction via **B** may occur, perhaps since steric interactions are not overly prohibitive or because there is a modicum of internal chelation present between the ether oxygen and the transition metal.[23]

Generally, in connection to stereocontrol in reactions of allylic ethers, the above scheme offers an explanation for the selective outcome of reactions of substrates in which the α-alkyl and ether substituents are sterically well differentiated. For instance, methyl ether **23** (Table II) may be expected to afford high levels of stereocontrol (96:4, α-cyclohexyl vs OMe), since approach through **B** would be sterically demanding due to the interaction between the cyclohexyl and Cp groups. However, in reactions of substrates such as **13**, where 90:10 anti:syn stereoselection is obtained, it is unlikely that steric factors are primarily responsible for the observed diastereoselection, as $-OCH_2OCH_2CH_2OCH_3$ (OMEM) and *n*-nonyl groups have very similar steric requirements. It is reasonable that in catalytic ethylmagnesations of allylic ethers, in addition to steric factors, *electronic* elements are operative as well in determining the more reactive face of the alkene. As mentioned previously, high reactivity of the zirconate of the reacting olefin may be due to the fact that the electron-rich alkene complex (high Lewis basicity) can better associate with the incoming Lewis acidic **40** (interaction with vacant $1a_1$ orbital). Therefore, any factor that diminishes electron density at the π-cloud should render the π-metal complex less Lewis basic and more hesitant toward association with zirconacyclopropane **40**, decelerating the rate of formation of the zirconacyclopentane.[24] As illustrated in Scheme VI, in the zirconate stereoisomer that leads to **C**, π_{C-C} is properly aligned to donate electrons to the low lying σ^*_{C-O}; this type of interaction would attenuate the Lewis basicity of the metal–olefin complex and retard its association with the incoming zirconacyclopropane. In contrast, en route to **F**, overlap between the π-system and the σ^*_{C-O} is minimal, allowing this conformer to better establish interaction with **40** and undergo cycloaddition more readily.

Similar arguments as presented for reactions of allylic alcohols may be applied to account for selectivity and reactivity patterns observed in ethylmagnesations of homoallylic alcohols and ethers (Table III). The lower stereoselectivity observed with syn homoallylic alcohol **33** (vs anti **31**) indicates that local chirality plays an important role in determining reaction yields and π-facial selectivities. If the magnesium alkoxide salt of **31** or **33** forms

Scheme VII



a complex with the transition metal prior to the formation of a carbon bond, then there may exist energetically costly torsional strain in the complex derived from **33** but not **31** (vide infra). Anti homoallylic substrates (e.g., **31** and **35** in Table III) undergo carbomagnesation more stereoselectively than syn isomers (e.g., **33** and **37**), since internal coordination between the heteroatom and the transition metal in the latter set of substrates results in unfavorable steric interactions (Scheme VII, compare **G** with **I**). When both syn and anti homoallylic magnesium alkoxides are protected (e.g., OMEM), the oxygen substituent has reduced Lewis basicity, which results in (1) less efficient substrate–zirconate formation and lower substrate reactivity and (2) weaker internal chelation (RO → Zr) and diminution in diastereocontrol (cf. Table III). This proposal implies that homoallylic ethers are capable of chelating to zirconium when allylic ethers are not; this difference may be attributed to the higher degree of strain involved in heteroatom–metal interaction in chelation of an allylic heteroatom.[25]

Site-Selective Cleavage of Zirconacyclopentane.[26] It remained to be determined what factors control the rupture of the intermediate zirconacyclopentanes, where the two C–Zr bonds are of the same substitution pattern (primary C–Zr). In this study, in the zirconacyclopentane derived from the allylic and homoallylic substrates, one primary C–Zr bond is more proximal to the alkyl substituent and its heteroatom functionality than the other. To differentiate between steric effects (α- vs β-alkyl groups relative to the C–Zr bond) and any possible influence by the heteroatom, we examined the regiochemistry of cleavage through a model zirconacyclopentane wherein the sole difference between the two primary carbon–zirconium bonds is that only one such bond is within reach of the heteroatom.

As reported previously,[27] when diene **55** is treated with 1 equiv of dibutylzirconocene, **56** is formed (Scheme VIII). Quenching of the resulting metallacyclopentane with D_2O/D_2SO_4 affords the doubly deuterated **57** (75-MHz ^{13}C NMR analysis). When **56** is subjected to 3 equiv of EtMgCl (3 h) and then the reaction is quenched with D_3O^+, only one methyl group is site-specifically deuterated (>95%, **58**).[28] Similar results are obtained when the reaction is performed under catalytic conditions[3c] with 4 equiv

(23) As the size of the alkyl group is increased (to cyclohexyl), the latter pathway becomes energetically too costly and stereocontrol is enhanced (compare entries 1 and 7 of Table II). Since internal chelation plays only a minor role in controlling π-facial selectivity in carbomagnesations of allylic ethers, the presence of THF does little to influence the observed levels of stereocontrol (Table II).

(24) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Loncharich, R. J. *Science* **1986**, *231*, 1108–1117.

