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Stereospecific Synthesis of Optically Active Phenylpropylene Oxides

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The stereospecific lithiation of diastereomeric phenylpropylene oxides has been studied as well as the trapping reaction with electrophiles. The reduction of the *cis*-α-benzoylpropylene oxide to give prevalently the *anti*-epoxy alcohol has been investigated as well.

Introduction

Optically active phenylpropylene oxides are highly versatile building blocks for asymmetric syntheses.[1] Indeed, they have been successfully employed for the design of silica-supported dendritic chiral catalysts[2] and as key intermediates in the stereoselective construction of multisubstituted tetrahydrofurans[3a] whose unit occurs frequently in natural products, e.g., antibiotics and *C*-glycosides.[3b] Phenylpropylene oxides are usually made by asymmetric epoxidation of trisubstituted olefins[1b] with chiral (salen)Mn(III) complexes,[4] ketone catalysts,[5] dioxiranes,[6] and functionalized iminium salt systems,[7] whereas the corresponding chiral nonracemic epoxy alcohols, which are valuable molecules for the preparation of biologically active compounds such as *β*-blockers,[8] can be prepared by the Sharpless−Katsuki epoxidation[9] or by using a chiral Fe(porph)oxo complex.[10]

The oxiranyl anion-based methodology has undoubtedly become a valuable method for making functionalized epoxides. Stabilized and nonstabilized oxiranyl anions, mainly oxiranyllithiums, made available by deprotonation, transmetalation, desilylation, desulfinylation, or via a carbenoidic route, have been rather deeply studied and synthetically exploited for the preparation of target molecules.[11] Our involvement in the oxiranyl anion methodology[12a−e] has recently led us to discover that α-lithiated styrene oxides are chemically and configurationally stable so that they can be stereospecifically captured with electrophiles. Such a methodology has been successfully applied to the synthesis of optically active epoxylactones[12f] and a potent oral antifungal agent.[12g] Relying on the synthetic efficiency of the above-mentioned oxiranyl anion methodology, we decided to extend our investigation to the lithiation of *cis*- and *trans*-phenylpropylene oxides and to the use of the resulting lithiated species for the synthesis of more substituted stereodefined phenylpropylene oxides. Herein, we report the first stereospecific synthesis of trisubstituted phenylpropylene oxides based on the deprotonation−alkylation (hydroxylalkylation) of the simpler and easily available chiral nonracemic *cis*- and *trans*-phenylpropylene oxides.

Results and Discussion

Highly enantiomerically enriched (1*S*,2*S*)-(−)-1-phenylpropylene oxide **1a**, commercially available (ee 99%), can be eventually prepared (76% yield, ee ≥ 95% in our hands) from (1*S*,2*R*)-(+)-*N*-methylephedrine according to

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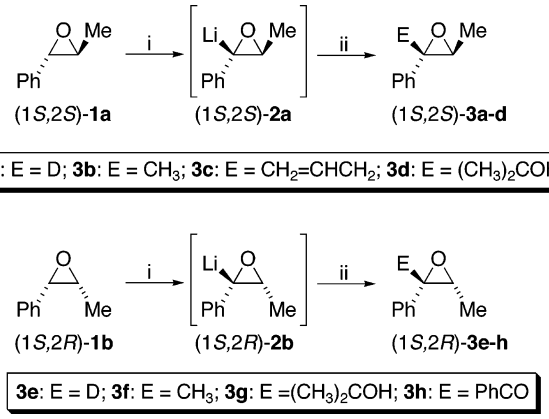
SCHEME 1[a]



[a] Reagents and conditions: (i) *s*-BuLi/TMEDA, THF, −98 °C, 2 h for (1*S*,2*S*)-**1a**, 30 min for (1*S*,2*R*)-**1b**; (ii) electrophile.

