Enantio-, Diastereo-, and Regioselective Zirconium-Catalyzed Carbomagnesation of Cyclic Ethers with Higher Alkyls of Magnesium. Utility in Synthesis and Mechanistic Implications

Mary T. Didiuk,[1a] Charles W. Johannes, James P. Morken,[1b] and Amir H. Hoveyda*

Contribution from the Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02167

Received December 2, 1994[⊗]

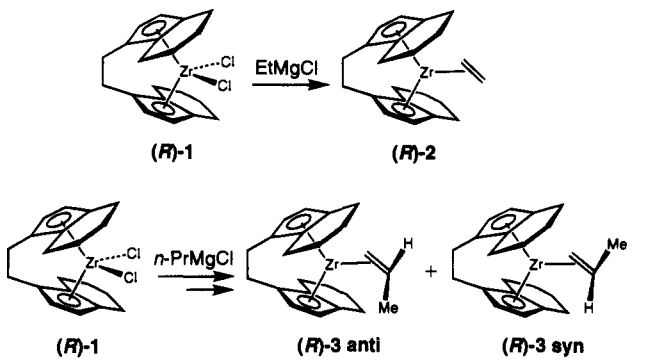
Abstract: Zirconocene-catalyzed carbomagnesation reactions of cyclic ethers **4** and **7** with *n*-PrMgCl and *n*-BuMgCl afford homoallylic and bishomoallylic alcohols **5**, **8**, **9**, and **11** in ~40% yield and exceptional levels of enantioselectivity and regiocontrol. Where *n*-BuMgCl is used as the alkylating agent, high levels of diastereochemical control are also observed (cf. **9** vs **10** in entries 4 and 5 of Table 1). Studies reported herein underline a number of important mechanistic issues: (i) Although zirconocene−alkene complexes **3** exist as a mixture of diastereomers in solution (syn and anti), it is only one of the isomers which reacts to afford the observed products. (ii) Whereas insertion of an alkene substrate into the unsymmetric complexes **3** and **18** proceeds with low levels of regioselectivity at 22 °C, at 70 °C high levels of regiocontrol are observed (cf. intermediacy of **20** *vs* **24** in Scheme 4). In this context, various mechanistic experiments shed light on factors that may be responsible for the observed temperature effect. (iii) Unusual modes of preference for the regioselectivity in β-hydride abstraction of intermediate dialkylzirconocene are reported; these observations may be accounted for through consideration of the steric effects imposed by the cyclohexyl groups of the chiral ligand and the stereoelectronic requirements of the elimination reaction.

Introduction

Recent work in these laboratories has demonstrated that the zirconium-catalyzed ethylmagnesation[2] offers a simple method for the enantioselective C−C bond formation through addition of EtMgCl to cyclic ethers in the presence of 0.4−10 mol % [EBTHI]$ZrCl_2$ (**1**).[3] A variety of cyclic allylic ethers can be used in this transformation, and products are obtained in 90−98% ee and 60−75% yields.[4] Furthermore, asymmetric catalytic ethylmagnesation has been employed to effect the kinetic resolution of unsaturated pyrans and furans.[5]

When higher alkyls of Mg are used in carbomagnesation—particularly in the presence of the chiral metallocene **1**—the catalytic cycle takes on added complexity. For example, unlike **2** (Scheme 1),[6] a critical intermediate in asymmetric ethylmagnesation, the related zirconocenes **3**, derived from *n*-PrMgCl,[7] may react through either of the metal−alkene isomers (*R*)-**3**-*syn* or -*anti* to afford different product diastereomers. In addition, unlike the relatively symmetric **2**, in **3** there can be two distinct modes of alkene insertion (from the more or less substituted face of the metal−alkene complex), leading to the formation of different products. Because of these and related mechanistic and structural considerations, [EBTHI]Zr-catalyzed carbomagnesation with higher alkyls of Mg expands the scope of the enantioselective bond forming process and provides useful insights into the inner workings of the asymmetric catalytic cycle. Herein, we report the results of our studies on the enantioselective addition of *n*-PrMgCl and *n*-BuMgCl to 2,5-dihydrofuran (**4**) and 5,6-dihydropyran (**7**), catalyzed by nonracemic **1**.

Scheme 1



Results and Discussion

Diastereo- and Enantioselective Carbomagnesations. When **4** is treated with 5 equiv of *n*-PrMgCl in the presence of 10

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1995.

(1) (a) Recipient of an American Chemical Society Graduate Fellowship, sponsored by Monsanto Co., 1994−1995. (b) Recipient of an American Chemical Society Graduate Fellowship, sponsored by Glaxo Inc., 1993−1994.

(2) (a) Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285*, 43−51 and references cited therein. (b) Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G.; Muslukhov, R. R.; Lomakina, S. I.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1992**, 770−788. (c) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079−5080. (d) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266−6268. (e) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268−6270. (f) Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950−8952. (g) Lewis, D. P.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *32*, 6797−6800. (h) Houri, A. F.; Didiuk, M. T.; Xu, Z-M.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614−6624. (i) Suzuki, N.; Kondakov, D. Y.; Takahashi, T. *J. Am. Chem. Soc.* **1993**, *115*, 8485−8486.

(3) (a) Wild, F. R. W. P.; Wasiucionek, M.; Huttner, G.; Brintzinger, H. *J. Organomet. Chem.* **1985**, *288*, 63−67. (b) Grossman, R. B.; Doyle, R. A.; Buchwald, S. L. *Organometallics* **1991**, *10*, 1501−1505.

(4) (a) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6697−6698. (b) Houri, A. F.; Xu, Z-M.; Cogan, D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943−2944.

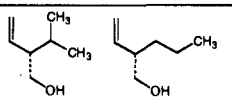
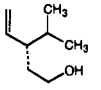
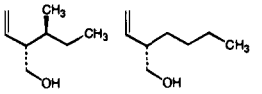
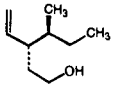
(5) (a) Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123−3124. (b) Visser, M. S.; Hoveyda, A. H. *Tetrahedron* **1995**, *51*, 4383−4394.

(6) Hoveyda, A. H.; Morken, J. P. *J. Org. Chem.* **1993**, *58*, 4237−4244.

(7) Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z-M. *J. Am. Chem. Soc.* **1992**, *114*, 6692−6697.