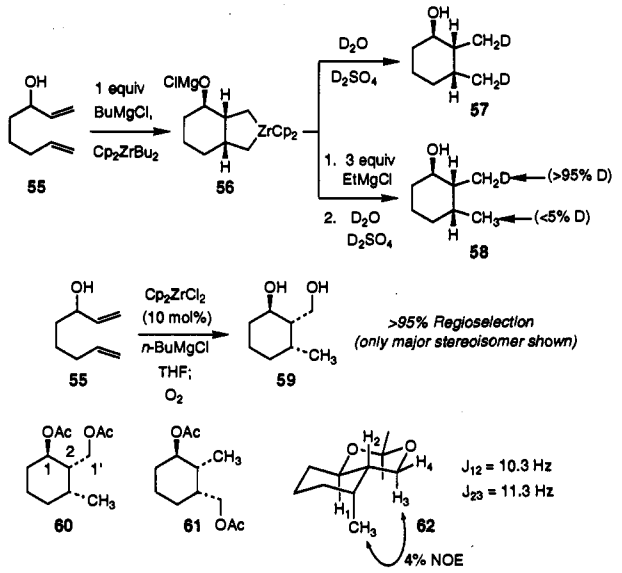
(25) The lower reactivity of syn homoallylic alcohol and ethers compared to that of their anti counterparts can be attributed to less effective internal chelation between the magnesium of zirconate and the internal heteroatom, which should lead to lower stability of the reactive zirconate (see above). Presumably, torsional interactions similar to those shown in I (Scheme VII) are present during RO → Mg chelation, rendering the transition-metal complex less favorable.

(26) For a recent report on regioselective cleavage of zirconacyclopentadienes, see: Chung, S. H.; Oh, D. Y. *Tetrahedron Lett.* **1992**, *33*, 5097–5098.

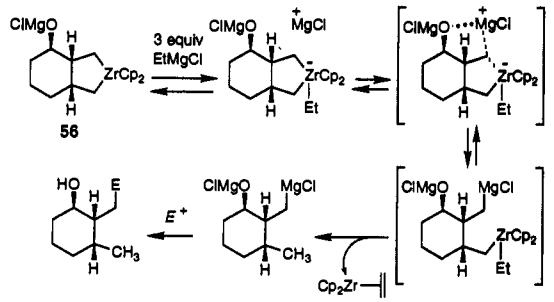
(27) (a) Nugent, W. A.; Taber, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6435–6437. (b) Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5105–5108.

(28) Similar levels of selectivity were achieved when *n*-BuLi was employed as the cleaving agent.

Scheme VIII



Scheme IX



of *n*-BuMgCl and 10 mol % Cp_2ZrCl_2 (**55** → **59**, 60% yield).[29] To determine the direction of the metallacyclopentane cleavage, the product of the catalytic reaction was quenched with O_2 to afford a single regioisomeric diol (>95%, 300-MHz ^1H NMR). Analysis of the ^1H NMR and J1 COSY spectra of the derived bisacetate indicates that both the C1 and C1′ protons are coupled with the proton at C2 (**60**, Scheme VIII); such would not be the case if regioisomeric **61**, resulting from the opposite sense of metallacycle cleavage, were the isolated product. Analysis of spectra of the corresponding acetonide **62** further supports this assignment.

A plausible mechanism for the influence of the resident heteroatom on the regioselective opening of the metallacyclopentane is presented in Scheme IX (only the major diastereomer is shown). Addition of EtMgCl to **56** leads to the formation of the derived zirconate, which undergoes site-selective cleavage due to chelation of the magnesium with the neighboring Lewis basic alkoxide. A subsequent β-hydride elimination–reductive elimination sequence provides the alkylmagnesium product and releases zirconacyclopropane. In short, these experiments underline the important role of the oxygen substituent on the selective cleavage of nearly symmetrical metallacyclopentanes.

Conclusions. Addition of EtMgCl to chiral acyclic allylic and homoallylic alcohols and ethers occurs readily and with high selectivity. Data put forth in this article demonstrate that stereoselective C–C bond formation and the regioselective generation of a primary C–Zr bond are particular to the catalytic process, that is, levels and trends in reactivity, regioselection, and diastereoselectivity are different from those obtained in the simple addition of **40** to chiral olefins. A mechanistic hypothesis based on detailed experimental evidence is provided that accounts for the characteristics of catalytic ethylmagnesation. The proposed paradigm includes a biszirconocene complex as its centerpiece and rationalizes the requirement for excess EtMgCl and the necessity for the presence of a Lewis basic heteroatom. With the support of the mechanistic data presented herein, studies in relation to asymmetric catalysis are underway.[30]

Experimental Section

General. All reactions were conducted in oven- (135 °C) and flame-dried glassware under an inert atmosphere of dry argon. Tetrahydrofuran and diethyl ether were distilled from sodium metal/benzophenone ketyl. Cp_2ZrCl_2 was purchased from Boulder Chemical Co. and used without further purification. Ethyl chloride (pure or as 2.0 M Et_2O solution), Mg (turnings), triethylamine, acetic anhydride, and MEM chloride were purchased from Aldrich Co. and used without further purification. Deuterium oxide and sulfuric acid-d_2 were purchased from Norell Chemical Co. and used as received. Bromoethane-*1,1*-d_2 was used as received from Merck Sharp & Dohme/Isotopes. Alcohol **31** was prepared according to the method of Hiyama.[31] Syn isomer **33** was prepared by inversion of the carbinol center in **31**.[32]

Typical Experimental Procedure for Zirconium-Catalyzed Ethylmagnesation. Alcohol **31** (0.85 g, 4.0 mmol) was dissolved in anhydrous Et_2O (20.0 mL). The mixture was cooled to 0 °C, and 20 mL (1 M, 20 mmol) of ethylmagnesium chloride was added dropwise by a syringe. The mixture was then allowed to warm to 20 °C, after which 58.4 mg of Cp_2ZrCl_2 (0.20 mmol) was added. The mixture was stirred at 25 °C for 12 h. The solution was chilled to −78 °C and charged with 11.0 mL (100 mmol) of freshly distilled trimethyl borate. The reaction was then allowed to warm to 25 °C; after 1 h, 100 mL of 2 M NaOH and 100 mL of 30% H_2O_2 were added. Twelve hours later, the mixture was washed with three 200-mL portions of CH_2Cl_2. The combined organic layers were then treated with a saturated solution of NaCl (200 mL) and subsequently dried over anhydrous $MgSO_4$. Removal of solvent and silica gel chromatography (8:1 hexanes/EtOAc) afforded 740 mg (72% yield) of **32**. Reaction on a 250-mg scale provided the desired product in 80% yield. GC analysis of the corresponding lactones (see below) and comparison with an authentic 1:1 diastereomeric mixture indicated a >95:5 ratio in favor of **32**.[33]

