Regio- and Stereoselective Carbon-Carbon Bond Formation through Transition Metal Catalysis. The Influence of Catalyst Chirality on Selective Ethylmagnesation of Chiral, Nonracemic Alcohols and Ethers

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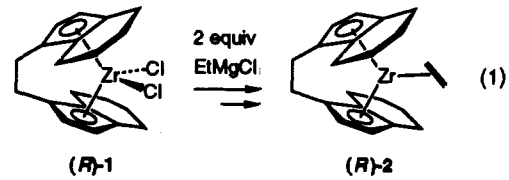
Reaction of chiral zirconium dichloride 1 with EtMgCl leads to the formation of (*R*)-2. The transition metal-alkene complex 2 may then be employed as an effective catalyst in ethylmagnesations of nonracemic allylic alcohols and ethers. These transformations proceed with varying levels of diastereochemical control, depending on which antipode of the chiral substrate is employed. The difference between the stereo- and regiochemical outcome in reactions catalyzed by the achiral Cp_2ZrCl_2 and 1, the variable sensitivity of these sets of reactions to competing ligating Lewis basic solvents, and the influence of the reaction temperature on the regiochemical outcome of carbometalation is described. These data provide important insights into various mechanistic aspects of the carbomagnesation process.

Introduction

In spite of impressive advances which have been made in the area of catalytic, asymmetric transformations,[2] development of related carbon-carbon bond forming reactions remains a significant goal in chemical synthesis. Thus, recent observations that addition of Grignard reagents to alkenes[3] occurs regio- and stereoselectively at 25 °C with catalytic amounts of Cp_2ZrCl_2 have significant implications.[4] Our initial investigation has been based on the principle that rational design of an effective chiral catalyst requires a detailed understanding of critical catalyst-substrate interactions and the mechanistic principles that underlie the basic process. One approach toward attaining these goals entails the study of the interaction of a chiral zirconocene with nonracemic starting materials. Whether significant differences in stereoselectivity are observed in carbomagnesations of enantiomeric forms of chiral olefins, and which antipode of the alkene substrate is matched and which is mismatched with the chiral catalyst, should offer insights into the mechanism of this process and challenge or validate the existing postulates. Herein we report our findings on the trends and variations in stereocontrol observed in the ethylmagnesation of chiral allylic and homoallylic alcohols and ethers catalyzed by Brintzinger's ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium dichloride ([EBTHI]$ZrCl_2$]) 1.[5]



Results and Discussion

A number of recent reports implicate metal-alkene complexes such as 2 (achiral variants) as "alkylating agents" in zirconium-catalyzed carbomagnesations.[6] Since there are no extant reports on the purported metal-alkene complex 2, we undertook to establish the formation of the chiral metallacyclopropane by means of ^1H NMR spectroscopy. Treatment of racemic 1 (tetrahydroindenyl proton signals at δ 6.28 (2H) and 5.85 (2H))[7] with 5 equiv EtMgCl in THF-d_8 at -78 °C for 2 h affords no alkylation products (as judged by 300-MHz NMR). When the reaction mixture is allowed to warm to -35 °C, gradual generation of the monoalkylated diastereomers is indicated by the appearance of four characteristic downfield signals (δ 6.48, 6.03, 5.72, 5.35; 1H each). When 3 equiv of EtMgCl are used and the temperature is allowed to reach 50 °C, complete disappearance of 1 and formation of the monoalkylated product is observed within 30 min. Concomitant with the formation of [(EBTHI)Zr(Et)Cl], small amounts (~10%) of a new compound appear, the spectral features of which are consistent with 2. Two doublets at δ 6.49 (2H) and 5.36 (2H) are assignable to cyclopentadienyl protons, and the protons of the metallacycle are repre-

(1) NSF National Young Investigator, 1992-1997; Eli-Lilly Grantee, 1992-1994; American Cancer Society Junior Faculty Research Awardee, 1993-1995.

(2) For recent examples, see: (a) Rajanbabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 6265-6266. (b) Evans, D. A.; Woerpel, K. A.; Hinman, M. A.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726-728. (c) Corey, E. J.; Imai, N.; Zhang, H-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728-729.

(3) (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.; Kukovineta, A. G.; Khalilov, A. M. *Izv. Akad. Nauk SSSR. Ser. Khim.* **1983**, *32*, 2053-2060. (c) Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285*, 43-51, and refs 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.

(4) (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.

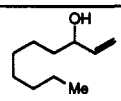
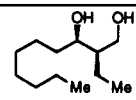
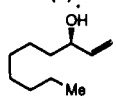
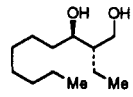
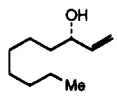
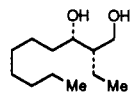
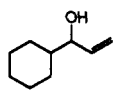
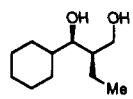
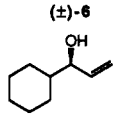
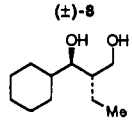
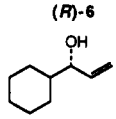
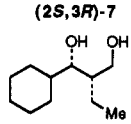
(5) Schafer, A.; Eberhard, K.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1987**, *328*, 87.

(6) Zirconacycles have been shown to be intermediates in the carbomagnesation reaction. See: (a) refs 3, 4, and 13. (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. (e) Wischmeyer, U.; Waymouth, R. M.; *Tetrahedron Lett.* **1992**, *33*, 7735-7738.

(7) All cyclopentadienyl signals are doublets with $J \simeq 2.7$ Hz.

0022-3263/93/1958-4237$04.00/0

Table I. Diastereocontrol in Ethylmagnesations of Nonracemic Chiral Allylic Alcohols with (*R*)-1[a]

entry	substrate	major product	precatalyst	solvent (% catalyst)	selectivity[b] *syn/anti*	yield (%)[c]
1	 (±)-3	 (±)-5	Cp_2ZrCl_2 (±)-1	Et_2O (5)	92:8	70
				THF (5)	67:33	85
				Et_2O (10)	60:40	80
2	 (*R*)-3	 (2*S*,3*R*)-4	(*R*)-1	Et_2O (15)	37:63	80
				THF (10)	20:80	80
3	 (*S*)-3	 (2*S*,3*S*)-5	(*R*)-1	Et_2O (15)	92:8	80
				THF (10)	85:15	65
4	 (±)-6	 (±)-8	Cp_2ZrCl_2	Et_2O (25)	75:25	70
				THF (25)	67:33	85
5	 (*R*)-6	 (2*S*,3*R*)-7	(*R*)-1	Et_2O (10)	25:75	15
				THF (10)	20:80	80
6	 (*S*)-6	 (2*S*,3*S*)-8	(*R*)-1	Et_2O (10)	80:20	15
				THF (10)	80:20	50

[a] Conditions: 5 equiv of EtMgCl, 10 mol% catalyst, at 25 °C (12 h); O_2 at 0 °C. [b] Diastereoselectivities determined by ^1H NMR (300 MHz) and GLC analysis. [c] Isolated yields of purified products (silica gel chromatography).

sented as a broad multiplet at δ 0.23 (4H). Upon addition of 3 equiv more of EtMgCl, complete conversion to the zirconacyclopropane is observed.