0002-7863/95/1517-7097$09.00/0

Table 1. Zirconium-Catalyzed Carbomagnesation of **4** and **7**[a]

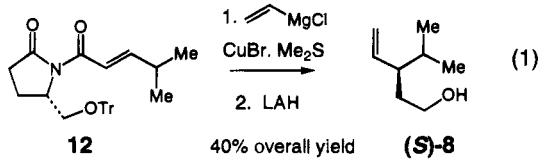
entry	substrate	major product(s)	temp (°C)	RMgCl	regioselectivity[b]	ee, %[c]	diastereoselectivity[d]
1			22	*n*-PrMgCl	2 : 1	99 (**5**), 99 (**6**)	--
2	**4**	**5** **6**	70	*n*-PrMgCl	20 : 1	94 (**5**)	--
3	 **7**	 **8**	22	*n*-PrMgCl	>25 : 1	98	--
4			22	*n*-BuMgCl	2 : 1	>99 (**9**), >99 (**10**)	15 : 1
5	**4**	**9** **10**	70	*n*-BuMgCl	15 : 1	90 (**9**)	13 : 1
6	 **7**	 **11**	22	*n*-BuMgCl	>25 : 1	>95	>25 : 1

[a] Conditions: 5 equiv of alkylMgCl, 10 mol % (*R*)-**1**, 16 h; all yields: 30–40% after silica gel chromatography. [b] Regioselectivities were determined by GLC (entries 1, 2, 4, and 5) or by ^{1}H NMR analysis (entries 3 and 6) in comparison with authentic regioisomers. [c] Enantiomeric excess determined by chiral GLC (CHIRALDEX-GTA by Alltech, entries 1–4) or analysis of the 300-MHz ^{1}H NMR spectrum of the derived (*S*)-MPTA esters in comparison with authentic enantiomers and authentic racemic materials (see supporting information). Analysis in entry 1 was performed on the derived acetates, and those of entries 4 and 5 on the derived epoxides (1:1 mixture of diastereomers). [d] Diastereomeric ratios determined by analysis of the 300-MHz ^{1}H NMR and 75-MHz ^{13}C NMR spectra.

mol % (*R*)-[EBTHI]$ZrCl_2$ in THF at 22 °C, products **5** and **6** are isolated in 35–40% yield and as a 2:1 ratio of isomers (Table 1, entry 1); GLC analysis indicates that both products are formed with 99% enantiomeric excess (ee). This is in contrast to the reaction of pyran **7** which, under identical conditions, affords the isopropyl adduct **8** as a single isomer (>25:1 in favor of the isopropyl adduct) and with excellent enantiofacial selectivity (98% ee). As shown in entry 2 of Table 1, *when carbomagnesation of furan 4 is performed at 70 °C, the level of regiochemical control is enhanced to 20:1 (GLC analysis)*; enantioselectivity is slightly diminished to 94% ee.

Similar results are obtained in reactions where *n*-BuMgCl is used. Catalytic asymmetric carbomagnesation of pyran **7** not only provides the *sec*-butyl derivative **11** with excellent enantioselectivity, but the reaction product is obtained with high diastereochemical control (minor isomer was not detected by ^{1}H NMR or ^{13}C NMR spectroscopy). In contrast, furan **4**, as shown in entries 4 and 5 of Table 1, affords the corresponding carbomagnesation product **9** with useful levels of regioselection only when the reaction is heated to 70 °C (90% ee, 15:1 diastereoselection, 40% yield).

Determination of Absolute Stereochemistry. The identity of the major enantiomers observed in reactions summarized in Table 1 was ascertained through comparison with authentic materials prepared according to established methods. The case of isopropyl adduct **8** is illustrative. As demonstrated in eq 1,



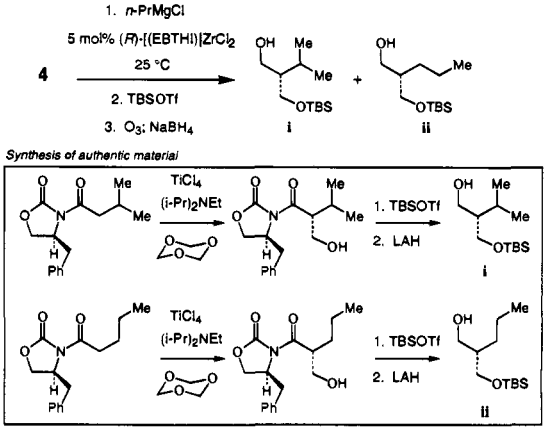
(1)

when non-racemic α,β-unsaturated imide **12** is treated with vinylmagnesium bromide and $CuBr{\cdot}Me_2S$ at −78 °C, the corresponding conjugate addition product is obtained with >95% diastereoselection (as judged by the 300-MHz ^{1}H NMR spectrum).[8] Comparison of the ^{1}H NMR of the derived (*S*)-MPTA ester clearly indicates that reduction of **13** with lithium aluminum hydride provides (*S*)-**8**, which is the enantiomer of the product obtained when (*R*)-[EBTHI]$ZrCl_2$ is used as the precatalyst in carbomagnesation of **7** with *n*-PrMgCl.[9]

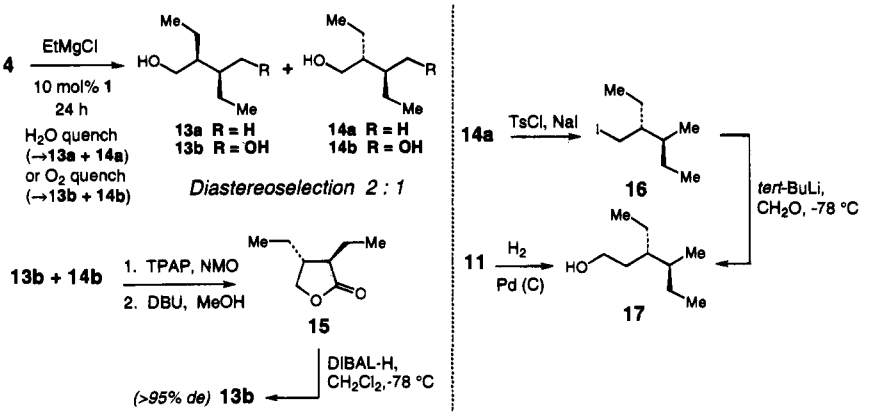
Determination of Relative Stereochemistry of Carbomagnesation Products. The stereochemical identity (relative) of **9** and **11** was established in the following manner: As shown in Scheme 2, ethylmagnesation of **4** with racemic [EBTHI]$ZrCl_2$ for an extended reaction time (24 h) affords double alkylation products **13** and **14** as a 2:1 mixture of diastereomers. When the diastereomeric mixture **13b** and **14b** (derived from O_2

(8) Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369–372.

(9) The streochemical identity of the isopropyl adduct (**5**) and *n*-propyl adduct (**6**) was determined in comparison to authentic materials, which were prepared in the manner illustrated below, according to procedures reported by Evans (see: (a) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049 and references cited therein); pure i was prepared when carbomagnesation was carried out at 70 °C. Analysis of the ^{1}H NMR spectra of the (*S*)-MTPA esters derived from **5** and **6** (i and ii, respectively) and comparison with authentic racemic mixtures indicated that the identity of the catalytic carbomagnesation product is as shown.