Typical Experimental Procedure for Stoichiometric Addition of 40 to Alkenes. Cp_2ZrCl_2 (292 mg, 1.0 mmol) was dissolved in 5.0 mL of freshly distilled anhydrous THF and then cooled to −78 °C. To this solution was added EtMgCl (2.0 mL, 2.0 mmol), and the mixture was stirred for 1 h at −78 °C. The Cp_2ZrEt_2 formed was then added to **11** (198 mg, 1.0 mmol) at 25 °C, and the solution was stirred for 4 h. The solution was quenched with 2.0 M HCl at 0 °C and washed with three 100-mL portions of CH_2Cl_2. Organic layers were washed with a saturated solution of sodium bicarbonate. Removal of solvent in vacuo afforded a yellow oil, which was passed through a short column of silica gel (2 cm). GLC analysis of the product showed 62% conversion to a 2:1 mixture of **44**:**43**.

2(*R,S*)-Ethyl-3(*R,S*)-hydroxydodecan-1-ol (2). IR (KBr): 3350 (br), 2970 (s), 2920 (s), 2810 (s), 1495 (m), 1080 (w), 1030 (m) cm^{-1}. ^1H NMR: δ 3.85 (m, 1H, CH_2CHOH), 3.79 (ddd, 2H, J = 10.6, 6.7, 3.7 Hz, CH_2OH), 2.27 (m, 2H, OH), 1.62–1.31 (m, 5H, CH_2CHOH, $CHCH_2CH_3$, $CHCH_2OH$), 1.28 (s, 14H, alkyl), 0.97 (t, 3H, J = 7.6 Hz, $CHCH_2CH_3$), 0.89 (t, 3H, J = 7.3 Hz, $CH_2CH_2CH_3$). ^{13}C NMR: δ 75.4, 64.4, 46.0, 33.2, 31.8, 29.7, 29.6, 29.5, 29.3, 26.3, 22.6, 19.0, 14.0, 12.3. Anal. Calcd for $C_{14}H_{30}O_2$: C, 73.07; H, 13.03. Found: C, 73.06; H, 12.79.

(2′(*R,S*),4′-Dihydroxy-3′(*R,S*)-ethylbutyl)cyclohexane (4). IR (KBr): 3350 (br), 2920 (s), 2850 (s), 1700 (w), 1450 (s), 1380 (s), 1320 (s), 1270 (m), 1150 (m), 1100 (s), 1050 (s), 980 (s), 900 (m) cm^{-1}. ^1H NMR: δ 3.97 (d, 1H, J = 8 Hz, $CHOH$), 3.75 (m, 2H, CH_2OH), 3.15

(29) See ref 3c. Catalytic cyclomagnesation of **55** proceeds smoothly in contrast to recent reports that hydroxyl-containing acyclic dienes are resistant to this type of cyclization. See: Wischmeyer, U.; Knight, K. S.; Waymouth, R. M. *Tetrahedron Lett.* **1992**, *33*, 7735–7738.

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(33) To quench the reaction with O_2, the reaction mixture was cooled to 0 °C. A gentle stream of O_2 gas (dried over P_2O_5) was introduced into the solution for 5 min at 0 °C and for 30 min at 22 °C. The reaction was subsequently treated with sodium bicarbonate and worked up as described above.

(s, 1H, CH_2OH), 2.91 (s, 1H, CHO*H*), 1.9–1.0 (m, 16H, cyclohexyl CH, CH_2CHOH, and CH_3CH_2, CH_3CH_2CH), 0.92 (t, 3H, J = 7.6 Hz, CH_3). ^{13}C NMR: δ 72.27, 64.35, 46.18, 40.57, 34.40, 34.06, 32.68, 26.57, 26.36, 26.14, 18.29, 12.23. Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.07. Found: C, 71.86; H, 12.33.

(2′(*R*,*S*),4′-Dihydroxy-3′(*R*,*S*)-ethylbutyl)benzene (6). IR (KBr): 3350 (br), 2950 (m), 2920 (m), 2860 (m), 2360 (m), 2340 (m), 1750 (s), 1450 (m), 1380 (m), 1240 (s), 1050 (s), 750 (s) cm^{-1}. ^1H NMR: δ 7.4–7.2 (m, 5H, phenyl CH), 4.2–3.6 (m, 3H, C*H*OH, CH_2OH), 2.9 (m, 2H, CH_2CHOH), 1.65 (m, 1H, $CHCH_2OH$), 1.5 (m, 2H, CH_3CH_2), 1.01 (t, 3H, J = 7.3, CH_3). ^{13}C NMR: δ 129.28, 128.68, 126.50, 76.28, 64.18, 45.41, 18.08, 12.21. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.87; H, 9.27.