Castedo's procedure,[13] which uses a phase-transfer catalyst. Racemic **1a** has been prepared by an in situ (CF_3COCH_3)-catalyzed epoxidation of *trans*-*β*-methylstyrene (H_2O_2 as primary oxidant at high pH), as reported by Shi.[14] (1*S*,2*R*)-(−)-1-Phenylpropylene oxide **1b** has been analogously synthesized (95% yield, ee ≥ 95%) starting from (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine[13] and racemic **1b** by reduction of 1-phenyl-1-propyne,[15] followed by the oxidation of the resulting *cis*-*β*-methylstyrene according to Shi's procedure (62% overall yield).[14]

Treatment of a precooled mixture (−98 °C) of (1*S*,2*S*)-(−)-1-phenylpropylene oxide **1a** (ee 99%) and TMEDA (3 equiv) in THF with *s*-BuLi (3 equiv) (*n*-BuLi and LDA were ineffective) gave a cherry-red solution likely to be ascribed to the lithiooxirane **2a**, which proved to be chemically stable at low temperature (−98 °C) for at least 2 h. The trapping reaction of **2a** with a deuterium source (D_2O) furnished the corresponding α-deuterated phenylpropylene oxide in a good yield after distillation (77%, > 98% D): the reaction took place with complete retention of configuration at the α-carbon (dr >98:2, ee >98%),[16] thus indicating that **2a** is also configurationally stable (Scheme 1).

The use of less than 3 equiv of either the base or TMEDA as well as a shorter reaction time led only to lower deuterium incorporation, but the observed diastereo- and enantioselectivity was still very high. Compared to the lithiation of the unsubstituted styrene oxide,[12g] the epoxide **1a**, probably for steric reasons,[17] underwent a slower α-deprotonation, but the resulting lithiated species showed a longer lifetime (2 h) (lithiated styrene oxide showed a lifetime of only 30 min).[12g] Here again, as in the case of lithiation of styrene oxide, the presence of TMEDA and of a donor solvent (THF) was unavoidable; in fact, the use of a nondonor solvent (hexane), the absence of TMEDA, and a higher temperature (> −98 °C) exalted the carbenoid nature of **2a**, thus leading to the formation of enediols **4** ("eliminative dimerization")[18] and alkenes **5** which are the result of a "reductive alkylation" process promoted by *s*-BuLi on **2a** with concomitant elimination of Li_2O (Scheme 2).[19]

SCHEME 2

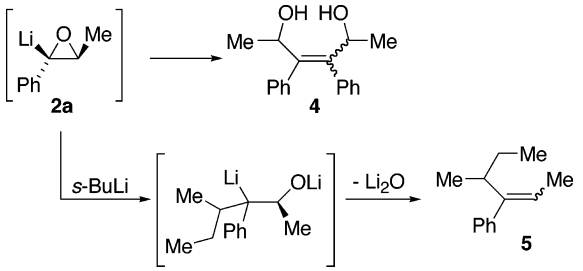


TABLE 1. Reaction of (1*S*,2*S*)-2a with Electrophiles

electrophile	product (% yield)[a]	convn (%)	dr[b]	er[c]	$[\alpha]^{20}_D$[d]
D_2O	(1*S*,2*S*)-**3a** (77)	>98	>98:2	>99:1	−38.0
CH_3I	(2*S*,3*S*)-**3b** (51)	>98	"	"	−16.0
CH_2=$CHCH_2Br$	(4*S*,5*S*)-**3c** (74)	98	"	97:3	+6.6
$(CH_3)_2CO$	(3*S*,4*S*)-**3d** (51)	83	"	>99:1	+7.0

[a] Isolated yield after distillation or column chromatography. [b] Diastereomeric ratio determined by ^1H NMR analysis of the crude reaction mixture. [c] Enantiomeric ratio by GC analysis on a Chiraldex B-DM capillary column. [d] *c* 1, $CHCl_3$.

The reaction of (1*S*,2*S*)-**2a** with other electrophiles (CH_3I,[20] allyl bromide,[21] and acetone) again occurred stereospecifically providing the corresponding α-substituted propylene oxides **3b**−**d** in good yields and high dr and er values (Table 1).