Scheme 2



quench) is subjected to oxidation and equilibration conditions (Scheme 2), the thermodynamically favored lactone **15** is obtained with >95% diastereoselectivity. Reduction of **15** with DIBAL-H regenerates **13b** in the diastereomerically pure form, thus establishing the identity of carbomagnesation products **13** and **14** as shown in Table 1.[10] The stereochemical assignment indicated in Table 1 for **9** and **11** is based on the observation that, as depicted in Scheme 2, **14a** is readily converted to **17** by the sequence shown; catalytic hydrogenation of **9** and **11** provides **14a** and **17**, respectively.

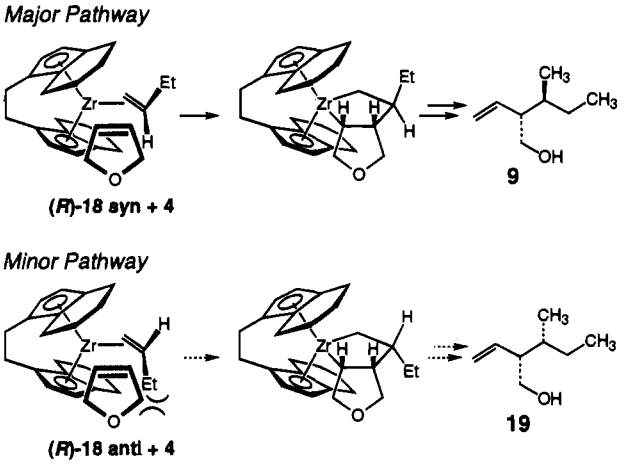
Thus, processes illustrated in Table 1 offer a one-step catalytic route to the enantio-, regio-, and diastereoselective formation of alcohols **5**, **8**, **9**, and **11**. Significantly higher yields can be attained but higher catalyst loadings are required. For example, with 50 mol % **1**, reaction of **4** with *n*-BuMgCl at 22 °C affords 75% yield of carbomagnesation products (after silica gel chromatography; 2.5:1 ratio of **5**:**6**, as judged by GLC analysis).

With 10 mol % chiral catalyst the yield of these reactions is ~35% after purification. However, since these processes generate little or no byproducts (simple passing of the unpurified residue through a small amount (plug) of silica gel is a sufficient method of purification), and because of the ready availability of the alkene substrates, the Zr-catalyzed carbomagnesation described above constitutes a useful route for the enantioselective synthesis of various chiral alcohols. The unsaturated alcohols prepared by this method may be subsequently functionalized to afford a number of other non-racemic materials.[4b]

The results summarized in Table 1 underline several important mechanistic issues which merit discussion:

(1) Diastereoselection in Reactions with *n*-BuMgCl. Mechanistic Implications. The high levels of diastereoselection observed in the formation of *sec*-butyl adducts **9** (as opposed to **19**, Scheme 3) and **11** have significant implications with regard to the reaction mechanism. These data illustrate that one of the two isomeric metal–alkene complexes ((*R*)-**18**-*syn*) reacts preferentially to afford the metallacyclopentane intermediate. To establish if the formation of one isomer of zirconocene–alkene complex (*R*)-**18** is inherently favored (syn or anti, see Scheme 3) or whether a mixture is formed but one metal–olefin complex reacts more rapidly, a simple ^{1}H NMR experiment was performed (in THF-d_8). Treatment of (*R*)-**1** with 3 equiv of *n*-PrMgCl at 0 °C leads to the disappearance of the two characteristic cyclopentadienyl signals at δ 6.28 (2H) and 5.85 (2H) and the appearance of four new doublets at δ 6.57, 5.89, 5.85, and 5.78, which can be assigned to the derived zirconocene alkyl chloride. After about 45 min at 22 °C, the aforementioned four signals are replaced by eight new doublets ($J \cong 3$ Hz) at δ 6.52, 6.50, 6.31, 6.08, 5.78, 5.74, 5.45, and 5.40 (1H each). The latter complex reacts with dihydrofuran **4** to afford carbomagnesation products **5** and **6** after addition of H_2O (see below for further discussion) and may be assigned to a 1:1 mixture of (*R*)-**3**-*syn* and (*R*)-**3**-*anti* (four doublets for each metal–olefin complex). Variations in temperature do not lead to any notable preference for one of the two diastereomers: formation at 22 °C followed by heating to 50 °C or preparation at 50 °C and cooling to 22 °C does not change the observed ratio. The aforementioned observations imply that, as shown in Scheme 3, steric interactions between the reacting cyclic ether and the alkyl substituent on the alkene ligand are significantly more prohibitive (in the minor pathway) than the repulsion that is caused by the latter group and cyclohexyl unit of the chiral ligand (in the major pathway). Thus, the zirconocene–olefin complex (*R*)-**18**-*syn* reacts with the alkene substrate to afford the corresponding anti diastereomer (*e.g.*, **9**) as the major product.[11]

