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ZIRCONOCENE-CATALYZED KINETIC RESOLUTION OF DIHYDROFURANS

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Abstract: Zirconocene-catalyzed kinetic resolution of dihydrofurans may be effected in the presence of 10 mol% non-racemic (EBTHI)$ZrCl_2$. Transformations reported herein proceed efficiently to afford two constitutionally distinct and readily separable products with excellent levels of diastereo- and enantioselectivity. Preparation and resolution of the substrate furans may be carried out in a single pot.

Introduction

The development of new methods that afford easily functionalizable molecules with high enantiomeric purity is one of the most valued goals in modern organic synthesis. Of particular significance are reactions that form carbon-carbon bonds through chiral catalysis and which utilize inexpensive and non-toxic starting materials. With regard to the design of catalytic asymmetric transformations, in general, two approaches may be considered: (1) Asymmetric synthesis, where an achiral substrate is converted to a chiral molecule.[1] (2) Kinetic resolution, where each enantiomer of a racemic chiral starting material faces a distinctly different energy profile in the course of the reaction.[2] The asymmetric synthesis method has the important advantage that the transformation may be carried out to completion (100% maximum yield), whereas the kinetic resolution protocol, under ideal circumstances, affords a yield of ~50%. However, an advantage of the latter approach is that only a few additional percent conversion can provide materials with significantly higher levels of enantiopurity.[3] With asymmetric synthesis, the percent conversion does not provide the same convenient handle for control of enantioselectivity. Nonetheless, aforementioned considerations do dictate that if a practical catalytic kinetic resolution protocol is desired, it would be advantageous if preparation of the requisite starting materials were to be rendered trivial.

With regard to the catalytic resolution strategy, two possible scenarios can be operative: (a) One enantiomer may react faster than the other, such that the "slow" isomer is recovered after ~50% conversion with high

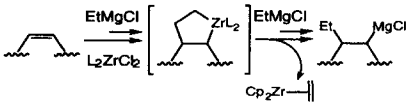
enantioselection. (b) Both enantiomers might react to provide different regio-, diastereo- or constitutional isomers.[4] In the first case, if the reaction product (and not only the recovered starting material) is also formed in high enantiomeric excess (ee), and in the latter instance if the products are readily separable, then the asymmetric catalytic procedure is of even greater utility in synthesis.

In this article we present the results of some of our studies in connection to the zirconocene-catalyzed kinetic resolution of cyclic unsaturated ethers. Asymmetric catalytic carbomagnesation[5] allows for the effective resolution of both the five- and the six-membered ring substrates.[6] The asymmetric protocol described herein provides rapid entry to a variety of easily functionalizable non-racemic starting materials.

Results & Discussion

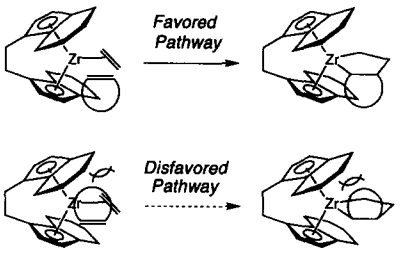
Mechanistic studies by us and others[7] have illustrated that the zirconocene-catalyzed addition of alkyl Grignard reagents to alkenes involves the intermediacy of zirconacyclopentanes, which undergo ligand exchange (metallacycle cleavage) with the alkylmagnesium halide to afford eventually the carbomagnesation product (Scheme I). We reasoned that if the formation of the metallacyclopentane is the stereochemistry determining step, then absolute π-facial selectivity would have to occur in the formation of the zirconacycle.

Scheme I



As is illustrated in Scheme II, simple modeling indicated that if the chiral metallocene, ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium dichloride ([EBTHI]$ZrCl_2$]), introduced by Brintzinger,[8] were to be employed as the precatalyst,[9] disubstituted - and not terminal - alkenes would be the most suitable substrates for catalytic asymmetric carbomagnesation. As shown below (Scheme II), whereas the top mode of attack by a cyclic alkene would be devoid of any costly interactions (favored pathway), the alternative route (bottom) would engender unfavorable interactions: the approach of the incoming substrate may lead to steric strain with the protruding cyclohexyl portion of the chiral indenyl ligand.