Interestingly, **2b**, obtained by deprotonation of optically active (1*S*,2*R*)-(+)-1-phenylpropylene oxide **1b**, proved to be more reactive with respect to the trans isomer **2a** and configurationally stable. Under the same conditions as above, the deprotonation of **1b**, at −98 °C, required only 30 min for completion, and the corresponding oxiranyllithium **2b** was quantitatively deuterated (> 98% D) with complete retention of configuration at the α-carbon (Table 2).[16] The temperature was also crucial: a temperature higher than −98 °C (e.g., −78 °C), even in the presence of 3 equiv of TMEDA, caused nucleophilic attack of *s*-BuLi and formation of products of the kind of **5**. The observed configurational stability

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(16) (a) Deuterated **3a** and **3e** showed almost the same optical rotation of the starting epoxides **1a** ($[\alpha]^{20}_D$ −44.8, *c* 1 $CHCl_3$) and **1b** ($[\alpha]^{20}_D$ +41.3, *c* 1 $CHCl_3$), respectively. (b) Having used up to 3 equiv of *s*-BuLi and in consideration of the fact that unactivated epoxides can also undergo direct deprotonation (*s*-BuLi/TMEDA) to give destabilized oxiranyllithiums (Hodson, D. M.; Gras, E. *Angew Chem., Int. Ed.* **2002**, *41*, 2376−2378), we also checked enantiomeric purity of all the chiral nonracemic substituted phenylpropylene oxides synthesized, even if the dr would have been sufficient to ascertain the configurational stability of their lithiated precursors.
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(21) Spectroscopic data of racemic *trans*-epoxide **3c** have been reported in: Yano, K.; Hatta, Y.; Baba, A.; Matsuda, H. *Synthesis* **1992**, 693−696.

TABLE 2. Reaction of (1*S*,2*R*)-2b with Electrophiles

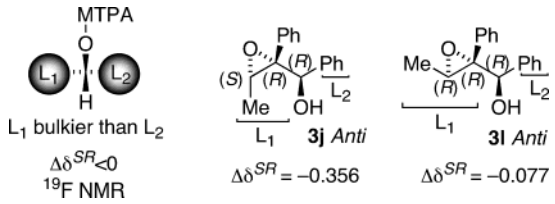
electrophile	product (% yield)[a]	convn (%)	dr[b]	er[c]	$[\alpha]^{20}_D$[d]
D_2O	(1*S*,2*R*)-**3e** (>98)	>98	>98:2	>99:1	+38.0
MeI	(2*S*,3*R*)-**3f** (84)	>98	”	”	+26.7
Me_2CO	(3*S*,4*R*)-**3g** (60)	80	”	99:1	+35.4
$C_6H_5CONMe_2$	(2*S*,3*R*)-**3h** (70)[e]	>98	”	>99:1	+198.7

[a] Isolated yield after distillation or column chromatography. [b] Diastereomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Enantiomeric ratio by GC analysis on a chiraldex B-DM capillary column or by ^{1}H NMR analysis in the presence of a chiral solvating agent (see the Experimental Section). [d] *c* 1, $CHCl_3$. [e] In this case, 2 equiv of *s*-BuLi was used.

of *cis*-**2b** is worth noting as, in contrast to what was found by our group[12a] for lithiated cis-disubstituted oxazolinyloxiranes and by Molander[22] for silicon-stabilized *cis*-*tert*-butyl-substituted oxiranyllithiums, the strain created in forcing the methyl and the phenyl groups both on the same side of the oxirane ring of **2b** did not promote any interconversion between *cis*-**2b** and *trans*-**2a**. Moreover, the observed diastereo- and enantiospecificity was not time dependent. Indeed, deuteration of **2b** at different reaction times (30 min and 2 h) gave only **3e** with the same enantiomeric enrichment of the starting epoxide *cis*-**1b**. Equally highly stereospecific was the reaction with other electrophiles such as CH_3I, acetone, and *N*,*N*-dimethylbenzamide; the corresponding α-adducts **3f**−**h** were isolated in good yields and high dr and er values (Scheme 1, Table 2).