(1′(*R*,*S*),3′-Dihydroxy-2′(*R*,*S*)-ethylpropyl)cyclohexane (8). IR (KBr): 3350 (br), 2910 (s), 2850 (s), 2810 (s), 1490 (m), 1050 (m), 1010 (m) cm^{-1}. ^1H NMR: δ 3.90 (m, 1H, CH_2OH), 3.78 (br d, 1H, J = 10.1 Hz, CH_2OH), 3.53 (br d, 1H, J = 8.5 Hz, C*H*OH), 2.41 (br s, 2H, OH), 2.00–1.05 (m, 14H, cycloalkyl, CH_2), 0.92 (t, 3H, J = 8 Hz, CH_2CH_3). ^{13}C NMR: δ 80.1, 64.5, 42.2, 40.5, 29.7, 29.0, 26.3, 26.0, 25.8, 15.6, 12.1. Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.99; H, 11.80. Found: C, 70.79; H, 11.52.

(1′(*R*,*S*),3′-Dihydroxy-2′(*R*,*S*)-ethylpropyl)benzene (10). IR (KBr): 3350 (br), 2960 (s), 2930 (s), 2880 (s), 1730 (s), 1600 (w), 1500 (m), 1450 (s), 1360 (s), 1240 (s), 1100 (m), 1030 (s), 700 (s) cm^{-1}. ^1H NMR: δ 7.35 (m, 5H, phenyl CH), 5.00 (br s, 1H, C*H*OH), 3.71 (d, 2H, J = 4.9 Hz, CH_2OH), 3.30 (br s, 1 H, CHO*H*), 2.73 (br s, 1H, CH_2OH), 1.85 (m, 1H, $CHCH_2OH$), 1.28 (m, 2H, J = 7.3 Hz, CH_3CH_2), 0.87 (t, 3H, J = 7.3 Hz, CH_3). ^{13}C NMR: δ 128.1, 127.2, 126.2, 77.0, 63.6, 47.8, 17.8, 12.0. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.28; H, 9.13.

2(*R*,*S*)-Ethyl-3(*S*,*R*)-methoxydodecan-1-ol (12). IR (KBr): 3420 (br), 2960 (s), 2910 (s), 2840 (s), 1480 (m), 1390 (w), 1100 (s), 1010 (m) cm^{-1}. ^1H NMR: δ 3.84 (dd, 1H, J = 10.0, 1.0 Hz, CH_2OH), 3.59 (ddd, 1H, J = 4.6, 2.1, 1.2 Hz, CH_2OH), 3.38 (s, 3H, OCH_3), (1H, ddd, J = 10.4, 5.5, <1 Hz, C*H*OCH_3), 2.95 (br s, 1H, CH_2OH), 1.58 (m, 1H, $CHCH_2OH$), 1.46 (m, 2H, CH_2CHOCH_3), 1.28 (s, 16H, alkyl, $CHCH_2CH_3$), 0.96 (t, 3H, J = 7.3 Hz, $CHCH_2CH_3$), 0.89 (t, 3H, J = 6.7 Hz, $CH_2CH_2CH_3$). ^{13}C NMR: δ 86.74, 64.35, 59.25, 45.56, 33.19, 32.26, 31.2, 30.9, 30.8, 30.6, 26.4, 23.9, 22.78, 15.4, 13.1. Anal. Calcd for $C_{15}H_{32}O_2$: C, 73.71; H, 13.20. Found: C, 73.42; H, 12.98.

2(*R*,*S*)-Ethyl-3-(*S*,*R*)-((methoxyethoxy)methoxy)dodecan-1-ol (14). IR (KBr): 3472 (br), 2930 (s), 2855 (s), 1465 (m), 1383 (w), 1100 (m), 1010 (s) cm^{-1}. ^1H NMR: δ 4.78 (d, 1H, J = 7.4 Hz, $OCH_2OCH_2CH_2OCH_3$), 4.75 (d, 1H, J = 7.0 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.89 (ddd, 1H, J = 11.3, 4.3, 1.9 Hz, CH_2OH), 3.80 (dt, 1H, J = 10.3, 4.6 Hz, CH_2OH), 3.70 (t, 2H, J = 6.6 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.61 (m, 1H, $CH_2CHOCH_2OCH_2CH_2OCH_3$), 3.58 (t, 2H, J = 4.4 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.40 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 2.76 (ddd, 1H, J = 6.1, 4.3, 1.6 Hz, CH_2OH), 1.39–1.65 (m, 5H, CH_2CHOH, $CHCH_2CH_3$, $CHCH_2OH$), 1.28 (s, 14H, alkyl), 0.94 (t, 3H, J = 7.6 Hz, $CHCH_2CH_3$), 0.88 (t, 3H, J = 7.1 Hz, $CH_2CH_2CH_3$). ^{13}C NMR: δ 96.2, 81.9, 73.0, 68.7, 62.9, 60.3, 45.8, 33.2, 33.1, 31.1, 30.9, 30.8, 30.6, 26.3, 24.0, 22.3, 15.4, 13.2. Anal. Calcd for $C_{18}H_{38}O_4$: C, 67.95; H, 11.94. Found: C, 67.76; H, 11.75.

2(*R*,*S*)-Ethyl-3(*S*,*R*)-*tert*-butoxydodecan-1-ol (16). IR (KBr): 3471 (br), 2965 (br), 2874 (br), 1464 (m), 1389 (m), 1364 (m), 1194 (m), 1094 (m), 1074 (m) cm^{-1}. ^1H NMR: δ 4.05 (d, 1H, J = 7.8 Hz, CH_2OH), 3.7 (dt, 1H, J = 9.0, 3.0 Hz, $(CH_3)_3COCH$), 3.55 (t, 1H, J = 5.4 Hz, CH_2OH), 1.85 (m, 1H, CH_3CH_2CH), 1.30 (s, 14H, aliphatic CH), 1.20 (s, 9H, $OC(CH_3)_3$), 0.97 (t, 3H, J = 7.0 Hz, $CHCH_2CH_3$), 0.89 (t, 3H, J = 6.9 Hz, $CH_2CH_2CH_3$). ^{13}C NMR: δ 76.2, 74.3, 62.3, 43.3, 31.8, 29.9, 29.8, 29.6, 29.5, 29.2, 28.9, 26.8, 28.8, 25.3, 22.1, 14.1, 12.0. Anal. Calcd for $C_{18}H_{38}O_2$: C, 75.46; H, 13.37. Found: C, 75.38; H, 13.24.