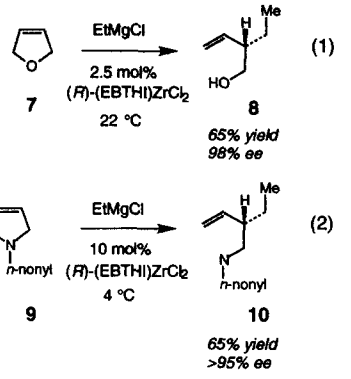
Scheme II



Therefore, at least initially, a successful enantioselective carbomagnesation would be predicated upon the availability of a suitable class of disubstituted olefins. Since simple disubstituted alkenes, such as cyclohexene, were found to be unreactive under the carbomagnesation conditions, we required modifications in substrate structure such that a notable boost in reactivity could be attained. In the course of our mechanistic studies on the diastereoselective ethylmagnesation of chiral terminal alkenes,[7i] we realized that a neighboring heteroatom can enhance the rate of reaction of an alkene with zirconacyclopropane, an effect which allowed for the formation of the

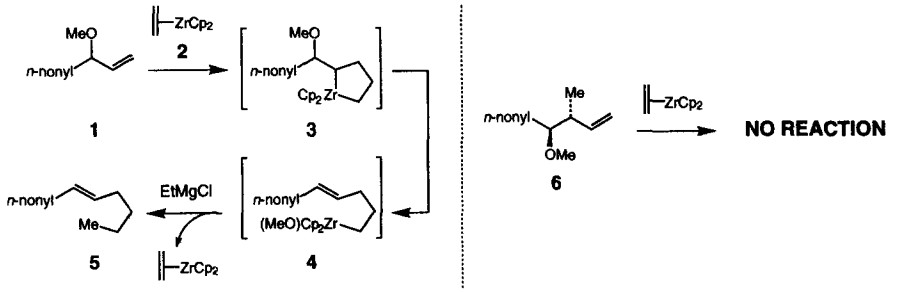
derived metallacyclopentane at an appreciable rate. For example, as shown in Scheme III treatment of allylic ether **1** with one equivalent of metal-alkene complex **2**[10] affords **5** in 60% yield at 22 °C; the reaction presumably occurs through intermediacy of alkylzirconocenes **3** and **4**. In contrast, similar treatment of the homoallylic ether **6** leads to the complete recovery of the starting material. Although the exact reason for the ease of formation of the intermediate metallacycles with substrates that bear an allylic heteroatom is yet to be rigorously determined, we reasoned that cyclic allylic ethers may be excellent substrates for the enantioselective zirconocene-catalyzed carbomagnesation: the resident heteroatom would serve to enhance reactivity and the disubstituted olefin would allow us to obtain high enantioselection.

Accordingly, when substrates such as 2,5-dihydrofuran **7** or amine **9** are treated to catalytic ethylmagnesation reaction conditions, with (*R*)-(EBTHI)$ZrCl_2$ as the precatalyst, **8** and **10** form in 65% yield and excellent enantioselectivity (eq 1-2). The stereochemical identity of the major enantiomer in both transformations presumably arises from what was labeled as the "favored pathway" in Scheme II.