Epoxides *trans*-**2a** and *cis*-**2b** also reacted smoothly with PhCHO leading in good yields to products **3i**,**j** and **3k**,**l** (Table 3), respectively, although with poor diastereoselectivity at the newly created stereogenic center: dr anti/syn **3i**,**j** 70/30, dr anti/syn **3k**,**l** 60/40. Stereoisomers could be separated by preparative HPLC and spectroscopically characterized. The assignment of syn (or anti)[23] stereochemistry was made on the basis of the characteristic resonance of the carbinol proton: in the case of the syn isomer it was always shifted downfield compared to that of the anti isomer (*δ* 5.01 vs 4.99 for **3i** and **3j**; 4.93 vs 4.85 for **3k** and **3l**, respectively), as reported and demonstrated for similar epoxy alcohols derived from styrene oxide.[12g] The relative configuration (anti) of (±)-**3j** was also confirmed by crystallographic X-ray analysis.[24] Moreover, the absolute configuration of (−)-**3j** and (+)-**3l** was ascertained to be that depicted in Table 3 by the modified Mosher method.[25] Because of the overlapping of the aromatic proton resonances, we decided to use ^{19}F NMR instead of ^{1}H NMR; for this purpose, both the (*R*)- and (*S*)-2-methoxy-2-(trifluoromethyl)phenyl acetate (MTPA) esters were prepared. According to this procedure,[25] when the bulkier substituent (e.g., L_1, Scheme 3) is on the same side as the phenyl group, the CF_3 resonates at a higher field. For an alcohol having the configuration represented in Scheme 3, in which L_1 is bulkier than L_2, the sign of the parameter $\Delta\delta^{SR}$ (^{19}F)-CF_3 = $\delta CF_3(S)$-$\delta CF_3(R)$ would be negative. A $\Delta\delta^{SR} < 0$ was observed for both (−)-**3j** and (+)-**3l** (Scheme 3); these data allowed the absolute configuration at the carbinol carbons to be assigned as *R* thus supporting, at the same time, the above-presumed stereochemistry of these two epoxy alcohols (anti).

SCHEME 3



The above epoxy alcohols **3i,j** and **3k**,**l** are interesting precursors of both erythro and threo aldols usually obtained by the Sharpless asymmetric epoxidation of allylic alcohols followed by a stereocontrolled rearrangement of the corresponding optically active epoxy silyl ethers, as reported.[26]

The stereoselective synthesis of α,*β*-epoxy alcohols is a challenging problem in synthetic organic chemistry: they are, indeed, excellent starting materials for the preparation of stereodefined polyols, natural products, or biologically active compounds.[27] In view of this, we decided to study the carbonyl reduction of the α,*β*-epoxy ketone (±)-**3h**.[27] As can be seen in Table 4, the reduction of **3h** with $NaBH_4$/MeOH took place in good yield and reasonable anti diastereoselectivity. No stereoselective improvement was observed when the reduction with $NaBH_4$ was carried out in the presence of Lewis acids such as $CaCl_2$, $ZnCl_2$, and $CeCl_3$, thus excluding the possibility of a chelated cyclic transition state.[28] The reduction with L-Selectride was even less diastereoselective.

The observed anti diastereoselectivity could be accounted for with a modified Felkin−Ahn model[29] by choosing the phenyl group as the “large” group not only for its bulkiness but also for having the lowest lying C_{sp^3}−C_{sp^2} σ^* orbital.[30] Of the two possible conformers depicted in Scheme 4, the most reactive one[30] should be that in which the hydride ion attacks the carbonyl group (acti-

(22) Molander, G. A.; Mautner, K. *Pure Appl. Chem.* **1990**, *62*, 707−712.

(23) The convention employed for describing syn and anti diastereomers is as follows: if the main chain is written in an extended (zigzag) conformation, the diastereomer that has the oxiranyl ring and the hydroxy group both projecting either forward (bold bonds) or away from the viewer (dashed bonds) is called syn.