Initial studies indicated that the derived *C*2-symmetric **2** (eq 1) is an efficacious catalyst for the carbomagnesation of a number of alkenes. As shown in entry 1 of Table I, reaction of racemic allylic alcohol **3** with EtMgCl (5 equiv) and 10 mol% racemic **1** in Et_2O affords (±)-**4** with little selectivity (60:40 syn/anti); reaction selectivities when Cp_2ZrCl_2 is used as catalyst are indicated for comparison (entry 1). In contrast, as illustrated in Table I, treatment of the (*S*) enantiomer of allylic alcohol **3** with EtMgCl in Et_2O in the presence of 10 mol% (*R*)-**1**[8] (25 °C, 12 h) affords the syn carbomagnesation product (2*S*,3*S*)-**5** with 92:8 diastereocontrol (entry 3).[9] When (*R*)-**3** is subjected to these conditions, not only is stereocontrol significantly eroded, the *anti* isomer (2*S*,3*R*)-**4** now is formed with modest selectivity (entry 2).[10] Thus, with (*R*)-**1**, (*S*)-**3** serves as the matched substrate, whereas the corresponding (*R*) antipode has a mismatched interaction with the chiral catalyst (entry 2).

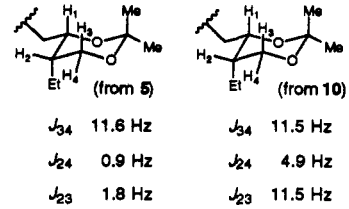
With THF as solvent, in the ethylmagnesation of the two enantiomeric allylic alcohols **3**, a near complete turnover in diastereocontrol is observed: (*S*)-**3** affords the syn diastereomer (**5**) with 85:15 preference, but (*R*)-**3** provides the anti isomer (**4**) with 80:20 selectivity. It is worthy of note that whereas under catalysis by Cp_2ZrCl_2 in reactions of the allylic alcohol **3** the syn stereoisomer is obtained preferably (entries 1 and 4), with **1**, proper combination of the chiral catalyst and substrate can lead to the selective formation of the anti ethylmagnesation product **4** (entry 2, Table I). Similar observations are made in reactions of derivative **6** (entries 5 and 6, Table I); stereochemical control is less effective with substrates which are branched at the β position (e.g., 80:20 for (*S*)-**3** vs 92:8 for (*S*)-**6**).[11]

When racemic **1** (10 mol%) is used in the ethylmagnesation of (*R*,*S*)-**9**, alcohol **10** is obtained with 78:22 anti/syn diastereoselectivity (entry 1, Table II). Entries 2 and 3 (Table II) show that with (*R*)-**9** as substrate, **10** is formed with 90:10 stereoselectivity, whereas when (*S*)-**9** is used, a near equal mixture of diastereomers is obtained. The difference in selectivity is more dramatic in the case of ethers **11** and **13**. In the latter instance, the matched system affords the anti carbomagnesation product (3*S*,4*R*)-**14** with 93:7 selectivity (entry 5); in contrast, the mismatched combination affords little π-facial control (60:

(8) All the chiral, nonracemic alcohols (and their derived ethers) were prepared according to the method of Sharpless. The enantiopurity of these materials was established by GLC analysis of the derived (*S*)-MTPA (Mosher) esters; the reported levels of diastereoselectivity are corrected. (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780. (b) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106–113 and refs. cited therein.

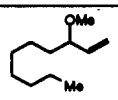
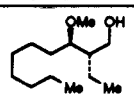
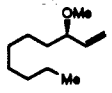
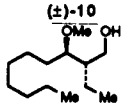
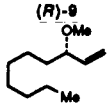
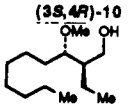
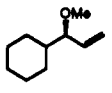
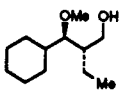
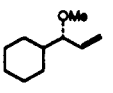
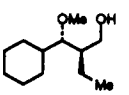
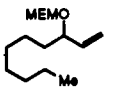
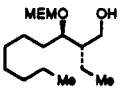
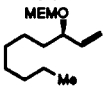
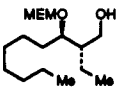
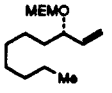
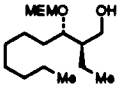
(9) The stereochemical identities of all compounds were determined through comparison with authentic materials and anlysis of ^1H NMR coupling constants on the corresponding methylene acetal and acetonide derivatives. See the Experimental Section.

(10) Stereochemical identities of all compounds were determined by ^1H NMR analysis of the derived acetonides. GLC analysis of the acetonides and analysis of the ^1H NMR spectra of the reaction products provided the ratios shown herein. As illustrated below, the acetonides obtained from syn and anti diastereomers have distinct coupling patterns.



(11) The reaction of cyclohexyl alcohol **6** is sluggish in Et_2O since the reaction mixture is highly heterogeneous. In THF the solution is completely homogeneous.

Table II. Diastereocontrol in Ethylmagnesations of Nonracemic Chiral Allylic Ethers with (*R*)-1[a]

entry	substrate	major product	precatalyst	solvent	selectivity[b] *syn/anti*	yield (%)[c]
1	 (±)-9	 (±)-10	Cp_2ZrCl_2	Et_2O	11:89	70
				THF	11:89	85
			(*R*)-1	THF	22:78	85
2	 (*R*)-9	 (3*S*,4*R*)-10	(*R*)-1	Et_2O	11:89	70
				THF	11:89	85
3	 (*S*)-9	 (3*R*,4*S*)-10	(*R*)-1	THF	40:60	40
4	 (*S*)-11	 (3*S*,4*R*)-12	(*R*)-1	Et_2O	<5:95	75
				THF	6:94	65
5	 (*R*)-11	 (3*R*,4*S*)-12	(*R*)-1	THF	25:75	45
6	 (±)-13	 (±)-14	Cp_2ZrCl_2	THF	17:83	70
7	 (*R*)-13	 (3*S*,4*R*)-14	(*R*)-1	THF	7:93	70
8	 (*S*)-13	 (3*R*,4*S*)-14	(*R*)-1	THF	40:60	45

[a] Conditions: 5 equiv of EtMgCl, 10 mol% catalyst at 25 °C for 12 h. [b] Diastereoselectivities were determined by ^1H NMR (300 MHz) and GLC analysis in comparison with authentic material. [c] Isolated yields of purified products (silica gel chromatography).