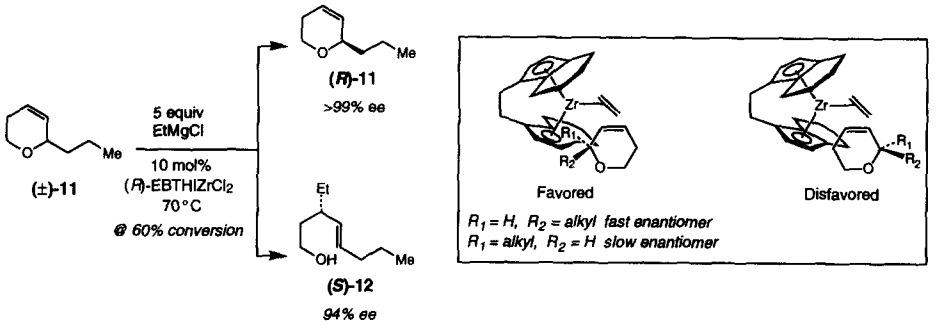


The levels of enantioselectivity observed in the catalytic asymmetric carbomagnesation (cf. eq 1-2) imply highly ordered association of the chiral metal-alkene complex with the substrate. A critical issue that arises as a result of such organized binding is the influence of a preexisting stereogenic center in the cyclic ether. Our initial studies with substituted dihydropyrans indeed proceeded with excellent levels of enantiocontrol: for example, reaction of **11** with 10 mol% (*R*)-(EBTHI)$ZrCl_2$ and five equiv EtMgCl at 70 °C, when quenched at ~60% conversion, yielded recovered (*R*)-**11** in >99% ee (GLC analysis) and ethylmagnesation product (*S*)-**12** in 94% ee (GLC analysis).

Scheme III

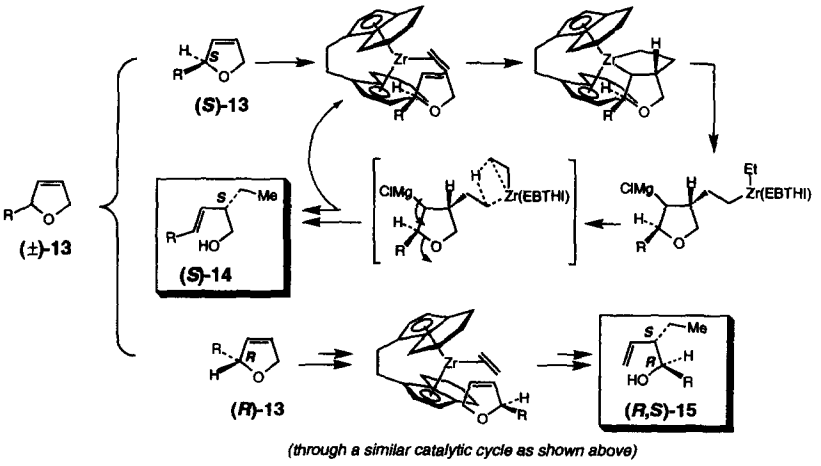


Scheme IV



It is important to note that, as shown in Scheme IV, transformations that involve regiochemically unsymmetric ethers (*e.g.*, pyrans) benefit from an added organizational factor in the transition state that leads to the intermediate metallacyclopentane (presumably the stereochemistry-determining step): C-Zr bond is formed preferentially at the site α to the C-heteroatom bond (*e.g.*, C-O). With dihydrofurans, on the other hand, as a result of structural symmetry, the latter regiochemical principle is not applicable. That is, as illustrated in Scheme V, both enantiomers may find an energetically acceptable pathway through which they undergo reaction. However, as detailed in Scheme V, if the two pathways do not cross over (if the *S* isomer only affords the primary alcohol and the *R* enantiomer the secondary alcohol), kinetic resolution may be accomplished in the manner where each enantiomer of the racemic starting material is converted to two constitutionally distinct

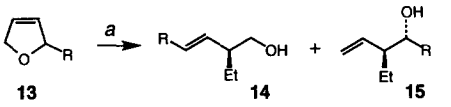
Scheme V



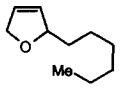
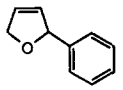
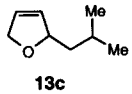
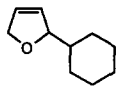
products. The resolution protocol would be particularly noteworthy if: (1) the starting racemic material can be prepared easily, (2) reaction products are formed in high ee and diastereoselection, and (3) if the reaction products can be separated readily.