(24) CCDC-232045 contains the supplementary crystallographic data for compound (±)-**3j**. These data can be obtained free of charge at www.ccdc.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK.; Fax: (int) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk.

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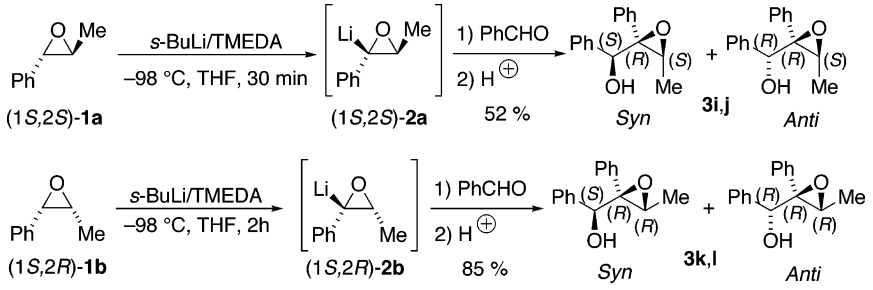
(29) Equilibrium geometry was preliminarily calculated for **3h** and a systematic conformer distribution analysis was carried out at a semiempirical level (PM3) rotating about the C_α-C=O bond. To introduce electron correlation in the computation of the energetics, the two local minimum-energy conformers found (corresponding just to those represented in Scheme 4 with the phenyl ring perpendicular to the C=O moiety) were subjected to single-point calculations using the density functional theory (DFT) at the B3LY/6−31 + G*//PM3 level of theory: the conformer having the oxiranyl oxygen anti to the C=O group, predicted to be the more reactive one, also resulted to be the more stable one of about 3.7 kcal/mol.

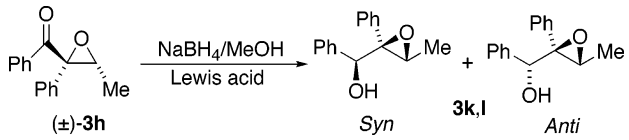
TABLE 3. Reaction of (1*S*,2*S*)-2a and (1*S*,2*R*)-2b with PhCHO



substrate	product[a] (% yield)[b]	convn (%)	er[c]	$[\alpha]^{20}_D$[d]
(1*S*,2*S*)-**1a**	(1*S*,2*R*,3*S*)-**3i** (52)[e,f]	67	98:2	+69.4
	(1*R*,2*R*,3*S*)-**3j**			−44.6
(1*S*,2*R*)-**1b**	(1*S*,2*R*,3*R*)-**3k** (85)[g]	>98	”	+20.6
	(1*R*,2*R*,3*R*)-**3l**			+53.7

[a] Absolute configuration ascertained as described. [b] Overall yields in both diastereoisomers after column chromatography. [c] Enantiomeric ratio by ^{1}H NMR analysis in the presence of a chiral solvating agent (see the Experimental Section). [d] *c* 1, $CHCl_3$. [e] dr anti/syn = 70/30, separated by preparative HPLC. [f] In this case, 1.5 equiv of *s*-BuLi was used. [g] dr anti/syn = 60/40, separated by preparative HPLC.

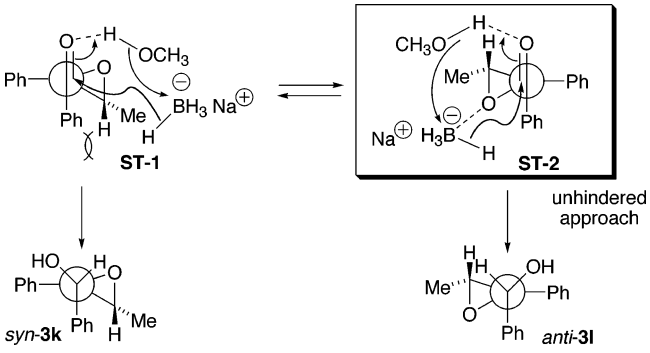
TABLE 4. Stereoselective Reduction of (±)-3h with $NaBH_4$ in MeOH



reagent[a]	*T*[b] (°C)	yield (%)[c]	convn (%)	anti/syn ratio[d]
$NaBH_4$	−78	86	97	86:14
$NaBH_4$−$CaCl_2$	0	70	97	70:30
$NaBH_4$−$CaCl_2$	−78	65	95	83:17
$NaBH_4$−$ZnCl_2$	”	64	63	85:15
$NaBH_4$−$CeCl_3$	”	90	>98	78:22
L-Selectride	”[e]	50	39	70:30