40, entry 6). Thus, the data illustrated in Table II indicate that when the hydroxyl group is protected as a methyl or MEM ether,[12] the substrates derived from mismatched alcohols become matched.

Similar trends in stereoselectivity are observed with homoallylic bicyclic substrates **15** and **17**. As indicated in Table III, in contrast to (*R*)-**15** which affords >200:1 regioselectivity (preferable C5 alkylation), as judged by GLC analysis, (*S*)-**15** provides a 13:1 mixture of isomers. Whereas ether (*R*)-**17** affords C5 alkylation product with 5:1 selectivity, (*S*)-**17** slightly favors C–C bond formation at C6. Ethylmagnesation of the derived MEM ethers are significantly more sluggish than the parent alcohols, providing another manifestation of the significance of a strong internal Lewis base to substrate reactivity. It is worthy of note that, generally, higher levels of reactivity are observed with zirconocene dichloride. Unlike when Cp_2ZrCl_2 is used as catalyst, **1** does not effectively initiate addition of *n*-PrMgCl[13] and *n*-BuMgCl to **15** and **17**. The comparably less efficient ethylmagnesation, when **1** is employed as catalyst, presumably arises from the larger bulk of the zirconium ligand, particularly since our data implicate a bimetallic complex as an intermediate.[14]

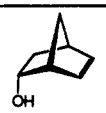
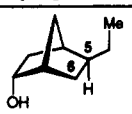
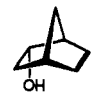
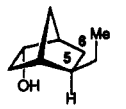
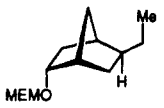
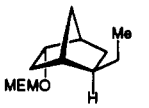
To draw reliable mechanistic conclusions from aforementioned variations in stereoselectivity, we felt it necessary to establish that the general principles observed in studies involving Cp_2ZrCl_2,[13,14] shown in Scheme I, are valid when **1** is used as catalyst. Subjection of racemic **9** with 1 equiv [(EBTHI)$ZrEt_2$] (precursor to **2**) affords ≤10% ethylmagnesation product (25 °C, 6 h), whereas upon addition of four equiv EtMgCl, 30% conversion occurs. Similarly, treatment of **15** with one equiv [(EBTHI)$ZrEt_2$] affords ≤15% carbomagnesation product with only 60:40 regioselectivity. When the reaction is run with 5 equiv of excess EtMgCl, >99:1 regiocontrol in favor of alkylation at C5 is observed (>95% conversion).[14] Additional amounts of EtMgCl are therefore necessary for high selectivity and the basic concepts proposed by us[13,14] with regard to the mechanism of catalytic carbomagnesation of heteroatom-containing substrates can be employed here as well. These mechanistic principles are: (1) In reactions catalyzed by **2**, simple addition of the zirconacyclopropane to the reacting alkene does not account for the data shown in Tables I-III. (2) When excess alkylmagnesium halide is present, the derived zirconate **19** is formed. Ligand exchange in the presence of excess EtMgCl leads to the formation of zirconate **20**,

(12) Abbreviation: MEM = $CH_3OCH_2OCH_2$.

(13) With *n*-PrMgCl, **15** affords only 20% of the corresponding isopropyl adduct (12 h, 25 °C). This observation, however, does show that the alkylating agent is the zirconacyclopropane **2**. See: Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z-M. *J. Am. Chem. Soc.* **1992**, *114*, 6692–6697.

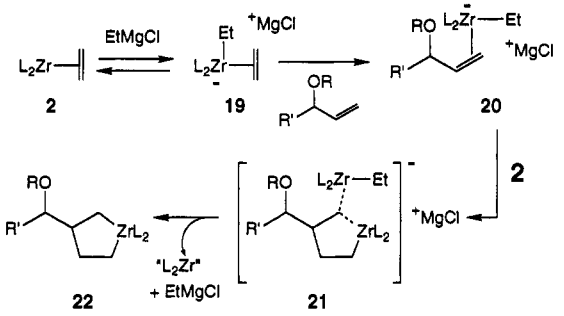
(14) For details of studies on the mechanism of zirconocene-catalyzed carbomagnesation of acyclic allylic alcohols and ethers, see Houri, A. F.; Didiuk, M. T.; Xu, Z-M.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *114*, in press. Rate studies reported therein support the intermediacy of a bimetallic complex.

Table III. Diastereocontrol in Ethylmagnesations of Nonracemic Chiral 15 and 17 with (*R*)-1[a]

entry	substrate	major product	selectivity[b] C5/C6	% conversion[c]	% yield[d]
1	 (*R*)-15	 (2*R*,5*S*)-16	>200:1	>99	97
2	 (*S*)-15	 (2*S*,5*R*)-16	13:1	65	50
3	 (*R*)-17	 (2*R*,5*S*)-18	5:1	25	25
4	 (*S*)-17	 (2*S*,5*S*)-18	1:2	25	25

[a] Conditions: 5 equiv of EtMgCl, 10 mol% catalyst in Et_2O, 14 h; 2 M HCl at 0 °C. [b] Ratios determined by GLC analysis of the acetates; ~3% (total) of endo isomers were formed in all reactions. [c] Ratios determined by GLC analysis of reaction products. [d] Isolated yields after purification by silica gel chromatography.

Scheme I

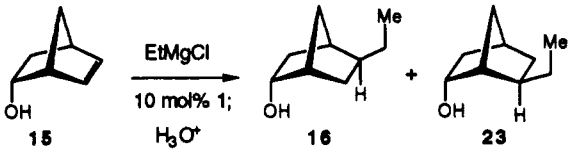


L = EBTHI
R' = *n*-nonyl or cyclohexyl
R = MgCl, Me or MEM

which undergoes ethylmagnesation with high levels of regio- and stereoselectivity via bimetallic **21**.[15] Reaction through a zirconate complex such as **20** is favored, since (i) the electron-rich olefin complex should better associate with the incoming Lewis acidic metallacyclopropane, and (ii) due to intermediacy of a bimetallic complex, the developing electron density at C1 (generated upon formation of Cl–Zr bond) can interact with two available transition metal orbitals.