As is illustrated in the Table, when 2-substituted furan **13a** is treated with five equivalents of EtMgCl and 10 mol% (*R*)-(EBTHI)$ZrCl_2$ in THF and the mixture is heated to 70 °C, primary alcohol **14a** and secondary alcohol **15a** are obtained in 48% yield each after silica gel chromatography (96% overall yield). Not only are **14a** and **15a** formed efficiently, but the observed levels of enantiofacial selectivity are excellent (98% ee, as judged by chiral GLC analysis). Furthermore, **15a** is produced in high levels of diastereochemical control (95:5) and **14a** is formed with >95:5 *trans*:*cis* alkene stereoselectivity.[11] The identity of the

Table. Zirconocene-Catalyzed Kinetic Resolution of Dihydrofurans.



13 **14** **15**

substrate	reaction time (hr)	yield (%, of **14**)[b]	*ee* (%, of **14**)[c]	yield (%, of **15**)[b]	*ee* (%, of **15**)[c]	anti:syn (**15**)[d]
 **13a**	10	48	**98**	48	**98**	95:5
 **13b**	10	49	**96**	49	**>95**	95:5
 **13c**	14	31	**98**	33	**98**	95:5
 **13d**	48	23	**>95**	26	**99**	99:1

a. Conditions: Five equiv EtMgCl, 10 mol% (*R*)-(EBTHI)$ZrCl_2$, THF, 70 °C. *b*. isolated yields of purified products (silica gel chromatography). *c*. Enantiomeric excess determined by GLC analysis (BETA-DEX 120 chiral column by Supelco, compounds **14a, 14b, 15a, 15c** and **15d**), or by HPLC (CHIRACEL OB-H chiral column by DuPont, **14b**), or through analysis of the 300 MHz ^1H NMR spectrum of the derived (*S*)-MPTA esters in comparison with authentic enantiomers and authentic racemic material (compounds **14d** and **15b**, see the Experimental section for further detail). *d*. Diastereomeric ratios were determined by GLC analysis of the derived methylene acetals.

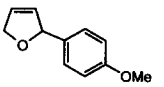
predominant enantiomers and diastereomers is consistent with the prediction outlined in Scheme V (for proof of sterechemistry, see the Experimental Section).

Thus, the two enantiomers of the racemic **13a** are readily converted to two easily separable reaction products which are formed with excellent diastereo- and enantiocontrol. Several additional examples are illustrated in the Table. Phenyl-substituted dihydrofuran **13b** is a suitable resolution substrate; less efficient are dihydrofurans **13c** and **13d** (overall yields of 64% and 49%, respectively); nonetheless, asymmetric ethylmagnesation of the latter two compounds provides the corresponding primary and secondary alcohols in similarly exceptional levels of relative and absolute stereochemical control.

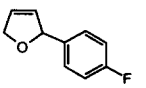
Two issues with regard to the data presented in the Table merit elaboration:

(1) Since the rate of catalytic ethylmagnesation appears to diminish as the size of the alkyl goup increases (**13a** vs. **13c** vs **13d**), it is likely that in the course of the catalytic process the substituents either interact with the catalyst ligand structure, or that the conformation required for the formation of the metallacyclopentane orients the alkyl unit in such a position so as to lead to unfavorable torsional interactions. Depictions illustrated in Scheme V may be considered with at least one caveat. If the pathways shown did represent reality to a higher degree (the alkyl group pointing away from the ligand system), one would expect little variation in the rate of the carbomagnesation as a function of the size of the alkyl group.

(2) Zirconocene-catalyzed ethylmagnesation of the phenyl substituted furan **13b** vs that of **13d** hints that an electronic effect may be operative in the catalytic cycle. In an effort to determine whether such a rate difference is electronic or perhaps steric in nature, we examined the relative efficiency of reactions of dihydrofurans **16** and **17**. Whereas treatment of the *p*-methoxyphenyl substrate for 10 h to identical conditions described in the Table only resulted in 50% recovered starting material, reaction of the *p*-fluoro substrate proceeded efficiently to afford the expected products in 96% total yield (primary alcohol: 46% yield and 99% ee; secondary alcohol, 50% yield and 97% ee). Although additional data are necessary for a meaningful conclusion with regard to the presence of any electronic effect in these transformations, on a more basic level, these observations do indicate that subtle changes in the electronic properties of the substrate can significantly influence the efficiency of the asymmetric carbomagnesation.