Scheme 3

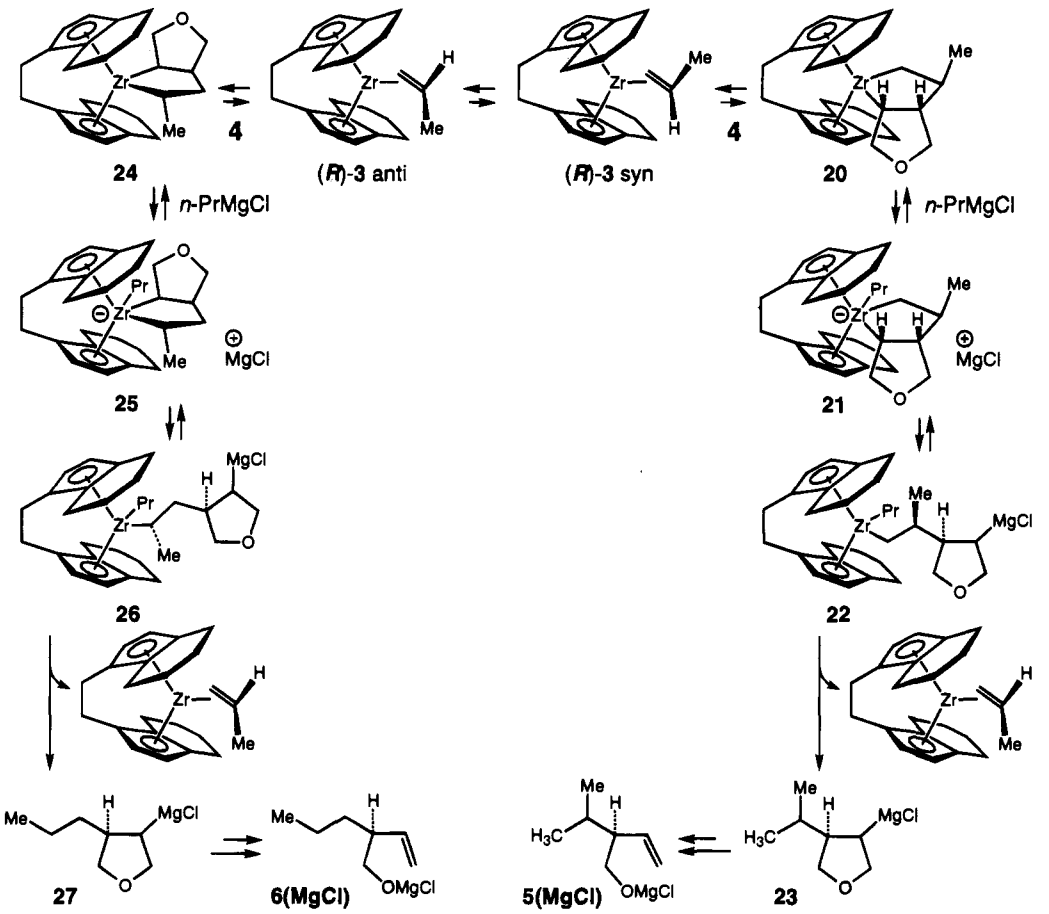


(2) Origin of Enhanced Regioselectivity at Elevated Temperatures. The increase in the observed levels of regioselectivity in the addition of *n*-PrMgCl and *n*-BuMgCl to 2,5-dihydrofuran (**4**) at elevated temperatures is notable. As shown

(10) The stereochemical identity of **13** and **14** was further ascertained through GLC analysis of the derived ethylidene acetals, indicating that it is the major diastereomer (**13b**) that is the chiral product (the minor compound (**14b**) is *meso*).

(11) The mechanism through which the two isomeric metal–alkene complexes may interconvert is not clear at the present time. Among various possibilities, isomerization through a zwitterionic intermediate (Negishi, E.; Choueiry, D.; Nguyen, T. B.; Swanson, D. R.; Suzuki, N.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 9751–9752) or by an associative olefin exchange appear plausible. These and related mechanistic issues are under investigation.

Scheme 4



in Scheme 4 (only catalytic cycles for *n*-PrMgCl are shown for clarity), it is likely that isopropyl adduct **5** and the *sec*-butyl product **9** arise from insertion of alkene in **4** into the more substituted side of the unsymmetrical metal–alkene complexes **3**-*syn* and **18**-*syn*, respectively. Addition proceeds in a manner such that steric interactions between the cyclic substrate and the protruding cyclohexyl unit of the chiral ligand are avoided, leading to the observed levels of enantioselectivity (≥90% ee). The corresponding *n*-alkyl adducts **6** and **10**, on the other hand, are obtained when olefin insertion occurs from the less-substituted front of the Zr–alkene complex (→**27** in Scheme 4).[12]

To gain a better understanding of the temperature-dependent selectivity variations, a set of experimental data were collected. These observations are summarized below:

i. In connection with the catalytic propylmagnesation of **4** (with *n*-PrMgCl) at 70 °C, measurements were carried out for reactions past the first catalytic cycle. Catalytic propylmagnesation is zero order in RMgCl (compare entries 2, 6, and 7 of Table 2) and the olefin substrate **4** (compare entries 2, 4, and 5 of Table 2) but first order in zirconocene (compare entries 1, 2, and 3 of Table 2). These findings suggest that the Zr–Mg ligand exchange step, *i.e.*, **21** → **22** or **25** → **26**, or the β-hydride abstraction event (**22** → **23** or **26** → **27**) is the turnover limiting step. However, carbomagnesations with $CH_3CH_2CH_2MgBr$ and $CD_3CD_2CD_2MgBr$ proceed at similar rates ($d[\mathbf{5}]/dt = 2.00 \times 10^{-6}$ M·s^{-1}, $d[\mathbf{6}]/dt = 4.83 \times 10^{-7}$ M·s^{-1}; $d[\mathbf{5}\text{-}d_7]/dt = 2.52 \times 10^{-6}$ M·s^{-1}, $d[\mathbf{6}\text{-}d_7]/dt = 4.17 \times 10^{-7}$ M·s^{-1}). Since previous reports indicate that β-hydride abstraction reactions of dialkylzirconocenes exhibit notable deuterium isotope effect ($k_H/k_D \cong 7$),[13] significant rate differences between reactions of deuterated and protiated alkylmagnesium halides would have otherwise been detected. These data suggest that the Zr–Mg ligand exchange step, *i.e.*, **21** → **22** and **25** → **26**, may be the turnover limiting step.[14]

Table 2. Representative Kinetic Data for Catalytic Propylmagnesation of **4** in the Presence of **1**[a]

				rate ($\times 10^{-6}$ M·s^{-1})	
entry	[Zr], M	[4], M	[RMgCl], M	**5**	**6**
1	0.016	0.2	1.0	6.2	2.3
2	0.020	0.2	1.0	8.3	3.1
3	0.024	0.2	1.0	9.0	3.7
4	0.020	0.4	1.0	8.7	3.5
5	0.020	0.6	1.0	8.7	3.1
6	0.020	0.2	0.7	8.6	3.4
7	0.020	0.2	0.8	8.2	3.5

[a] Reactions were carried out at 70 ± 2 °C in tetrahydrofuran under an argon atmosphere.

(12) In Cp_2Zr systems, in contrast to tetrahydroindenyl–Zr complexes, insertion of the olefin substrate to the more substituted face of a zirconocene-alkene is in general inherently preferred; for example, treatment of **4** with *n*-PrMgCl in the presence of 5–10 mol % Cp_2ZrCl_2 affords **5** exclusively. The reason for this difference in selectivity is not clear. (a) Reference 2f. (b) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521–3523.

(13) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1988**, *110*, 3171–3175. (b) Negishi, E.; Nguyen, T.; Maye, J. P.; Choueiri, D.; Suzuki, N.; Takahashi, T. *Chem. Lett.* **1992**, 2367–2370. (c) Coles, N.; Harris, M. C. J.; Whitby, R. J.; Blagg, J. *Organometallics* **1994**, *13*, 190–199.

(14) Carbomagnesations with alkylmagnesium bromides are significantly more sluggish than those with alkylmagnesium chlorides; this rate difference may well be due to the slower rate of ligand exchange between an alkylzirconocene and $MgCl^+$ (vs $MgBr^+$). It is important to note that formation of the zirconate complexes **21** and **25** is expected to be facile, particularly with the Zr:RMgCl ratio of 1:50. See: (a) Takahashi, T.; Suzuki, N.; Kageyama, M.; Nitto, Y.; Saburi, M.; Negishi, E. *Chem. Lett.* **1991**, 1579–1582. (b) Lewis, D. P.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron* **1995**, *51*, 4551-4562.