To examine whether decrease in reaction temperature would enhance the difference between regio- and stereoselectivity of the enantiomeric substrates, we repeated a number of ethylmagnesations at +4 °C and −20 °C. We

Scheme II



Temperature	**16 : 23**	*conversion*
22 °C	>200 : 1	>99% (12 h)
4 °C	7 : 1	80% (12 h)
-20 °C	2 : 1	40% (24 h)

discovered that with bicyclic substrates (e.g., **15**) *lowering of temperature leads to a dramatic drop in regiochemical control.* For example, as shown in Scheme II, catalytic ethylmagnesation of **15** affords nearly a single isomer at 25 °C, whereas at 4 °C significantly less selectivity, and at −20 °C inferior levels of regiochemical control are attained (ratios and conversion determined by GLC; mass balance >80%). A plausible explanation for this trend is that as the reaction temperature is decreased, ligand exchange is less favored, and simple addition of **2** to the alkene—a process that occurs nonselectively—becomes a significant or predominant pathway.

Aside from the fact that the chiral nature of **1** leads to varying levels of diastereoselectivity with enantiomeric chiral olefins, a number of differences in regio- and stereocontrol in reactions initiated by **1** vs Cp_2ZrCl_2 arise as a result of the larger size of the indenyl catalyst. These variations in selectivity have mechanistic implications and merit elaboration.

(i) As illustrated in Scheme I, with THF as solvent and (*R*-[(EBTHI)$ZrCl_2$]) ((*R*)-**1**) as catalyst, the diminution in stereocontrol is less pronounced than that observed with Cp_2ZrCl_2. In ethylmagnesations of allylic alcohols, with Cp_2ZrCl_2 as catalyst, the presence of THF results in significant reduction in diastereoselectivity; π-facial selectivity observed in ethylmagnesations of allylic ethers is insensitive to the presence of tetrahydrofuran.[4a,14] Moreover, allylic alcohols (magnesium alkoxides) and ethers undergo carbomagnesation with opposite sense of diastereocontrol. These observations have been accounted for by the proposal that with the highly Lewis basic metal alkoxide (but not ethers), at some point along the reaction coordinate, there is simultaneous association of a metal (either magnesium or zirconium) with the alkene and the internal heteroatom.[14,16] Thus, tetrahydrofuran may alter such interaction and reduce stereoselectivity when allylic alcohols are used.

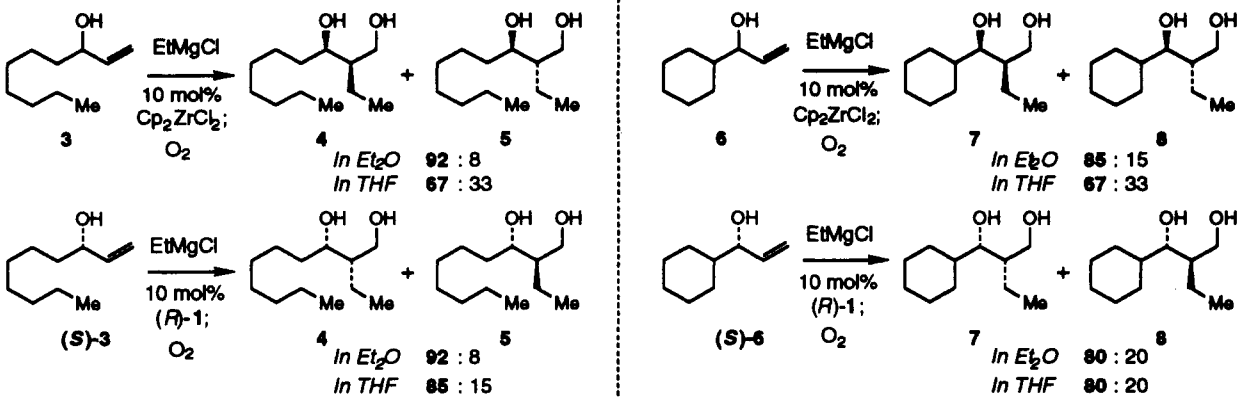
The data shown in Scheme III support the paradigm that it is zirconium, not magnesium, that serves as the chelating metal. With the more sterically demanding tetrahydroindenyl ligands, THF cannot as effectively compete with the internal metal alkoxide for a ligation site on the transition metal. If magnesium were the chelating metal, modification of the ligand structure on zirconium would not render the reaction π-facial selectivity more impervious to the Lewis basicity of tetrahydrofuran.

(ii) Our studies indicate that there is no inherent regiochemical preference in the addition of **2** to an allylic alcohol or ether.[14] When (±)-**9** is treated with 5 equiv

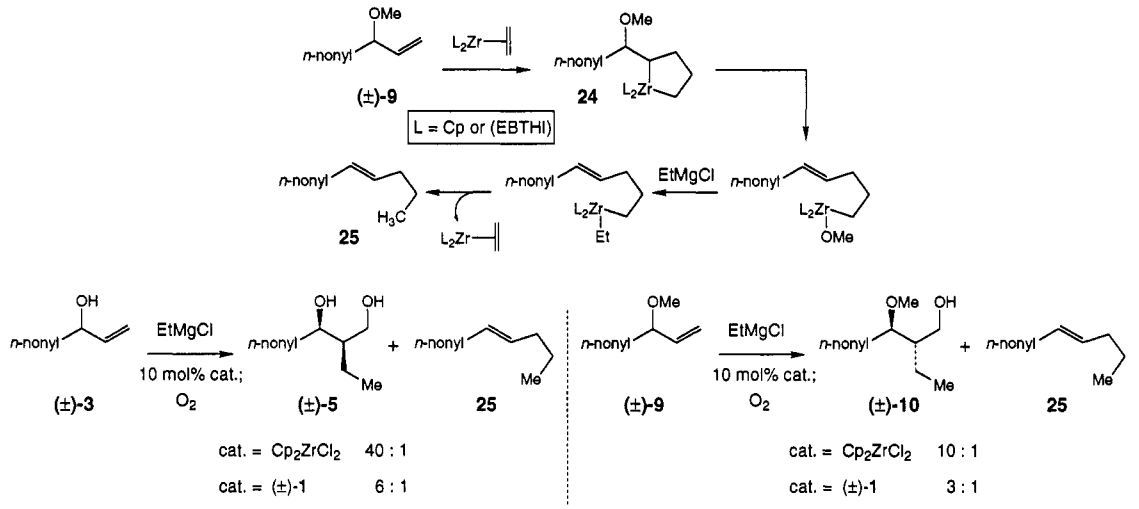
(15) Trigonal bipyramidal methyl groups which are bridged by two zirconocene groups have been reported: (a) Waymouth, R. M.; Santarsiero, B. D.; Grubbs, R. H. *J. Am. Chem. Soc.* **1984**, *106*, 4050–4051. (b) Waymouth, R. M.; Santarsiero, B. D.; Coots, R. J.; Bronikowski, M. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 1427–1441. (c) Buchwald, S. L.; Lucas, E. A.; Davis, W. M.; *J. Am. Chem. Soc.* **1989**, *111*, 397–398. (d) Horton, A. D.; Orpen, A. G. *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 876–878. (e) Binger, P.; Langhauser, F.; Gabor, B.; Herrmann, A. T.; Kruger, C. *J. Chem. Soc., Chem. Commun.* **1992**, 505–506.