2(*R*,*S*)-ethyl-3(*S*,*R*)-(benzyloxy)dodecan-1-ol (18). IR (KBr): 3444 (br), 2957 (s), 2854 (s), 1464 (m), 1378 (w), 1087 (s), 733 (m), 697 (m) cm^{-1}. ^1H NMR: δ 7.25 (m, 5H, phenyl CH), 4.65 (d, 1H, J = 11.2 Hz, $OCH_2C_6H_5$), 4.40 (d, 1H, J = 11.5 Hz, $OCH_2C_6H_5$), 3.90 (d, 1H, J = 11.23 Hz, $CHCH_2OH$), 3.62 (m, 2H, $CHCH_2OH$, $CHOCH_2Ph$), 1.65 (m, 1H, $CHCH_2OH$), 1.45 (m, 2H, $CH_3CH_2CHCH_2OH$), 1.28 (s, 14H, aliphatic CH), 0.97 (t, 3H, J = 7.0 Hz, $CHCH_2CH_3$), 0.89 (t, 3H, J = 5.5 Hz, $CH_2CH_2CH_3$). ^{13}C NMR: δ 127.4, 127.7, 83.3, 72.3, 62.8, 44.4, 31.9, 31.3, 29.8, 29.7, 29.6, 29.5, 29.3, 27.3, 26.3, 14.0, 12.0. Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.71; H, 11.31. Found: C, 78.80; H, 11.50.

(3′(*R*,*S*)-Ethyl-4′-hydroxy-2′(*S*,*R*)-methoxybutyl)cyclohexane (20). IR (KBr): 3450 (br), 2930 (s), 2850 (m), 1450 (w), 1090 (m), 1050 (w) cm^{-1}. ^1H NMR: δ 3.83 (dt, 1H, J = 11, 3.1 Hz, C*H*OCH_3), 3.56 (m, 1H, HC*H*OH), 3.35 (s, 3H, OCH_3), 2.91 (dd, 1H, J = 7.1 Hz, 3.9), 1.8–1.1 (m, 16H, cyclohexyl CH_2 and $CHCH_2$), 0.94 (t, 3H, J = 7.2 Hz, CH_3). ^{13}C NMR: δ 85.1, 62.6, 58.2, 44.7, 39.4, 34.3, 33.7, 26.5, 26.3, 21.6, 12.0. Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23. Found: C, 73.00; H, 12.18.

(2′(*R*,*S*)-Methoxy-3′(*S*,*R*)-Ethyl-4′-hydroxybutyl)benzene (22). IR (KBr): 3475 (br), 3050 (s), 2946 (br), 1750 (s), 1610 (m), 1505 (s), 1495 (s), 1350 (m), 1250 (m), 1100 (br), 743 (s), 699 (s) cm^{-1}. ^1H NMR: δ 7.3 (m, 5H, phenyl CH), 3.95 (d, 1H, J = 11.1 Hz, CH_2OH), 3.7 (m, 1H, CH_2OH), 3.5 (dt, 1H, J = 6.3, 4.2 Hz, C*H*OCH_3), 3.3 (s, 3H, OCH_3), 2.9 (dd, 2H, J = 14.1, 6.0 Hz, CH_3OCH_2), 1.6–1.4 (m, 3H, $CHCH_2OH$, $CHCH_2CH_3$), 0.90 (t, 3H, J = 7.3, CH_2CH_3). ^{13}C NMR: δ 129.2, 128.3, 126.1, 86.7, 62.4, 58.7, 44.0, 38.1, 21.6, 11.6. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.87; H, 9.64.

(2′(*R*,*S*)-Ethyl-3′-hydroxy-1′(*S*,*R*)-methoxypropyl)cyclohexane (24). IR (KBr): 3450 (br), 2910 (s), 2850 (s), 1450 (m), 1080 (s), 1005 (m) cm^{-1}. ^1H NMR: δ 3.84 (br dt, 1H, J = 10.9, 4.1 Hz, CH_2OH), 3.62 (ddd, 1H, J = 11.3, 6.7, 4.6 Hz, CH_2OH), 3.47 (s, 3H, OCH_3), 3.05 (dd, 1H, J = 7.0, 4.2 Hz, CH_2OH), 2.94 (dd, 1H, J = 6.7, 3.7 Hz, C*H*OCH_3), 1.94–1.03 (m, 14H, alkyl), 0.97 (t, 3H, J = 7.3 Hz, CH_2CH_3). ^{13}C NMR: δ 90.9, 62.6, 61.6, 42.7, 41.3, 30.1, 28.8, 26.5, 26.3, 26.2, 22.5, 11.8. Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.07. Found: C, 71.73; H, 11.89.