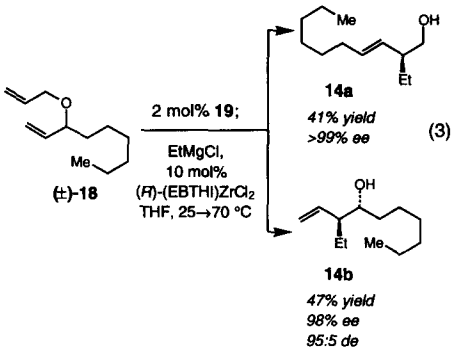


16



17

In connection to the simplicity with which these transformations can be carried out, it is worthy of note that preparation of the starting furan and its subsequent resolution may be carried out in tandem in a single pot by two sequential catalytic processes. As is exemplified in eq 3, when diene **18**, prepared from simple alkylation of the corresponding allylic alcohol with allylbromide, is treated with 2 mol% of the diene metathesis catalyst $(PCy_3)_2Cl_2Ru{=}CHCH{=}CPh_2$ (**19**),[12] and the reaction mixture is then treated with 10 mol% (*R*)-(EBTHI)$ZrCl_2$ and five equivalents EtMgCl at 70 °C, **14a** and **14b** are obtained in 41% and 47%



yield after silica gel chromatography, respectively. Thus, from simple starting materials, in a single operation, compounds of excellent optical purity can be obtained efficiently (88% total yield).

Conclusions

Zirconocene-catalyzed ethylmagnesation of chiral 2-substituted dihydrofurans proceeds efficiently to afford products of high optical and diastereomeric purity. Although the procedure presented herein for the preparation of non-racemic chiral molecules can only afford a maximum yield for each product of no more than 50%, the ease of the operation, that reactions proceed without any appreciable formation of side products, and the facility with which the requisite starting materials are generated (tandem metathesis/carbomagnesation) render this technology an attractive means for enantioselective synthesis. The reaction protocol presented herein should be of use, since the resulting alkene and hydroxyl functionalities present in the products (**14** and **15**) can be modified for access to a large number of other non-racemic chiral materials.

Experimental Section

General. Infrared (IR) spectra were recorded on a Perkin Elmer 781 spectophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra were recorded on a Varian Unity 300 (300 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: 7.24 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a Varian Unity 300 (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.0 ppm). An Alltech Associates DB-1 capillary column (30m x 0.32mm) was used to determine conversions. Enantiomer ratios were determined by GLC with either a BETA-DEX 120 (30m x 0.25mm) chiral column by Supelco or a CHIRALDEX GTA (20 x 0.25mm) chiral column by Alltech Assoc., Inc., or by HPLC where a chiral column supplied by DuPont (CHIRACEL OB-H) was utilized. Microanalyses were performed by Robertson Microlit Laboratories (Madison, New Jersey).

All reactions were conducted in oven (135 °C) and flame-dried glassware under an inert atmosphere of dry argon. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl. Ethylmagnesium chloride was prepared from ethylchloride and Mg (turnings) which were purchased from Aldrich and used without further purification. (EBTHI)$ZrMe_2$ was prepared and resolved by the method of

Buchwald,[8b] and converted to the corresponding dichloride by treatment with ethereal HCl (2.5 equiv) at -10 °C for 2 min. Non-racemic (EBTHI)$ZrCl_2$ catalyst batches were stored under argon in glovebox. $(PCy_3)_2Cl_2Ru$=CHCH=CPh_2 was prepared by the method of Grubbs.[12]

Representative experimental procedure for the asymmetric zirconium-catalyzed ethylmagnesation of chiral dihydrofurans. A 5.0 mL flame dried round bottom flask was charged with 50.0 mg (0.32 mmol) of **13b**, 0.80 mL of anhydrous THF and 0.80 mL of freshly prepared EtMgCl (1.60 mmol). The precatalyst was subsequently added to this mixture (13.6 mg, 0.03 mmol). The reaction flask was first equipped with a flame dried reflux condenser and then immersed in a 70 °C oil bath. The reaction was allowed to stir at 70 °C for 10 h. The reaction flask was cooled by an ice bath, after which excess Grignard reagent was quenched by dropwise addition of 2.0 mL of a 1.0 M solution of HCl. The mixture was diluted with 15.0 mL distilled H_2O and washed with 3x25 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$. Removal of the drying agent through filteration, and evaporation of organic solvents *in vacuo* left behind a pale yellow oil. Silica gel chromatography with 20:1 hexanes : EtOAc provided 29.0 mg (49% yield) of **14b** and 28.9 mg (49% yield) of **15b** as colorless oil.