(16) For an example of nonmetal-catalyzed carbomagnesation, where Mg is believed to be the π-chelating metal, see: Felkin, H.; Kaesberg, C. *Tetrahedron Lett.* **1970**, 4587–4590.

Scheme III



Scheme IV



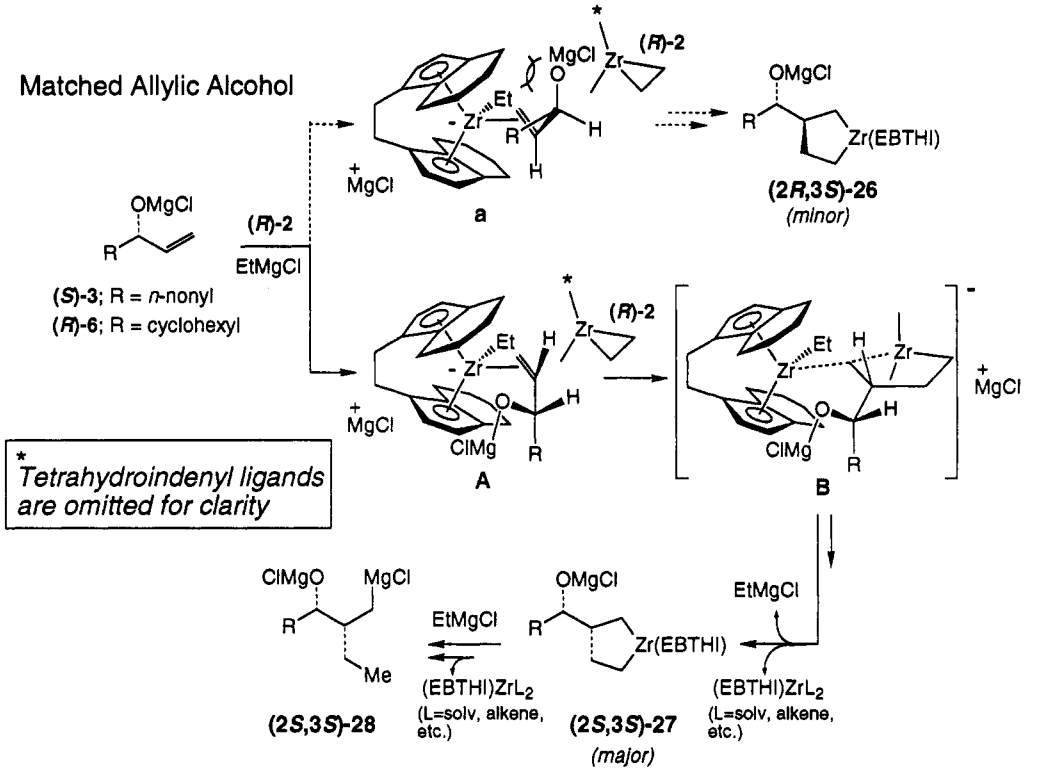
[(EBTHI)]$ZrCl_2$, ~10% each of carbomagnesation product (via **22**, but nonstereoselectively) and 4-tetradecene (**25**) is formed. As shown in Scheme IV, the latter product arises from the regioisomeric head-to-tail metallacyclopentane. In the catalytic process, not only is the reaction more efficient but regioselectivity is in favor of **22** due to the involvement of the bicyclic system (cf. **21**): positioning of the two metallocene groups at the terminal carbon is sterically more favored. However, with the larger indenyl ligands (as compared to cyclopentadienyl ligands), one would expect less dramatic turnover in regioselectivity favoring **22**, since the bimetallic complex derived from **1** (as opposed to that arising from Cp_2ZrCl_2) would be somewhat more cumbersome. Indeed, whereas in zirconocene-catalyzed ethylmagnesations of racemic **3** the ratio of **4**/**25** is 40:1 (see Scheme IV, GLC analysis), with **1** as catalyst, this ratio is diminished to 6:1. As another example, with allylic ether **9**,**10**/**25** is 10:1 when Cp_2ZrCl_2 is used as catalyst, but only 3:1 when **1** is employed. If under the catalytic conditions, formation of the two regioisomeric metallacyclopentanes arose from simple addition of the zirconacyclopropane to the alkene, *opposite* trends in regiochemistry would be observed: steric interactions would then favor more of the head-to-tail adduct (**22**), and thus the ethylmagnesation product would be formed more predominantly with larger terahydroindenyl as compared to cyclopentadienyl ligands.

Involvement of zirconocene group in chelation with the alkene and the neighboring heteroatom provides a plausible rationale for the stereochemical outcomes shown in Tables I and II. The mechanistic principles discussed below parallel those reported by us for the regio- and stereoselective catalytic carbomagnesations of bicyclic homoallylic alcohols and ethers.[13,14] As illustrated in Scheme V, matched association of the reacting alkene with zirconocene (→**A**) should be such that the allylic substituents are oriented away from the cyclohexyl moiety of the transition metal ligand. Coordination of olefinic substrate with the opposite diastereotopic face of the π system would result in significant unfavorable steric interactions (**a**, Scheme V); this pathway would lead to the formation of the minor isomer (2*R*,3*S*)-**26**. It is plausible that addition of **2** to the zirconate occurs syn to the small H group. The oxygen group would be oriented such that, as the carbon–carbon bond is being formed at C2 and C2–Zr interaction is weakend, the heteroatom can associate with an available empty orbital on the transition metal.[17] Thus, through intermediacy of the bis(zirconocene) substrate **B**, the *syn*-zirconacyclopentane (2*S*,3*S*)-**27** is formed selectively. The resulting zirconacycle is subsequently cleaved with regiocontrol to afford the carbomagnesation product **28**.[14]