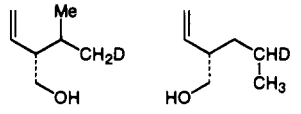
Table 3. Deuterium Incorporation in Propylmagnesation of **4** as a Function of Time

time (min)	conversion (%)[a]	**5**:**6**[a]	**5**-d_1:**6**-d_1[b]
10	07	2:1	50:50
190	20	4:1	<2:98
1000	26	20:1	

[a] Measured by GLC analysis after quench with HCl. Reaction carried out at 70 °C. [b] Measured by 300-MHz ^{2}H NMR analysis after quench with D_2O/D_2SO_4 and silica gel chromatography.

ii. Treatment of **4** with 10 mol % (*R*)-**1** and 1 equiv of *n*-PrMgCl (vs 5 equiv) at 70 °C affords **5** and **6** in a 2:1 ratio (GLC). Under these conditions, the ratio of **5**:**6** is constant at ~2:1. Similar observations are made when the reaction is run at 22 °C with 5 equiv of *n*-PrMgCl.

At 70 °C, when the reaction is quenched with D_2O/D_2SO_4 at various points, **5**-d_1 and **6**-d_1 are detected according to ^{2}H NMR. Importantly, as the transformation progresses, the ratio of **5**-d_1:**6**-d_1 is decreased as the reaction proceeds (**5**-d_1:**6**-d_1 = 1.5:1 at

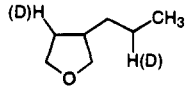


5-d_1 **6**-d_1

5% conversion, vs <2:98 at 20% conversion). It is important to note that deuterated products must arise from quench of a C−M bond, implying that such entities (those which react with D^+) are slowly released from the catalytic cycle (see below for additional discussion).

When propylmagnesation of **4** is performed at 70 °C with 5 equiv of *n*-PrMgCl the ratio of **5**:**6** *increases* with time. As illustrated in Table 3, the initial ratio is 2:1, identical to what is observed when the transformation is carried out at 22 °C with 5 equiv of *n*-PrMgCl or at 70 °C with 1 equiv of the Grignard reagent. However, as the reaction proceeds, the ratio of the two isomeric products **5**:**6** increases (Table 3).

iii. GLC analysis, in comparison with an authentic sample, indicates that **28** is not formed (<1%) in the zirconocene-catalyzed propylmagnesation of **4** at 22 °C (in the presence of 1 or 5 equiv of *n*-PrMgCl; determined through GLC analysis in comparison with authentic material).



28

iv. When a 2:1 mixture of **5** and **6** is subjected to 10 mol % [EBTHI]$ZrCl_2$ and 5 equiv of *n*-PrMgCl at 70 °C in THF for ~20 h, the ratio of the two product isomers remains unaltered.

v. When zirconocene−alkene complexes (*R*)-**3** (syn and anti, see Scheme 1)[15] are treated with 2 equiv of **4** at 50 °C and the reaction is monitored by ^{1}H NMR (500 MHz), <2% olefin products **5** and **6** are observed.[16] However, upon addition of H_2O, propylmagnesation products (**5** and **6**) are obtained in ~2:1 regioselectivity and >99% ee (30−40% conversion, GLC analysis). These data suggest that metallacyclopentanes **20** and **24** are likely formed under stoichiometric conditions and that zirconocene−alkoxide elimination within these metallacycles does not occur spontaneously: the presence of H_2O or excess alkylmagnesium halide is required to facilitate the rupture of metallacyclopentanes (see below for further detail).

vi. As was mentioned above, treatment of zirconocene−alkene complex (*R*)-**3** at elevated temperatures (50−70 °C) with 2 equiv of **4** affords a 2:1 ratio of **5** and **6** after aqueous workup. When the reaction mixture is heated to 70 °C and allowed to stir at that temperature for 12 h, or when the mixture is cooled to 22 °C, 20 equiv of *n*-PrMgCl is added and the reaction is then stirred at 22 °C for 6 h, there is little or no change in the observed regioselectivity (**5**:**6** ≅ 2:1). In contrast, when the reaction mixture is treated with 20 equiv of *n*-PrMgCl and then heated to 70 °C for 12 h,[17] ratio of **5**:**6** is increased to 18:1 (GLC analysis).

A plausible mechanistic picture which accounts for the above observations can be put forth. It is tenable that formation of regioisomeric metallacyclopentanes **20** and **24** at 22 or 70 °C in the absence of excess alkylmagnesium halide is only slowly reversible and product determining, but not turnover limiting. Under such circumstances, since the kinetic ratio for **20**:**24** is 2:1, in spite of the fact that the activation barrier for the turnover limiting step for formation of **5**(MgCl salt) might be lower than that for generation of **6**(MgCl salt), the final **5**:**6** ratio remains 2:1. That is, although **20** may leave the catalytic cycle somewhat more readily than **24** (as indicated by a decrease in **5**-d_1:**6**-d_1 as a function of time but not in the *final* **5**:**6** ratio), it is the initial selectivity—determined by the formation of the metallacyclopentane—that establishes the eventual product preference. Because at 70 °C, after 20% conversion, a portion of **6** still remains deuterated (see above) it is plausible that **24** exits the cycle more slowly (quench of which affords **6**-d_1).

When the reaction is performed at 70 °C and in the presence of excess alkylmagnesium halide, the two regioisomeric metallacycles may interconvert more rapidly, such that the turnover limiting steps (*e.g.*, **21** → **22**) become product determining as well. Under this regime, even though the initial metallacyclopentane selectivity may be 2:1, since the two zirconacycles can rapidly equilibrate, the one which more readily leaves the catalytic cycle becomes the major product. It thus follows that as the **5**:**6** ratio increases, the amount of deuterated isopropyl product (**6**-d_1) decreases (Table 2): as the reaction proceeds forward, increasing amounts of **5**(Mg salt) are formed and escape deuteration upon quench, while some of **24** or **25** remains within the cycle (and is deuterated after quench). These data suggest that metallacyclopentane equilibration is slower than release of the branched carbomagnesation product from the catalytic cycle; otherwise, **5**-d_1:**6**-d_1 would remain constant at ~2:1.

It is expected that higher reaction temperatures are necessary to initiate metallacyclopentane equilibration. However, the requirement for excess alkylmagnesium halide is less clear and may be attributed to at least two factors. (1) Without excess Grignard reagent (where metallacycle cleavage does not occur) **20** and **24** may interconvert, but since the thermodynamic ratio is ~2:1, little change in selectivity is observed. Additional alkylmagnesium halide allows one metallacyclopentane (*e.g.*, **20**) to be converted to its corresponding carbomagnesation product (*e.g.*, **5**) more rapidly, thus leading to an enhancement in regioselection. (2) Excess alkylmagnesium halide, as well

(15) To minimize the possibility of the presence of any remaining alkylmagnesium halide (which may cause cleavage of metallacyclopentanes), 1.8 equiv of *n*-PrMgCl is used to prepare (*R*)-**3**.