[a] (±)-**3h**/$NaBH_4$/metal chloride molar ratio = 1.0/1.0/2.0/2.0 according to the experimental procedure described in ref 28a; the above molar ratio was instead 1.0/2.0/1.5 in the case of the reduction using $NaBH_4$ in the presence of $ZnCl_2$, as reported in ref 28c. [b] The reaction time was always 30 min. [c] Overall yields in both diastereoisomers after column chromatography. [d] Diastereomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [e] (±)-**3h**/L-Selectride molar ratio = 1.0/2.0, using THF as the solvent in this case, as reported in ref 28c.

SCHEME 4



vated by a hydrogen bonding with the MeOH) close to the oxiranyl oxygen; this “flight path” from the least hindered side should be the most favorable one leading to the major adduct. Moreover, the coordination of borohydride by the oxiranyl oxygen in the transition state ST-2 ending with the anti isomer has also to be considered.

Conclusion

In summary, this paper reports a new route to optically active phenylpropylene oxides. The observed high stereospecificity of the reactions of *trans*-**2a** and *cis*-**2b** with electrophiles can be reasonably ascribed to their configurational stability; moreover, it has been experimentally proved that *cis*-**2b** is more reactive than *trans*-**2a**. The coupling reaction with PhCHO leads to almost equimolar mixtures of the corresponding syn/anti epoxy alcohols, whereas the reduction with $NaBH_4$ of the α-benzoyl *cis*-epoxide **3h** was markedly anti-stereoselective; a possible explanation for the observed diastereoselectivity has been also proposed. However, more work is needed and is underway, and results will be reported in due course.

Experimental Section

Preparation of α-Substituted Phenylpropylene Oxides 3a−l. General Procedure. A solution of (1*S*,2*S*)-**1a** (150 mg, 1.12 mmol) and TMEDA (0.51 mL, 3.36 mmol) in 5 mL of dry THF at −98 °C (methanol/liquid nitrogen bath) and under N_2 was treated with *s*-BuLi (2.58 mL, 3.36 mmol, 1.3 M), and the resulting deep red mixture was stirred for 2 h at this temperature. In the reaction of (1*S*,2*S*)-**1a** with PhCHO and of (1*S*,2*R*)-**1b** with $PhCONMe_2$, 1.5 equiv and 2.0 equiv of *s*-BuLi were used, respectively. Then, the electrophile (3.36 mmol) was added at once as pure liquid or as a solution in 1 mL of THF if solid. The resulting reaction mixture was allowed to warm to room temperature and quenched with saturated aqueous NH_4Cl. Then, it was poured into 20 mL of saturated brine, extracted with Et_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude mixture was flash chromatographed (silica gel; petroleum ether/AcOEt 9−7/1−3) (or distilled by a Kugelrohr apparatus) and volatiles removed under reduced pressure by means of a Büchi vacuum controller B-721 (240 mbar at 40 °C) to give the corresponding α-substituted propylene oxides, which showed the following data:

(1*S*,2*S*)-(−)-1-Deutero-1-phenyl-1,2-epoxypropane (3a): colorless oil (bp 47 °C, 10^{-3} Torr); 77% yield; convn > 98%, > 98% D, dr >98:2, er >99:1 [$t_{R\text{major}}$ = 20.64 min, $t_{R\text{minor}}$ = 21.22 min on a Chiraldex B-DM (Astec) (30 m × 0.25 mm i.d. × 0.25

(30) (a) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353−3361. (b) Gawley, R. E.; Aubè J. In *Principle of Asymmetric Synthesis*; Baldwin, J. E., FRS, Magnus P. D., Eds.; Elsevier: New York, 1996.