(*R*)-2-Ethyl-*trans*-3-decene-1-ol (14a). IR (KBr): 3367 (br,m), 2959 (m), 2925 (s), 2873 (w), 2856 (m), 1462 (m), 1040 (m), 969 (m) cm^{-1}; ^1H NMR: δ 5.55 (1H, dt, J=15.6, 6.84, vinylic C**H**CH_2), 5.12 (1H, ddd, J=15.1, 8.8, 1.0, vinylic CHC**H**), 3.54 (1H, dd, J=10.3, 5.1, CH_2OH), 3.34 (1H, dd, J=10.5, 8.5 Hz, CH_2OH), 2.04 (1H, m, allylic C**H**), 1.20-1.34 (12H, m, aliphatic CH), 0.87 (6H, t, J=7.32, CH_2CH_3); ^{13}C NMR: δ 134.3, 130.9, 65.7, 47.7, 32.7, 29.5, 28.8, 24.0, 22.6, 14.1, 11.6. Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.35; H, 13.40.

(*R*)-3-Ethyl-1-decen-(*S*)-4-ol (15a). IR (KBr): 3396 (br,m), 2958 (m), 2930 (s), 2873 (w), 2858 (m), 1464 (w), 911 (m) cm^{-1}; ^1H NMR: δ 5.62 (1H, dt, J=17.1, 10.3, vinylic C**H**), 5.18 (1H, dd, J=10.5, 2.2, *cis* vinylic CH), 5.08 (1H, dd, J=17.3, 2.2, *trans* vinylic CH), 3.47 (1H, m, C**H**OH), 1.90 (1H, m, allylic CH), 1.25-1.50 (12H, m, aliphatic CH), 0.87 (6H, t, J=7.1, CH_2CH_3); ^{13}C NMR: δ 138.7, 117.8, 73.4, 52.1, 34.8, 29.3, 25.7, 23.7, 22.6, 14.0, 11.9. Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.42; H, 13.36.

(*R*)-2-Ethyl-*trans*-4-phenyl-3-butene-1-ol (14b). IR (KBr): 3360 (br, m), 3040 (w), 2961 (s), 2928 (s), 2873 (m), 2360 (m), 2350 (m), 1038 (m), 966 (m), 746 (s), 693 (s) cm^{-1}; ^1H NMR: δ 7.34 (5H, m, aromatic CH), 6.50 (1H, d, J=15.9, vinylic CH), 5.99 (1H, dd, J=15.9, 9.0, vinylic CH), 3.67 (1H, m, CH_2OH), 3.52 (1H, m, CH_2OH), 2.31 (1H, m, allylic CH), 1.46 (1H, s, OH), 1.19-1.63 (2H, m, CH_2CH_3), 0.94 (3H, t, J=7.3, CH_2CH_3); ^{13}C NMR: δ 132.6, 131.3, 128.5, 127.3, 126.1, 65.8, 48.1, 24.1, 11.7. Anal. Calcd for $C_{12}H_{16}O$: C, 81.82; H, 9.09. Found: C, 81.78; H, 9.35.