(2′(*R*,*S*)-Ethyl-3′-hydroxy-1′(*S*,*R*)-methoxypropyl)benzene (26). IR (KBr): 3450 (br), 3030 (m), 2960 (s), 2930 (s), 2820 (s), 1600 (w), 1500 (m), 1450 (s), 1370 (m), 1350 (m), 1100 (s), 1040 (s), 760 (s), 700 (s) cm^{-1}. ^1H NMR: δ 7.4–7.25 (m, 5H, phenyl CH), 4.13 (d, 1H, J = 7.8 Hz, C*H*OMe), 3.9–3.6 (m, 2H, CH_2OH), 3.35 (br s, 1H, CH_2OH), 3.19 (s, 3H, OCH_3), 1.75 (m, 1H, $CHCH_2$), 1.18 (m, 2H, CH_2CH_3), 0.83 (t, 3H, J = 7.3 Hz, CH_3). ^{13}C NMR: δ 128.3, 127.8, 127.3, 89.1, 64.4, 57.2, 48.4, 20.9, 11.6. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.88; H, 9.39.

(2′(*R*,*S*)-Ethyl-3′-hydroxy-1′(*R*,*S*)-((methoxyethoxy)methoxy)propyl)cyclohexane (28). IR (KBr): 3400 (br), 2954 (br), 1710 (w), 1490 (m), 1250 (w), 1102 (m), 1020 (m) cm^{-1}. ^1H NMR: δ 4.7 (d, 1H, J = 6.0 Hz, $CH_3OCH_2CH_2OCH_2O$), 4.65 (d, 1H, J = 6.0 Hz, $CH_3OCH_2CH_2OCH_2O$), 3.8 (m, 2H, CH_2OH), 3.6 (m, 4H, $CH_3OCH_2CH_2OCH_2O$), 3.3 (s, 3H, $OCH_2CH_2OCH_3$), 3.25 (m, 1H, $CHOCH_2OCH_2CH_2OCH_3$), 2.9 (br s, 1H, CH_2OH), 1.8–1.0 (m, 13H, cyclohexyl CH and CH_3CH_2CH), 0.9 (t, 3H, J = 6.2, CH_2CH_3). ^{13}C NMR: δ 97.6, 86.6, 71.5, 67.7, 61.4, 58.8, 43.0, 40.9, 30.3, 27.7, 26.3, 26.1, 21.7, 11.8. Anal. Calcd for $C_{15}H_{30}O_4$: C, 65.65; H, 11.02. Found: C, 65.52; H, 10.80.

Proof of Stereochemistry for Reactions of Allylic Alcohols and Ethers. GLC analysis of the derived acetonides and methylene acetals provided all the ratios indicated in the text and tables. Key data are shown in Table VII. Derivatives **i**, **ii**, and **v** were obtained from reactions of allylic ethers, and **iii**, **iv**, and **vi** were prepared by treatment of 1,3-diols isolated from reactions of allylic alcohols with 2,2-dimethoxypropane or *p*-formaldehyde with catalytic *p*-TsOH. Methyl esters were first deprotected ($SiCl_4$, NaI,[34] or $TiCl_4$[35]). Treatment of ethylmagnesation products of MEM ethers with $ZnCl_2$ afforded methylene acetals **v** and **vi** (minor isomer).

Typical Procedure for Measurement of the Effect of Zirconocene Concentration on Reaction Rate. A series of five reactions was set up in accordance with the catalytic procedure, except that the reactions were performed at 0.02 M. As an example, in studies with regard to allylic ether **11**, reaction vessels respectively contained 188 mg (0.95 mmol), 178 mg (0.90 mmol), 205 mg (1.04 mmol), 189 mg (0.96 mmol), and 187 mg (0.95 mmol) of the substrate. After addition of requisite amounts of THF, 1.4 mg (0.5 mol %), 2.6 mg (1.0 mol %), 4.5 mg (1.5 mol %), 5.6 mg (2.0 mol %), and 6.9 mg (2.5 mol %) of Cp_2ZrCl_2 were added, respectively. After addition of the internal reference (hexadecane, 1.0 equiv with respect to alkene) and EtMgCl (3 equiv), aliquots (~0.1 mL) were removed at 10-min intervals via cannula. This process continued until GLC analysis indicated ~10% product formation (based on standard reference and starting material). Conversion was plotted against time to obtain the initial rate. The resulting reaction rates were then plotted against the zirconium concentration to afford a nonlinear dependence of the rate on the amount of zirconocene.

2(*S*,*R*)-Ethyl-3(*R*,*S*)-methyl-4(*S*,*R*)-hydroxytridecan-1-ol (32). IR (KBr): 3420 (br), 2960 (s), 2910 (s), 2840 (s), 1480 (m), 1390 (w), 1100

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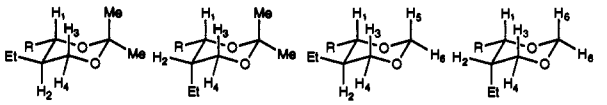
(35) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809–812.

Table VII. Spectral Data for Acetonides and Methylene Acetals from Products of Ethylmagnesations of Allylic Alcohols and Ethers **1**, **7**, **11**, and **23** (Tables I and II)



i R=*n*-nonyl ii R=cyclohex. iii R=*n*-nonyl iv R=cyclohex. v R=*n*-nonyl vi R=*n*-nonyl

i		ii		iii		iv		v		vi	
	J, Hz		*J*, Hz		*J*, Hz		*J*, Hz		*J*, Hz		*J*, Hz
J_{34}	11.5	J_{34}	11.6	J_{34}	11.6	J_{34}	10.8	J_{34}	11.1	J_{34}	11.2
J_{24}	4.9	J_{24}	5.2	J_{24}	0.9	J_{24}	1.6	J_{24}	4.6	J_{23}	~1
J_{23}	11.5	J_{23}	9.8	J_{23}	1.8			J_{46}	0.7		
								J_{23}	11.1		