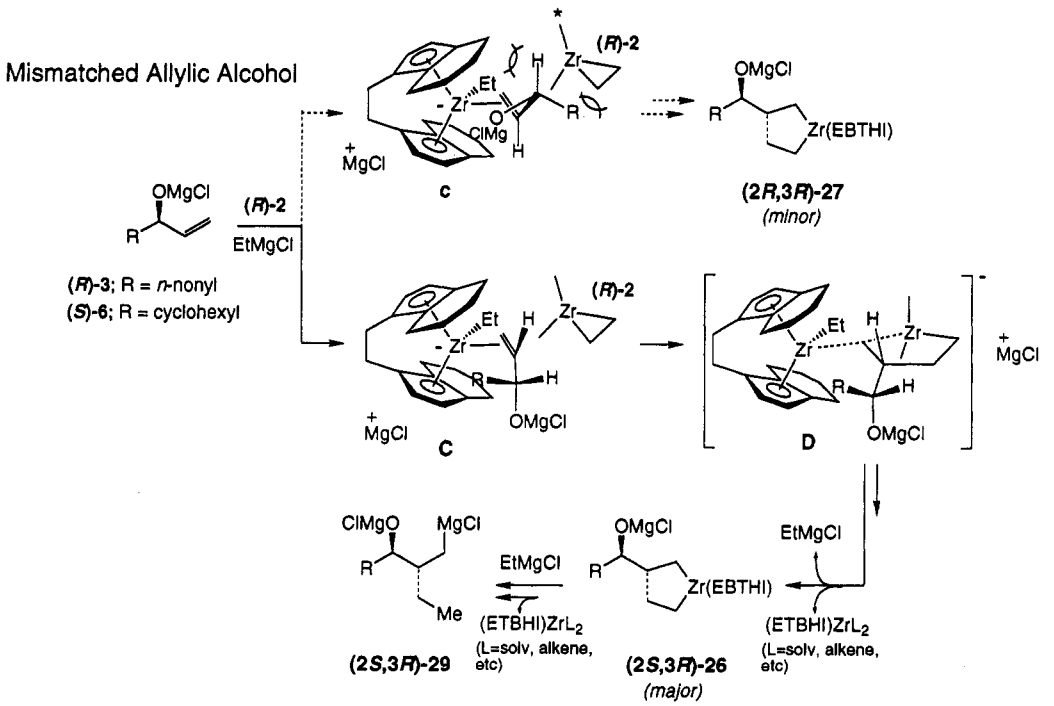
The mechanism delineated in Scheme V predicates that, whereas (*S*)-**3** and (*R*)-**6** should fit the chiral cavity of the catalyst (through **A**) and afford **28** with high stereoselectivity (entries 1 and 3, Table I), the related antipodes

(17) Our mechanistic studies involving reactions catalyzed by zirconocene dichloride (ref 14) indicate that the addition process may well be the turnover-limiting step. If so, then the addition reaction involves a relatively late transition structure where the bound zirconocene is relatively free of the alkene and can thus readily chelate with the nearby heteroatom.

Scheme V

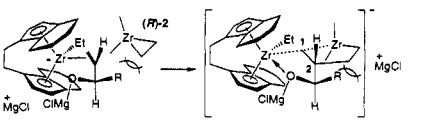


Scheme VI

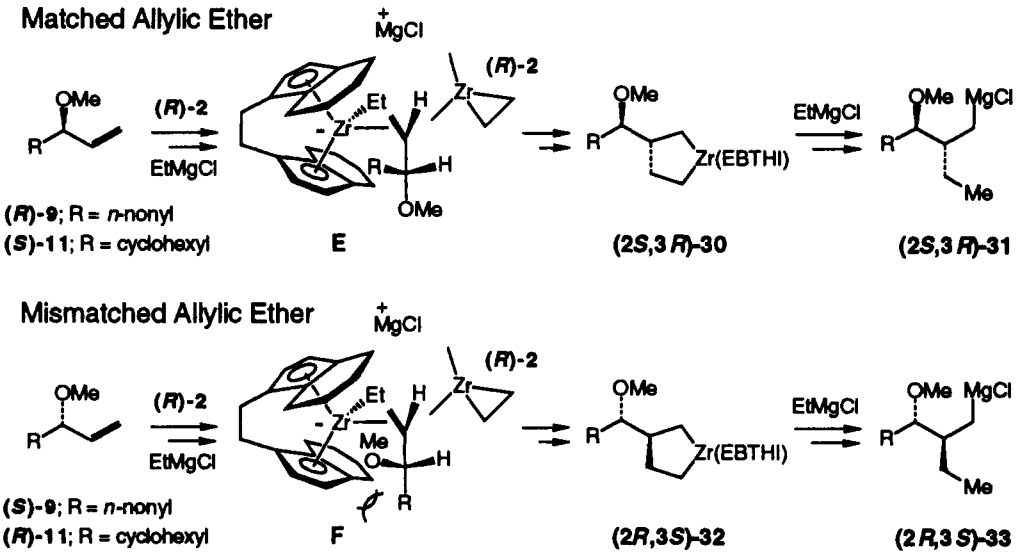


((*R*)-3 and (*S*)-6)) would be mismatched; stereocontrol should be significantly lower and carbomagnesations may even favor the corresponding anti isomer (see entires 2 and 4, Table I).[18] As shown in Scheme VI (c), interaction of the chiral metallocene with the reacting alkene, in a manner that allows for association of the resident heteroatom with the $1a_1$ orbital of zirconium, would lead to severe steric interactions between the alkyl group and the terahydroindenyl ligand. As a result, zirconacyclopentane **27** becomes the minor diastereomeric product. Complex **C** is more favored, since the reacting alkene is bound such that the allylic substituents are positioned away from the cyclohexyl moiety and the incoming zirconacyclopropane

(18) Addition of zirconacyclopropane syn to the allylic proton (see Scheme VI) should be favored on steric grounds. As shown, if addition occurs syn to the α-alkyl group, severe torsional strain may develop.



Scheme VII



adds syn to the small H and anti to the large alkyl unit. Addition of **2**, via **D**, leads to the formation of (2*S*,3*R*)-**26** and, eventually, the anti isomer **29** (80:20). In the presence of THF, in the case of the matched alcohol, a solvent molecule, instead of the neighboring alkoxide, may interact with the transition metal, resulting in the diminution of diastereocontrol (e.g., Table I, entry 1). With the mismatched alcohol, the presence of THF should either have little effect on stereocontrol, as there is no O–Zr chelation in **C**, or enhance anti selectivity, as complex **c** (Scheme VI) would become even less of a favored pathway (see Table I).