μm film thickness) capillary column, Det. FID 300 °C, column head pressure 12 psi, He flow 1.5 mL/min, split ratio 100/1, oven temperature 100 °C]; $[\alpha]^{20}_D = -38.0$ (*c* 1, $CHCl_3$).

(2*S*,3*S*)-(−)-2-Phenyl-2,3-epoxybutane (3b): colorless oil (bp 47 °C, 10^{-3} Torr); 51% yield; convn > 98%, dr >98:2, er >99:1 [t_{Rmajor} = 4.22 min, t_{Rminor} = 4.32 min on a Chiraldex B-DM (Astec) (30 m × 0.25 mm i.d. × 0.25 μm film thickness) capillary column, Det. FID 300 °C, column head pressure 12 psi, He flow 1.5 mL/min, split ratio 100/1, oven temperature 100 °C]; $[\alpha]^{20}_D = -16.0$ (*c* 1, $CHCl_3$); ^{1}H and ^{13}C NMR have been reported in the case of (2*R**,3*R**)-**3b** in ref 20; GC−MS (70 eV) *m*/*z* 148 (49, M^+), 147 (16), 133 (100), 119 (46), 104 (73), 103 (94), 91 (35), 78 (81), 65 (15); FT-IR (film, cm^{-1}) 3059, 1448, 1383, 1277, 1071, 1028, 842, 775, 742, 700.

(4*S*,5*S*)-(+)-4-Phenyl-4,5-epoxy-1-hexene (3c): colorless oil (bp 43 °C, 10^{-3} Torr); 74% yield; convn 98%, dr >98:2, er 97:3 [t_{Rmajor} = 9.70 min, t_{Rminor} = 10.04 min on a Chiraldex B-DM (Astec) (30 m × 0.25 mm i.d. × 0.25 μm film thickness) capillary column, Det. FID 300 °C, column head pressure 12 psi, He flow 1.5 mL/min, split ratio 100/1, oven temperature 100 °C]; $[\alpha]^{20}_D = +6.6$ (*c* 1, $CHCl_3$); ^{1}H and ^{13}C NMR have been reported in the case of (4*R**,5*R**)-**3c** in ref 21; GC−MS (70 eV) *m*/*z* 174 (3, M^+), 173 (11), 159 (11), 145 (17), 129 (67), 120 (30), 115 (48), 105 (100), 91 (16), 77 (36), 51 (12); FT-IR (film, cm^{-1}) 3063, 1642, 1449, 1264, 990, 916, 748, 700.

(3*S*,4*S*)-(+)-2-Methyl-3-phenyl-3,4-epoxypentan-2-ol (3d): colorless oil (bp 47 °C, 10^{-3} Torr); 51% yield; convn 83%, dr >98:2, er >99:1 [t_{Rmajor} = 6.29 min, t_{Rminor} = 6.13 min on a Chiraldex B-DM (Astec) (30 m × 0.25 mm i.d. × 0.25 μm film thickness) capillary column, Det. FID 300 °C, column head pressure 12 psi, He flow 1.5 mL/min, split ratio 100/1, oven temperature 100 °C]; $[\alpha]^{20}_D = +7.0$ (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz) δ: 1.06 (s, 3 H), 1.43 (s, 3 H), 1.73 (d, *J* = 5.9 Hz, 3 H), 2.49 (s, 1 H, exchanges with D_2O), 3.05 (q, *J* = 5.9 Hz, 3 H), 7.24−7.37 (m, 5 H); ^{13}C NMR (75 MHz) δ 12.7, 23.9, 28.6, 60.6, 68.5, 69.1, 125.8, 126.2, 126.5, 133.2; GC−MS (70 eV) *m*/*z* 174 (3, M^+), 173 (11), 159 (11), 145 (17), 129 (67), 120 (30), 115 (48), 105 (100), 91 (16), 77 (36), 51 (12); FT-IR (film, cm^{-1}) 3063, 1642, 1449, 1264, 990, 916, 748, 700.