(16) Twelve new cyclopentadienyl signals appear in the ^{1}H NMR spectrum (THF-d_8): δ 5.91, 5.83, 5.76, 5.60, 5.55, 5.37, 5.18, 5.08, 5.03, 5.01, 4.96, 4.92. Although exact assignment of these signals is not possible at the present time, it is plausible to suggest that these signals belong to the three metallacyclopentanes **21** and **25**, which may exist as a mixture of two *n*-alkyl isomers (4 signals each). Although metallacyclopentane **24** is depicted as a single isomer in Scheme 4, a mixture of the corresponding stereoisomers may exist in solution.

(17) To ensure that after addition of exess *n*-PrMgCl additional "catalytic" reactions do not occur, only 0.7 equiv of **4** was used (to gurantee complete consumption of the alkene substrate before excess *n*-PrMgCl was added).

as elevated temperatures, is required for metallacyclopentane equilibration; it is nonetheless difficult to surmise the origin of such an effect at the present time.

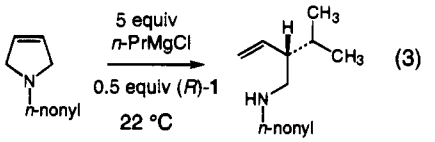
Regioselective Cleavage of Intermediate Metallacyclopentanes. The data presented herein illustrate that cleavage of the metallacyclopentanes (**20** or **24**) occurs with excellent regioselection by (1) an alkylmagnesium halide and (2) H_3O^+, albeit in the opposite sense:

(a) Metallacycle Cleavage by RMgCl. With regard to the rupture of a zirconacyclopentane with a Grignard reagent, the mode of cleavage shown in Scheme 4, namely, formation of a primary dialkylzirconium and a secondary alkylmagnesium, is supported by the appropriate deuterium labeling experiments. Reaction of **4** with EtMgCl and 10 mol % **1** followed by quench with D_2O/D_2SO_4 affords the corresponding ethylmagnesation product with <2% deuterium incorporation (^2H NMR analysis). Furthermore, when n-CD_3CD_2MgBr is used and the reaction is quenched with H_3O^+, analysis of ^2H NMR indicates exclusive addition of the CD_3CD_2 group (>95%, as judged by ^2H NMR analysis; metallacycle cleavage with opposite selectivity would afford a CD_2HCD_2 group).

(b) Metallacycle Cleavage by Protic Acids. Since treatment of the reaction mixture with D_3O^+ leads to the formation of **5**-d_1 or **6**-d_1 without generation of **28** (see above), it must be that reaction of zirconacyclopentanes with H_3O^+ or D_3O^+ proceeds with excellent regiochemical control, where C−Zr bond β to the C−O bond of the heterocycle initiates Zr alkoxide elimination before it is quenched by aqueous acid;[18] subsequent Zr alkoxide elimination leads to the formation of **5** or **6**.[19] The reason for the observed regioselection is the subject of ongoing studies.

It is noteworthy that with the less reactive pyran **7**, as opposed to furan **4**, at ambient temperature high product selectivity is observed (compare entries 1 and 4 to entries 3 and 6 in Table 1). This difference in selectivity may be attributed to the higher activation barrier necessary for the insertion of the less reactive pyran (compared to **4**) to the zirconocene−alkene complex in a manner that eventually affords the n-alkyl adduct. That is, with **7** as substrate, at 22 °C formation of the less favored metallacycle may be the slow step that is significantly higher in energy than the slow step en route to the branched product. Indeed, in contrast to **4**, when propylmagnesation of **7** is monitored by GLC, the branched product **8** is formed exclusively (the corresponding n-propyl product is not detected; there is no change in product ratio as a function of time). With the more reactive **4**, both regioisomeric metallacycles are relatively accessible at 22 °C.

Data presented herein indicate that subtle variations in alkene structure can dramatically alter the observed selectivities in the zirconocene-catalyzed carbomagnesation. The latter principle is highlighted further by the observation that, as shown in eq 3, cyclic amine **29**, in contrast to **4**, affords **30** with excellent regioselectivity even when the reaction is performed at 22 °C (>25:1, minor isomer could not be detected by 300-MHz ^1H NMR).



29 **30**

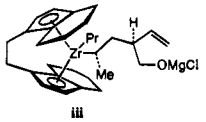
>95% enantiomeric excess
<2% n-propyl adduct
50% yield

(3) Regioselectivity in the β-Hydride Abstraction of Intermediate Dialkylzirconocenes. In reactions illustrated in Table 1, where a mixture of n-alkyl and branched alkyl products is obtained, a critical issue with regard to the regioselection in β-hydride abstraction presents itself. Consistent with previous reports,[2f,15b] in intermediate **22** (Scheme 4) β-hydride abstraction from the methylene position on the n-Pr group is preferred over involvement of the alternative methine β-hydride. However, an unusual sense of regioselectivity is observed with regard to dialkylzirconocene **26**, where β-hydride elimination may occur either through the CH_3 site (*via* **26a**) or the n-Pr methylene group (*via* **26b**). Since <2% **31** (300-MHz ^1H NMR analysis) is observed, it must be that the expected mode of hydride abstraction through the less hindered CH_3 group is disfavored. This outcome is striking, since, with Cp_2ZrR_2 systems β-hydride abstraction of a *sec*-butyl group is found to be *more* rapid than even an Et unit, which in turn reacts faster than an n-Bu group. Because the furan-containing ligand in **26** is structurally analogous to a *sec*-butyl unit, the observed trends in β-H abstraction of [EBTHI]Zr complexes represent a reversal of regiochemical selectivity compared to those recorded for the corresponding Cp_2Zr derivatives.

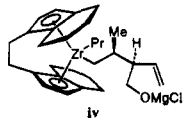
As shown in Scheme 5, a rational basis for this unexpected selectivity may be related to the unfavorable steric interactions that would be involved in β-hydride elimination from the CH_3 site (**26a** vs **26b**).[20] When the methylene of the n-propyl group is used (**26b**), the only steric interactions are those which are present in *any* β-hydride abstraction. That participation of a hydride from the methylene group in **26b** is less favored than that of the CH_2 unit in the n-alkyl group is expected, since the former is sterically more encumbered (the CH_2 group in **26b** bears two α substituents). Similar arguments can be used to explain the sense of regioselection in β-hydride abstraction in dialkylzirconocenes derived from reactions with n-BuMgCl.

(18) For a report on the regioselective protonation of one C−Zr bond of a zirconacyclopentane (CH_3OH, 25 °C), see: Takahashi, T.; Aoyagi, K.; Hara, R.; Noriyuki, S. *Chem. Lett.* **1992**, 1693−1696.