(*R*)-2-Ethyl-(*S*)-1-phenyl-3-butene-1-ol (15b). IR (KBr): 3450 (br, m), 3020 (w), 3082 (w), 2963 (s), 2932 (m), 2875 (m), 1454 (m), 1037 (m), 1028 (w), 914 (m), 700 (s) cm^{-1}; ^1H NMR: δ 7.33 (5H, m, aromatic CH), 5.65 (1H, dt, J=17.1, 9.5, vinylic CH), 5.28 (1H, dd, J=7.1, 2.0, *cis* vinylic CH), 5.20 (1H, dd, J=17.1, 2.0, *trans* vinylic CH), 4.40 (1H, dd, J=8.3, 1.2, CHOH), 2.18 (1H, s, OH), 2.21 (1H, m, allylic CH), 1.20 (2H,

m, CH_2CH_3), 0.79 (3H, t, J=7.6 Hz, CH_2CH_3); ^{13}C NMR: δ 139.1, 128.2 (2C), 127.6, 126.9 (2C), 118.8, 76.5, 54.5, 23.4, 11.7. Anal. Calcd for $C_{12}H_{16}O$: C, 81.82; H, 9.09. Found: C, 81.51; H, 9.10.

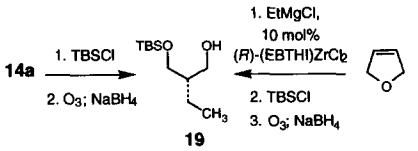
(*R*)-2-Ethyl-6-methyl-*trans*-3-heptene-1-ol (14c). IR (KBr): 3350 (br, m), 2956 (s), 2924 (s), 2870 (w), 1463 (m), 1041 (m), 970 (m), 735 (m) cm^{-1}; ^1H NMR: δ 5.55 (1H, dt, J=15.4, 6.8 Hz, vinylic $CHCH_2$), 5.12 (1H, ddd, J=15.1, 8.8, 1.2 Hz, vinylic CHCH), 3.55 (1H, dd, J=10.5, 5.4 Hz, CH_2OH), 3.36 (1H, dd J=10.5, 8.5 Hz, CH_2OH), 2.07 (1H, m, allylic CH), 1.93 (2H, m, allylic CH_2), 1.45-1.65 (3H, broad m, CH_3CH_2 and CH_3CHCH_3), 0.90 (6H, dd, J=6.8, 1.0 Hz, CH_3), 0.90 (3H, t, J=7.6 Hz, CH_3); ^{13}C NMR: δ 132.9, 132.2, 65.8, 47.8, 42.1, 28.3, 24.0, 22.3, 22.2, 11.7. Anal. Calcd for $C_{10}H_{20}O$: C, 76.85; H, 12.91. Found: C, 77.03; H, 13.00.

(*R*)-3-Ethyl-6-methyl-1-hepten-(*S*)-4-ol (15c). IR (KBr): 3481 (br, m), 2961 (s), 2927 (s), 2920 (m), 1493 (m), 1076 (m), 914 (m), 761 (m), 700 (s) cm^{-1}; ^1H NMR: δ 5.67 (1H, dt, J=17.1, 9.77, vinylic CH), 5.18 (1H, dd, J=10.3, 2.0,*cis* vinylic CH), 5.08 (2H, dd, J=17.1, 1.9, *trans* vinylic CH), 3.55 (1H, dd, J=10.3, 2.0 Hz, CHOH), 1.86 (1H, m, allylic CH), 1.3-1.5 (5H, m, aliphatic CH), 0.91 (6H, t, J=7.3, CH_3CHCH_3), 0.88 (3H, t, J=7.1, CH_2CH_3); ^{13}C NMR: δ 138.6, 117.9, 71.3, 52.7, 44.1, 24.6, 23.7, 23.6, 21.8, 11.9. Anal. Calcd for $C_{10}H_{20}O$: C, 76.85: H, 12.91. Found: C, 76.67; H, 12.65.

((*R*)-3-Ethyl-*trans*-1-buten-4-ol)cyclohexane (14d). IR (KBr): 3412 (br, m), 2932 (w), 2924 (s), 2852 (m), 1461 (m), 1038 (m), 969 (m) cm^{-1}; ^1H NMR: δ 5.52 (1H, dd, J=15.6, 6.8 Hz, vinylic CH), 5.08 (1H, ddd, J=15.4, 8.8, 1.2, vinylic CH), 3.35 (1H, dd, J=10.3, 5.1, CH_2OH), 3.32 (1H, dd, J=10.5, 8.6, CH_2OH), 2.04 (2H, m, allylic CH), 1.0-1.8 (12H, m, aliphatic CH), 0.88 (3H, t, J=7.3, CH_2CH_3); ^{13}C NMR: δ 147.9, 135.7, 73.2, 55.1, 48.3, 40.8, 33.6, 33.5, 31.5, 19.1. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.28; H, 11.90.