Since our studies indicated that the heteroatom substituent in allylic ethers does not associate with the transition metal (steric factors are central), similar arguments as presented for the mismatched-derived complex **C** may be used for reactions of allylic ethers. As illustrated in Scheme VII, formation of **E**, followed by a similar sequence as was described above, leads to the predominant formation of the anti ethylmagnesation product **31**. In contrast, in the reaction of a mismatched ether such as (*S*)-**11**, to ensure that the incoming zirconacyclopropane adds syn to the small H group, the alkyl substituent (R) has to be positioned pseudoaxially where it suffers from unfavorable interactions with the indenyl ligand (**F**).

The alternative mode of binding would situate the allylic substituents oriented toward the cyclohexyl moieties of the indenyl ligand (similar to **a** and **c**). Thus, unlike matched ethers (cf. **E**), with a mismatched allylic ether stereocontrol is low, since there is no energetically favored metal–alkene complex through which the ethylmagnesation process could proceed without severe steric interactions.[19]

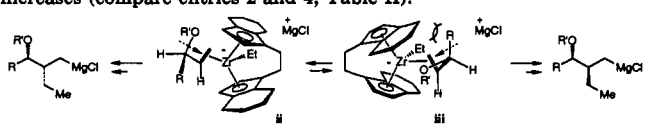
Conclusion

In summary, when chiral catalyst **1** is employed in ethylmagnesations of nonracemic allylic alcohols and ethers, significant differences in stereoselection between reactions of the two antipodes of the alkene substrates is observed. For example, whereas with (*R*)-**1** as catalyst, (*S*)-**3** affords the carbometalation product with high selectivity (92:8), (*R*)-**3** under identical conditions catalyzes the formation of (2*S*,3*R*)-**4** with little stereocontrol. Matched substrates fit the catalyst cavity properly to establish internal chelation without significant steric repulsion (in the case of alcohols), in a way that the zirconacyclopropane addition can readily occur by the sterically least-hindered pathway. In contrast, mismatched substrates can only bind the metallocene in a manner in which either internal chelation is not possible (**C** in Scheme V) or addition of the metallacyclopentane to the olefin complex would cause significant torsional and steric strain. It is most noteworthy that (1) the trends and levels of regio- and stereocontrol in the formation of the zirconacyclopentane, (2) the identity of the matched and the mismatched substrates, (3) the observed variations in solvent effect between reactions of zirconocene dichloride and **1**, and (4) the influence of temperature on reaction selectivity can readily be explained according to the mechanistic paradigm that it is the zirconate of the reacting alkene (not the naked olefin) that is involved in the catalytic process. The data presented herein will be used for the design of more effective chiral catalysts and in related studies in connection to absolute face selectivity and kinetic resolution.[20]

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

(19) A notable contrast between reactions of allylic alcohols and ethers is the opposite influence of the size of alkyl substituent on facial selectivity. With larger alkyl groups, complex **ii** is more favored. With allylic magnesium alkoxides, where complexes of type **iii** are necessary for internal chelation (the heteroatom is aligned to interact with $1a_1$ orbial on zirconium), levels of diasteroselectivity are diminished as the alkyl group is changed from *n*-nonyl to cyclohexyl (92:8 vs 80:20 syn/anti, Table I). In reactions of allylic ethers, with smaller alkyl substituents there is a small amount of leakage (~10%) through complex **iii** (but with no internal chelation) to afford the syn isomer as the minor product. With larger alkyl groups, this minor pathway becomes prohibitive and anti selectivity increases (compare entries 2 and 4, Table II).



(20) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.*, in press.

in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: 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 (deuterochloroform: δ 77.0 ppm). Microanalyses were performed by Robertson Laboratory, Inc. (Madison, NJ). 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. Ethyl chloride and Mg (turnings) were purchased from Aldrich Co. Oxygen gas was dried by passing through P_2O_5 before use.

A Typical Experimental Procedure for the Zirconium-Catalyzed Ethylmagnesation with Chiral Catalyst (*R*)-1. (R)-EBTHI$ZrCl_2$ (7.6 mg, 0.02 mmol) was added to an oven and flame-dried 10-mL pear-shaped flask. After addition of (*R*)-1-nonen-3-ol (3) (24.9 mg, 0.18 mmol), 0.17 mL of THF was introduced into the reaction vessel and the mixture was cooled to 0 °C. Ethylmagnesium chloride (0.55 mL, 1.07 mmol, 1.95 M in THF) was then added in a dropwise fashion. The mixture was stirred under an atmosphere of argon at 25 °C for 12 h, after which it was diluted with 2.0 mL of anhydrous THF. The concoction was cooled to 0 °C, after which gaseous O_2 was introduced to the reaction mixture for 20 min. The mixture was further diluted with 25 mL of saturated aqueous sodium bicarbonate solution, washed with 3 × 25 mL portions of CH_2Cl_2, and subsequently dried over anhydrous $MgSO_4$. Removal of solvent and subsequent silica gel chromatography (10:1 hexanes/EtOAc) afforded 23.3 mg (70% yield) of the carbomagnesation product. Conversion to the corresponding methylene acetal by treatment with paraformaldehyde and *p*-TsOH (cat.) in CH_2Cl_2 followed by capillary GC analysis (DB-1701, 30 m × 0.25 mm, 135 °C, 15 psi) indicated a 80:20 ratio of anti/syn (in favor of 5) by comparison with authentic material.

2(*S*)-Ethyl-3(*R*)-hydroxynonanol (4): IR (KBr) 3355 (br), 2958 (s), 2930 (s), 1463 (m), 1035 (m) cm^{-1}; ^{1}H NMR: δ 3.84 (m, 1H, CH_2CHOH), 3.66 (brd, 2H, J = 5.1, 4.8 Hz, $CHCH_2OH$), 2.79 (brs, 2H, O*H*), 1.6–1.4 (m, 5H, CH_2CHOH, $CHCH_2OH$, $CHCH_2CH_3$), 1.28 (s, 8H, alkyl), 0.93 (t, 3H, J = 7.6 Hz, $CHCH_2CH_3$), 0.85 (t, 3H, J = 6.8 Hz, $CH_2CH_2CH_3$); ^{13}C NMR δ 75.7, 63.7, 45.8, 35.7, 31.8, 29.3, 25.70, 22.5, 21.4, 14.0, 11.7. Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 69.95; H, 12.30.