(19) It is not suggested that protonation of the remaining C−Zr bond under these conditions is slow; we only suggest that the intramolecular zirconocene−alkoxide elimination is faster. Deuterated products **5**-d_1 and **6**-d_1 cannot be due to reactions of dialkylzirconocenes **iii** and **iv**, since these species cannot re-enter the catalytic cycle and interconvert (a process necessary for change of the **5**:**6** ratio as a function of time).

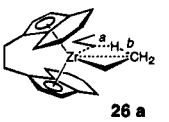


iii



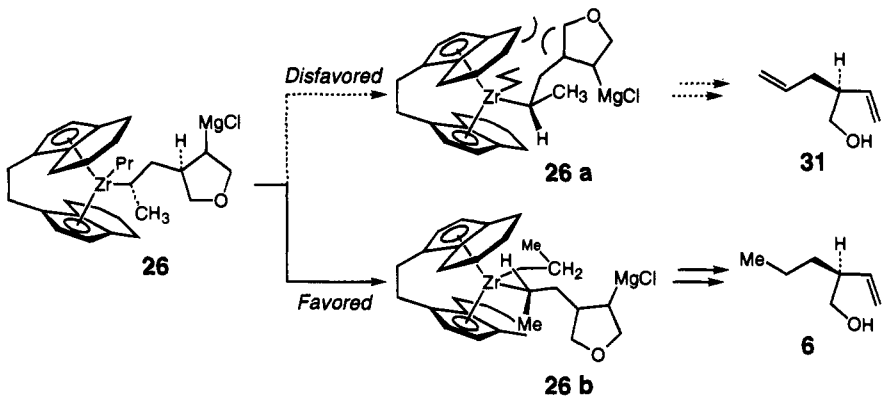
iv

(20) Mechanistic work by Buchwald (ref 14a) on a closely related system indicates that conversion of a dialkylzirconocene to a zirconocene−alkene complex and the corresponding alkane probably involves a concerted four-center process (illustrated below for **29a**; alkyl groups are omitted), rather than a stepwise β-hydride abstraction process. In this discussion, for the sake of simplicity and brevity, we refer to this process as simply a β-hydride elimination to emphasize the function with which the specific alkyl groups (methylene site vs a methyl site, etc.) are predominantly involved. The geometric preference depicted below readily favors the formation of the incipient C−H bond (a), and the Zr−C−H−C dihedral angle of 0° ensures proper alignment of the C−H bond (b) or C−M bond with the metallocene LUMO (Lauher, J. W.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1729−1742). Such geometric constraints are valid, even if the reaction involves a distinct β-hydride elimination step, since in such a case, a Zr−C−C−H dihedral angle of 0° would still be required for proper interaction between the C−H and the zirconocene LUMO (agostic interaction between the C−H bond and Zr). See ref 14b and: Negishi, E.; Swanson, D.; Takahashi, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1254−1255.



26 a

Scheme 5



Thus, the architecture of the chiral indenyl system appears to impart unusual modes of reactivity to the derived zirconocene complexes; such reactivity and selectivity patterns are in contrast with the chemistry of the related cyclopentadienyl (Cp_2) ensembles.

Conclusions

In summary, the work described herein illustrates the following: (1) *n*-PrMgCl and *n*-BuMgCl add to cyclic alkenes **4** and **7** in the presence of 10 mol % non-racemic [EBTHI]$ZrCl_2$ to afford the derived carbomagnesation products in modest yields but with excellent regio-, diastereo-, and enantioselectivity. (2) Whereas carbomagnesation regioselectivity is low at 22 °C, at elevated temperatures (70 °C), high levels of regiocontrol, in favor of branched alkylation products (isopropyl and *sec*-butyl adducts), are observed. (3) The sense of diastereoselection in reactions with *n*-BuMgCl indicates that one of the two isomeric chiral metal−olefin complexes is the more reactive species (formation of **9** vs **19**). (4) Unusual modes of β-hydride abstraction are observed with intermediate dialkylzirconocenes; the trends favored with the parent Cp_2Zr systems (β-H abstraction from methyl faster than methylene faster than methine) are not necessarily followed when chiral [EBTHI]Zr-based complexes are employed.

Further studies in the area of asymmetric, catalytic carbomagnesation continue in these laboratories.

Experimental Section

General. Infrared (IR) spectra were recorded on a Perkin Elmer 781 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). All spectra were calibrated with the 1601-cm^{-1} absorption of a polystyrene film. ^1H NMR spectra were recorded on a Varian Unity 300 (300 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: δ 7.24 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a Varian Unity 300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuteriochloroform: δ 77.0 ppm). 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. (EBTHI)$ZrMe_2$ was prepared and resolved by the method of Buchwald[21] and converted to the corresponding dichloride by treatment with ethereal HCl. Propyl and butyl chloride and Mg (turnings) were purchased from Aldrich Co. Bromoethane-d_5 was purchased from Merck Sharp & Dohme/Isotopes and bromopropane-d_7 was obtained from CDN isotopes of Quebec; these reagents were used without further purification.

Typical Experimental Procedure for the Enantio- and Regioselective Zirconium-Catalyzed Carbomagnesation. 2,5-Dihydrofuran (**4**, 60.0 mg, 0.85 mmol) was dissolved in 1.0 mL of anhydrous THF in a flamed-dried 10-mL round-bottom flask. After the addition of freshly prepared *n*-PrMgCl (3.29 mL, 4.28 mmol), the reaction mixture was allowed to stir for 5 min. At this time, 36.5 mg (0.08 mmol) of [EBTHI]$ZrCl_2$ was added. The reaction flask was then equipped with a reflux condenser and the mixture was allowed to stir at 70 °C for 12 h. After the solution was cooled to 0 °C, excess Grignard reagent was quenched through the dropwise addition of 2.0 mL of a 2.0 M solution of HCl. The mixture was diluted with 25 mL of distilled water and washed three times with 35-mL portions of diethyl ether. Combined organic layers were dried over anhydrous $MgSO_4$; filteration of the drying agent and removal of solvent in vacuo afforded a pale yellow oil. Silica gel chromatography (2:1 pentane:ether) afforded 39.0 mg of **5** as a colorless oil (40% yield).