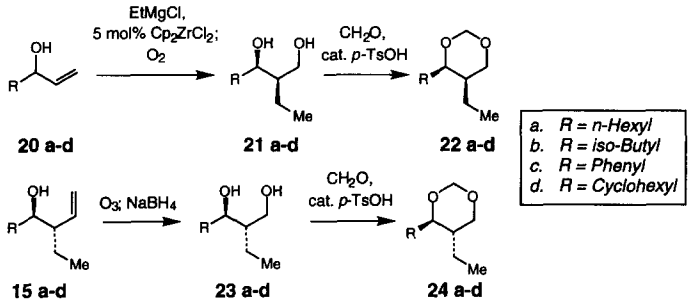
((*R*)-2-ethyl-3-Buten-(*S*)-1-ol)cyclohexane (15d). IR (KBr): 3436 (br, m), 2958 (w), 2924 (s), 2873 (m), 1449 (m), 977 (m) cm^{-1}; ^1H NMR: δ 5.65 (1H, ddd, J=17.1, 10.3, 9.0 Hz, vinylic CH), 5.19 (1H, dd, J=10.3, 2.0, *cis* vinylic CH), 5.07 (1H, dd, J=16.6, 2.2, *trans* vinylic CH), 3.18 (1H, t, J=5.7, CHOH), 2.08 (1H, m, allylic CH), 1.0-1.86 (12H, m, aliphatic CH), 0.87 (3H, t, J=7.3, CH_2CH_3); ^{13}C NMR: δ 138.6, 117.6, 77.4, 48.5, 40.4, 29.7, 27.6, 26.5, 26.4, 26.1, 23.9, 11.9. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.26; H, 12.24.

Proof of absolute stereochemistry for products 14. As is illustrated below, protection of the hydroxyl group of **14a** as its *tert*-butyldimethylsilyl ether, followed by ozonolysis/reduction of the olefin afforded the primary alcohol **19**. Authentic non-racemic **19** was prepared by enantioselective carbomagnesation of 2,5-dihydrofuran. Analysis of the ^1H NMR spectra of the derived Mosher's esters of the authentic and the reaction product indicated the identity of the product to be as shown.



19

Proof of relative stereochemistry for products 15. Diastereomerically enriched secondary alcohol **21** was synthesized by the zirconocene-catalyzed ethylmagnesation (followed by O_2 quench) to afford a 4:1 (syn:anti) mixture of diastereomers.[7j] The resulting diol (**21**) was subsequently converted to the derived methylene acetal **22**. Ozonolysis followed by reduction ($NaBH_4$) of products **15a-d** afforded diols and methylene acetals identical to those obtained from the first route (^1H NMR and GLC analysis; same as the minor diastreomers derived from diastereoselective ethylmagnesation).



Proof of absolute stereochemistry for products 15. The sequence illustrated below was employed for the preparation of authentic enatiomerically enriched **15**. Enatiomerically enriched secondary alcohol was prepared according to the kinetic resolution procedure reported by Sharpless.[2b] Protection of alcohol **25** as its MEM ether, followed by zirconium-catalyzed ethylmagnesation afforded **27** as a 4:1 (anti:syn) mixture of diastereomers.[7j] Treatment of **27** with $ZnCl_2$ (CH_2Cl_2)[13] afforded methylene acetal **28**. GLC analysis of the methylene acetal derived from **15a-d** and the authentic product clearly indicated the identity of the product is as shown.

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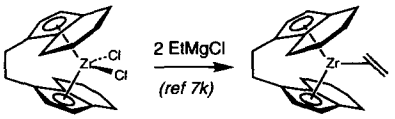

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