2(*S*)-Ethyl-3(*S*)-hydroxynonan-1-ol (5): IR (KBr) 3355 (br), 2958 (s), 2930 (s), 2863 (s), 1463 (m), 1035 (m) cm^{-1}; ^{1}H NMR δ 3.85 (m, 1H, C*H*OH), 3.79 (ddd, 2H, J = 10.7, 6.8, 3.2 Hz, CH_2CHOH), 2.8 (brs, 1H, O*H*), 2.6 (brs, 1H, O*H*), 1.6-1.4 (m, 5H, CH_2CHOH, $CHCH_2OH$ and $CHCH_2CH_3$), 1.3 (brs, 8H, alkyl), 0.94 (t, 3H, J = 7.6 Hz, $CHCH_2CH_3$), 0.87 (t, 3H, J = 6.8 Hz, $CH_2CH_2CH_3$); ^{13}C NMR δ 75.5, 64.5, 46.0, 33.2, 31.8, 29.4, 26.3, 22.6, 21.4, 17.9, 12.3.

(1′(*S*),3′-Dihydroxy-2′(*S*)-ethylpropyl)cyclohexane (8): IR (KBr) 3364 (br), 2926 (s), 2852 (m), 1449 (m), 1035 (m) cm^{-1}; ^{1}H NMR δ 3.80 (ddd, 2H, J = 10.5, 3.4, 1.7 Hz, CH_2OH), 3.51 (brd, 1H, J = 8.8 Hz, C*H*OH), 2.93 (brs, 1H, O*H*), 2.73 (brs, 1H, O*H*), 2.05–1.00 (m, 14H, cycloalkyl, CH_2CH_3 and $CHCH_2OH$), 0.95 (t, 3H, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR δ 80.5, 64.8, 42.2, 40.6, 29.6, 29.3, 29.0, 26.0, 25.8, 15.4, 12.1. Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.19; H, 11.03.

(1′(*R*),3′-Dihydroxy-2′(*S*)-ethylpropyl)cyclohexane (7): IR (KBr) 3357 (br), 2919 (s), 2853 (m), 1519 (m), 1113 (m) cm^{-1}; ^{1}H NMR δ 3.79 (ddd, 2H, J = 10.7, 4.6, 2.2 Hz, CH_2OH), 3.38 (brt, 1H, J = 5.1 Hz, C*H*OH), 2.97 (brs, 1H, O*H*), 2.60 (brs, 1H, O*H*), 2.05–1.00, (m, 14H, cycloalkyl, CH_2CH_3 and $CHCH_2CH_3$) 0.93 (t, 3 H, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR δ 79.9, 63.7, 42.0, 40.8, 29.7, 27.6, 26.4, 26.3, 26.0, 21.5, 11.6.

2(*R*)-Ethyl-3(*S*)-methoxynonanol (10): IR (KBr) 3425 (br), 2959 (s), 2932 (s), 2859 (s), 1463 (m), 1378 (m), 1096 (s), 1043 (m) cm^{-1}; ^{1}H NMR δ 3.84 (brd, 1H, J = 11 Hz, CH_2OH), 3.59 (m, 1H, CH_2OH), 3.56 (s, 3H, OCH_3), 3.24 (q, 1H, J = 5.6 Hz, $CHOCH_3$), 3.05 (brs, 1H, O*H*), 1.6–1.4 (m, 5H, CH_2CHOCH_3, $CHCH_2CH_3$ and CH_2CH_3), 1.3 (brs, 8H, alkyl), 0.93 (t, 3H, J = 7.6 Hz, $CHCH_2CH_3$), 0.89 (t, 3H, J = 7.1 Hz, $CH_2CH_2CH_3$); ^{13}C NMR δ 85.6, 63.2, 57.9, 44.2, 31.8, 29.5, 29.4, 25.00, 22.6, 14.0, 11.8. Anal. Calcd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95. Found: C, 71.07; H, 12.66.

(2′(*S*)-Ethyl-3′-hydroxy-1′(*R*)-methoxypropyl)cyclohexane (12): IR (KBr) 3432 (br), 2927 (s), 2853 (s), 1449 (m), 1087 (m) cm^{-1}; ^{1}H NMR δ 3.84 (ddd, 1H, J = 11.2, 3.6, 2.4 Hz, CH_2OH), 3.62 (ddd, 1H, J = 11.5, 7.1, 4.4 Hz, CH_2OH), 3.47 (s, 3H, OCH_3), 3.07 (dd, 1H, J = 7.1, 4.2 Hz, O*H*), 2.95 (dd, 1H, J = 6.8, 3.7 Hz, $CHOCH_3$), 2.00–1.05 (m, 14H, cycloalkyl, $CHCH_2CH_3$ and CH_2CH_3), 0.97 (t, 3H, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR δ 91.1, 62.6 (2 C), 42.6, 41.2, 30.0, 28.9, 26.5, 26.3, 26.2, 22.4, 11.9. Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.99; H, 12.12.

2(*R*)-Ethyl-3(*S*)-[(methoxyethoxy)methyl]nonanol (14): IR (KBr) 3472 (br), 2930 (s), 2855 (s), 1465 (m), 1383 (w), 1100 (m), 1010 (s) cm^{-1}; ^{1}H NMR δ 4.78 (d, 1H, J = 7.3 Hz, OCH_2O), 4.72 (d, 1H, J = 7.1 Hz, OCH_2O), 3.87 (brd, 1H, J = 11.3 Hz, CH_2OH), 3.80 (dt, 1H, J = 10.13, 4.6 Hz, CH_2OH), 3.67 (t, 1H, J = 4.6 Hz, C*H*OMEM), 3.57 (t, 4H, J = 4.4 Hz, OCH_2CH_2O), 3.38 (s, 3H, OCH_3), 2.80 (brs, 1H, O*H*), 1.8–1.4 (m, 5H, CH_2CHOCH_2, $CHCH_2CH_3$ and CH_2CH_3), 1.26 (brs, 8H, alkyl), 0.95 (t, 3H, J = 7.1 Hz, $CHCH_2CH_3$), 0.87 (t, 3H, J = 6.8 Hz, $CH_2CH_2CH_3$); ^{13}C NMR δ 94.8, 80.6, 71.7, 67.4, 61.6, 59.0, 44.5, 31.7 (2C), 29.5, 24.9, 22.5, 21.0, 14.0, 11.9.

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