(*S*)-2-Methyl-3-(hydroxymethyl)-4-pentene (5). IR (KBr) 3400 (br, m), 2970 (s), 2920 (s), 2860 (s), 1480 (m) cm^{-1}; ^1H NMR δ 5.60 (1H, ddd, J = 17.1, 10.3, 9.3 Hz, vinylic **CH**), 5.20 (2H, m, vinylic CH_2), 3.67 (1H, dd, J = 10.6, 4.9 Hz, CH_2OH), 3.45 (1H, dd, J = 10.4, 9.1 Hz, CH_2OH), 2.00 (1H, m, $CHCH_2OH$), 1.65 (1H, m, $CHCH_3$), 0.91 (3H, d, J = 6.7 Hz CH_3), 0.86 (3H, d, J = 6.7 Hz CH_3); ^{13}C NMR δ 138.1, 118.2, 63.7, 53.6, 28.5, 20.6, 19.5. (Due to substrate volatility, the derived MTPA ester was subjected to analysis.) Anal. Calcd for $C_{17}H_{21}F_3O_3$: C, 61.81; H, 6.41. Found: C, 61.86; H, 6.29.

(*R*)-2-Methyl-3-vinylpentan-1-ol (8). IR (KBr) 3420 (br), 2958 (s), 2930 (s), 2873 (s), 1640 (w) cm^{-1}; ^1H NMR δ 5.60 (1H, dt, J = 16.3, 9.6 Hz, vinyl CH), 5.03 (2H, m, vinyl CH_2), 3.66 (2H, m, CH_2OH), 2.00−1.20 (4H, m, $CHCHCH_2$, CH_2CH_2OH, $CH(CH_3)_2$), 0.89 (3H, d, J = 6.6 Hz, CH_3), 0.85 (3H, d, J = 6.6 Hz, CH_3); ^{13}C NMR δ 140.5, 115.8, 61.7, 47.5, 34.8, 31.8, 20.4, 18.9. (Due to substrate volatility, the derived MTPA ester was subjected to analysis.) Anal. Calcd for $C_{18}H_{23}F_3O_3$: C, 62.78; H, 6.73. Found: C, 62.51; H, 6.87.

(*R*)-2-Vinyl-3-methylpentan-1-ol (9). IR (KBr) 3420 (br), 3150 (m), 2961 (s), 2927 (s), 2875 (s), 1640 (w) cm^{-1}; ^1H NMR δ 5.60 (1H, dt, J = 17.1, 9.9 Hz, vinyl CH), 5.28 (2H, m, vinyl CH_2), 3.66 (1H, dd, J = 10.5, 5.1 Hz, CH_2OH), 3.45 (1H, dd, J = 10.2, 9.0 Hz, CH_2OH), 2.23 (1H, m, $CHCH_2OH$), 1.55 (1H, m, $CH_3CHCH_2CH_3$), 1.30 (2H, m, $CH_3CHCH_2CH_3$), 0.90 (3H, t, J = 6.9 Hz), 0.85 (3H, d, J = 6.3 Hz); ^{13}C NMR δ 137.3, 118.0, 63.9, 51.0, 34.9, 29.1, 15.3, 11.4. (Due to substrate volatility, the derived MTPA esters were subjected to analysis.) Anal. Calcd for $C_{17}H_{23}O_3F_3$: C, 62.78; H, 6.73. Found: C, 62.75; H, 6.89.

(*R*)-2-Vinylhexan-1-ol (10). IR (KBr) 3420 (br), 3150 (m), 2961 (s), 2927 (s), 2875 (s), 1640 (w) cm^{-1}; ^1H NMR δ 5.55 (1H, dt, J = 17.1, 9.9 Hz, vinyl CH), 5.15 (2H, m, vinyl CH_2), 3.60 (1H, dd, J = 10.8, 5.10 Hz, CH_2OH), 3.40 (1H, dd, J = 10.8, 8.4 Hz, CH_2OH), 2.20 (1H, m, $CHCH_2OH$), 1.50 (4 H, m, $(CH_2)_2CH_3$), 0.90 (3H, t, J = 6.9 Hz, CH_2CH_3); ^{13}C NMR δ 140.0, 116.8, 65.5, 46.8, 29.3, 22.5, 13.8, 11.4.

(*R*)-3-Vinyl-4-methylhexan-1-ol (11). IR (KBr) 3351 (br), 2928 (s), 2873 (s), 2858 (m), 1463 (w), 1054 (w) cm^{-1}; ^1H NMR δ 5.60

(21) Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 2321−2322 and references cited therein.

(1H, ddd, J = 17.1, 10.2, 9.6 Hz, vinyl CH), 5.00 (2H, m, vinyl CH_2), 3.65 (2H, m, CH_2OH), 2.15 (1H, m, $CH(CH_2)_2OH$), 1.60 (2H, m, CH_2CH_2OH), 1.30 (3H, m, $CHCH_2CH_3$), 0.98 (3H, t, J = 7.5 Hz, CH_2CH_3), 0.82 (3H, d, J = 6.9 Hz, $CHCH_3$); ^{13}C NMR δ 139.9, 115.8, 61.7, 45.0, 38.6, 29.3, 27.4, 15.1, 11.7. (Due to substrate volatility, the derived MTPA ester was subjected to analysis.) Anal. Calcd for $C_{19}H_{25}O_3F_3$: C, 62.84; H, 7.03. Found: C, 63.06; H, 7.28.

((*R*)-2-Isopropyl-3-buten-1-yl)-*n*-nonylamine (30). IR (KBr) 2957 (s), 2926 (s), 2871 (s), 2802 (s), 1465 (s), 1381 (m), 1129 (m) cm^{-1}; ^1H NMR δ 5.60 (1H, ddd, J = 16.8, 10.2, 9.3 Hz, vinyl CH), 5.10 (2H, m, vinyl CH_2), 2.55 (3H, m, CH_2NH), 2.10 (1H, m, $CHCH_2NH$), 1.62 (1H, m, $CH(CH_3)_2$), 1.45−1.18 (16H, *n*-alkyl CH_2), 0.90 (3H, d, J = 6.8 Hz, $CH(CH_3)_2$), 0.88 (3H, t, J = 6.3 Hz, *n*-nonyl CH_3), 0.86 (3H, d, J = 6.9 Hz, $CH(CH_3)_2$); ^{13}C NMR δ 139.5, 117.0, 51.6, 50.9, 50.0, 31.8, 30.1, 30.9, 29.5, 29.2, 27.4, 22.6, 20.7, 19.3, 14.0. HR EIMS requires 238.2535, found 238.2538.

Acknowledgment. This research was generously supported by the NIH (GM-47480). Additional support was provided by the NSF (CHE-9258287), Johnson & Johnson (Focused Giving Program), and Pfizer. A.H.H. is an Eli Lilly Grantee, an American Cancer Society Junior Faculty Research Awardee (JFRA-434), an Alfred P. Sloan Research Fellow, and a Camille Dreyfus Teacher-Scholar. We are most grateful to our colleagues Professor Marc Snapper and Dr. Ahmad Houri for their suggestions, insightful criticism, and numerous helpful discussions.

Supporting Information Available: Representative GLC, ^1H NMR, and rate measurement data (13 pages). This material is contained in many libraries on microfische, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA943901E