(s), 1010 (m) cm^{-1}. ^{1}H NMR: δ 3.54 (m, 1H, CH_2CHOH), 3.52 (dd, 1H, J = 11.0, 3.3 Hz, CH_2OH), 3.44 (dd, 1H, J = 11.0, 3.7 Hz, CH_2-OH), 1.82–1.72 (m, 2H, $CH_3CH_2CHCH_2OH$, $CH_3CHCHOH$), 1.51 (m, 2H, J = 4.3 Hz, CH_2CHOH), 1.23 (m, 16H, aliphatic), 0.94 (t, 3H, J = 7.3 Hz, $CHCH_2CH_3$), 0.91 (d, 3H, J = 7.0 Hz, $CHCH_3$), 0.88 (t, 3H, J = 7.0 Hz, $CH_2CH_2CH_3$). ^{13}C NMR: δ 86.7, 64.3, 59.2, 45.5, 33.2, 32.2, 31.2, 30.9, 30.8, 30.6, 26.4, 23.9, 22.78, 15.4, 13.1. Anal. Calcd for $C_{16}H_{34}O_2$: C, 74.36; H, 13.26. Found: C, 74.62; H, 13.44.

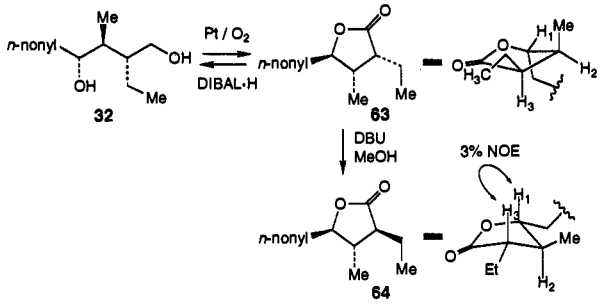
2(*R*,*S*)-Ethyl-3(*S*,*R*)-methyl-4(*S*,*R*)-hydroxytridecan-1-ol (34). IR (KBr): 3290 (br), 2970 (s), 2930 (s), 2870 (s), 1490 (m), 1400 (m), 1060 (m) cm^{-1}. ^{1}H NMR: δ 4.42 (br, 1H, CH_2OH), 3.56 (dd, 1H, J = 10.6, 6.7 Hz, CH_2CHOH), 3.45 (m, 2H, CH_2OH), 1.62 (m, 1H, $CHCH_3$), 1.45 (1H, m, $CHCH_2CH_3$), 1.31 (m, 1H, CH_2CHOH), 1.28 (br s, 16 H, alkyl), 0.90 (t, 3H, J = 7.6 Hz, $CHCH_2CH_3$), 0.84 (t, 3H, J = 7.3 Hz, $CH_2CH_2CH_3$), 0.77 (d, 3H, J = 7.2 Hz, $CHCH_3$). ^{13}C NMR: δ 76.1, 62.1, 48.3, 40.1, 35.7, 31.8, 29.7, 29.64, 29.6, 29.3, 26.6, 24.4, 22.6, 14.1, 12.5, 5.6. Anal. Calcd for $C_{16}H_{34}O_2$: C, 74.36; H, 13.26. Found: C, 74.50; H, 13.07.

2(*S*,*R*)-Ethyl-3(*R*,*S*)-methyl-4-(*S*,*R*)-((methoxyethoxy)methoxy)-tridecan-1-ol (36). IR (KBr): 3460 (br), 3470 (s), 3430 (s), 3350 (s), 1680 (w), 1490 (m), 1400 (m), 1310 (w), 1260 (w), 1210 (m), 1170 (s), 1120 (s), 1040 (s) cm^{-1}. ^{1}H NMR: δ 4.74 (dd, 2H, J = 7.8, 1.5 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.81–3.55 (m, 6H, $OCH_2OCH_2CH_2OCH_3$, CH_2OH), 3.35 (s, 3H, OCH_3), 1.8–1.76 (m, 1H, $CH_3CHCHCH_2CH_3$), 1.55 (m, 1H, $CH_3CH_2CHCH_2OH$), 1.35–1.10 (m, 22H, aliphatic), 0.89 (t, 3H, J = 6.1 Hz, $CHCH_2CH_3$), 0.86 (d, 3H, J = 6.1 Hz, $CHCH_3$), 0.84 (t, 3H, J = 6.1 Hz, $CH_2CH_2CH_3$). ^{13}C NMR: δ 95.1, 82.0, 71.7, 67.5, 62.3, 58.9, 41.5, 37.1, 31.8, 31.6, 29.7, 29.5, 29.4, 29.2, 25.1, 23.6, 22.6, 14.0, 12.2, 11.5. Anal. Calcd for $C_{20}H_{42}O_4$: C, 69.32; H, 12.22. Found: C, 69.58; H, 12.35.

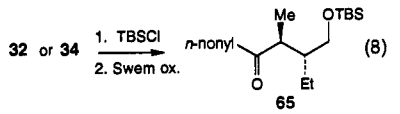
2(*R*,*S*)-Ethyl-3(*S*,*R*)-methyl-4(*S*,*R*)-((methoxyethoxy)methoxy)tridecan-1-ol (38). IR (KBr): 3446 (br), 2925 (s), 2855 (s), 1464 (s), 1379 (m), 1132 (s), 1043 (s) cm^{-1}. ^{1}H NMR (major diastereomer): δ 4.81 (d, 1H, J = 7.0 Hz, $OCH_2OCH_2CH_2OCH_3$), 4.71 (d, 1H, J = 7.1 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.60 (m, 7H, $OCH_2CH_2OCH_3$, $CHOCH_2$-$OCH_2CH_2OCH_3$, CH_2OH), 3.38 (s, 3H, OCH_3), 1.82–1.05 (m, 20H, aliphatic), 0.89 (m, 9H, CH_2CH_3, $CHCH_3$, $CHCH_2CH_3$). ^{13}C NMR (major diastereomer): δ 94.6, 81.5, 71.7, 67.5, 62.9, 58.9, 45.2, 36.4, 31.8, 31.5, 29.8, 29.7, 29.5, 29.2, 25.5, 23.1, 22.6, 14.0, 12.0, 9.2. Anal. Calcd for $C_{20}H_{42}O_4$: C, 69.31; H, 12.22. Found: C, 69.66; H, 12.16.

Proof of Stereochemistry for Products of Reactions of Homoallylic Alcohols and Ethers. As illustrated below, diol **32** was converted to lactone **63**, according to the procedure of Heyns.[36] Treatment of **63** with excess DIBAL-H (–78 °C) regenerated **32**; this experiment proves that no epimerization occurs under the lactone formation conditions. Partial ^{1}H NMR of **63** (500 MHz): δ 4.03 (ddd, 1H, J = 11.1, 8.5, 4.5 Hz, H1), 2.50 (1H, dd, J = 15.5, 8.0 Hz, H3), 2.30 (ddq, 1H, J = 10.2, 7.2, 2.8 Hz, H2). Irradiation of the CH_3 doublet at δ 1.51 resulted in the collapse of H2 into a dd (J = 8.0, 4.4 Hz); J_{12} = 4.4 Hz and J_{23} = 8.0 Hz. NOE experiments (500 MHz): irradiation of H1 gave enhancement for H2 (2.3%), whereas none was observed for H3. Irradiation of H3 afforded 2.3% enhancement of H2 and none for H1. Irradiation of H2 resulted in 8.1% and 3.8% enhancement of H3 and H1, respectively.

Treatment of **63** with LDA for 3 h (–78 °C) followed by quenching with MeOH gave a 1:1 mixture of diastereomers, **63** and, presumably, the all-equatorial **64**. Subjection of the mixture, as well as of the pure **63**, to equilibrating conditions (DBU/MeOH) for 12 h resulted in the exclusive formation of **64**. In accordance with our structural assignments, irradiation of H1 in **64** led to 3% enhancement of H3.



Equation 8 illustrates how it was established that the predominant isomer formed in carbomagnesations of **33** is **34**. Ketones **65** obtained from the selective silylation and oxidation (Swern) of **31** and **33** are identical according to ^{1}H NMR, ^{13}C NMR, and IR spectra.



4(*R*,*S*)-((*tert*-Butyldimethylsilyl)oxy)-3(*S*,*R*)-methoxy-2(*S*,*R*)-ethyltridecan-1-ol (51). IR (KBr): 3450 (br), 2957 (s), 2927 (s), 2856 (s), 1463 (w), 1255 (w), 1098 (br m), 835 (m), 774 (m) cm^{-1}. ^{1}H NMR: δ 3.83 (m, 1H, $CHOCH_3$), 3.6 (m, 1H, $CHOSi(t\text{-}Bu)Me_2$), 3.46 (s, 3H, OCH_3), 3.43 (m, 1H, CH_2OH), 3.16 (m, 1H, CH_2OH), 1.6–1.2 (m, 19H, alkyl CH_2 and $CHCH_2OH$), 0.89 (br s, 15H, $(CH_3)_3C$, CH_2CH_3, CH_2CH_3), 0.07 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$). ^{13}C NMR: δ 88.3, 73.2, 63.3, 42.2, 33.5, 31.9, 30.0, 29.5, 29.3, 25.9, 24.9, 22.7, 22.2, 14.1, 11.9, –4.5, –5.0. Anal. Calcd for $C_{22}H_{48}O_3$: C, 67.98; H, 12.45. Found: C, 67.81; H, 12.19.

1-(Benzyloxy)-2(*S*,*R*)-((*tert*-butyldimethylsilyl)oxy)-3(*S*,*R*)-(hydroxymethyl)pentane (53). IR (KBr): 3445 (br), 3036 (w), 2959 (s), 2931 (s), 2860 (s), 1461 (m), 1363 (w), 1250 (s), 1096 (s), 835 (s), 779 (s), 695 (m) cm^{-1}. ^{1}H NMR: δ 7.30 (m, 5H, phenyl CH), 4.50 (d, 2H, J = 4.64 Hz, $OCH_2C_6H_5$), 3.98 (dt, 1H, J = 5.6, 0.50 Hz, $C_6H_5CH_2$-$OCH_2CHOTBS$), 3.85 (d, 1H, J = 11.7 Hz, CH_2OH), 3.60 (m, 1H, CH_2OH), 3.45 (t, 2H, J = 5.8 Hz, $CH_2OCH_2C_6H_5$), 2.90 (br s, 1H, CH_2OH), 1.55–1.40 (m, 3H, $CHCH_2CH_3$, $CHCH_2CH_3$), 0.98 (t, 3H, J = 6.3 Hz, $CHCH_2CH_3$), 0.80 (s, 9H, $SiCH(CH_3)_3(CH_3)_2$), 0.50 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.25 (s, 3H, $SiC(CH_3)_3(CH_3)_2$). ^{13}C NMR: δ 127.4, 127.3, 74.9, 73.4, 73.0, 61.9, 43.9, 25.7, 21.4, 20.2, 20.1, 12.3, –4.3, –5.0. Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.11; Si, 8.29. Found: C, 67.37; H, 9.89; Si, 8.06.

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(36) Heyns, K.; Blazejewicz, L. *Tetrahedron* **1960**, *9*, 67–75.