(1*S*,2*R*)-(+)-1-Deutero-1-phenyl-1,2-epoxypropane (3e): colorless oil (bp 47 °C, 10^{-3} Torr); >98% yield, convn > 98%, >98% D, dr >98:2, er >99:1 [t_{Rminor} = 8.37 min, t_{Rmajor} = 9.12 min on a Chiraldex B-DM (Astec) (30 m × 0.25 mm i.d. × 0.25 μm film thickness) capillary column, Det. FID 300 °C, column head pressure 12 psi, He flow 1.5 mL/min, split ratio 100/1, oven temperature 100 °C]; $[\alpha]^{20}_D = +38.0$ (*c* 1, $CHCl_3$).

(2*S*,3*R*)-(+)-2-Phenyl-2,3-epoxybutane (3f): colorless oil (bp 47 °C, 10^{-3} Torr); 84% yield; convn > 98%, dr >98:2, er >99:1 ascertained by ^{1}H NMR (500 MHz, CCl_4 with $CDCl_3$ as external standard) in the presence of the chiral solvating agent (CSA) (*R*)-(−)-1-phenyl-2,2,2-trifluoroethanol (CSA/epoxide molar ratio = 3/1) δ 1.74 (s_{minor}, 3 H, CCH_3Ph), 1.75 (s_{major}, 3 H, CCH_3Ph); $[\alpha]^{20}_D = +26.7$ (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.98 (d, *J* = 5.5 Hz, 3 H), 1.64 (s, 3H), 3.17 (q, *J* = 5.5 Hz, 1 H), 7.24−7.34 (m, 5H); ^{13}C NMR (125 MHz) δ 14.4, 24.5, 61.2, 62.6, 126.5, 127.0, 128.0, 138.6; GC−MS (70 eV) *m*/*z* 148 (26, M^+), 147 (100), 133 (6), 104 (75), 91 (7), 78 (52), 77 (33), 63 (5), 51 (14), 43 (10); FT-IR (film, cm^{-1}) 3030, 2967, 1605, 1445, 1376, 1259, 765, 702.

(3*S*,4*R*)-(+)-2-Methyl-3-phenyl-3,4-epoxypentan-2-ol (3g): colorless oil (bp 47 °C, 10^{-3} Torr); 60% yield; convn 80%, dr >98:2, er 99:1 [t_{Rminor} = 31.48 min, t_{Rmajor} = 33.59 min on a Chiraldex B-DM (Astec) (30 m × 0.25 mm i.d. × 0.25 μm film thickness) capillary column, Det. FID 300 °C, column head pressure 12 psi, He flow 1.5 mL/min, split ratio 100/1, oven temperature 100 °C]; $[\alpha]^{20}_D = +35.4$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz) δ 0.96 (d, *J* = 5.5 Hz, 3 H), 1.10 (s, 3 H), 1.32 (s, 3 H), 2.20 (s, 1 H, exchanges with D_2O), 3.60 (q, *J* = 5.5 Hz, 1 H), 7.24−7.31 (m, 5 H); ^{13}C NMR (125 MHz) δ: 15.3, 25.4, 26.9, 55.9, 70.4, 70.8, 127.6, 135.9; GC−MS (70 eV) *m*/*z* 148 [M^+ − 44] (19), 134 (65), 133 (100), 115 (13), 105 (69), 91 (15), 77 (29), 59 (13), 43 (13); FT-IR (film, cm^{-1}) 3452, 2972, 1451, 1367, 1190, 958, 754, 704.

(2*S*,3*R*)-(+)-2,3-Epoxy-1,2-diphenylbutan-1-one (3h): colorless oil (bp 47 °C, 10^{-3} Torr); 70% yield, convn >98%, dr >98:2, er >99:1 [t_{Rmajor} = 39.69 min, t_{Rminor} = 40.47 min on a Chiraldex B-DM (Astec) (30 m × 0.25 mm i.d. × 0.25 μm film thickness) capillary column, Det. FID 300 °C, column head pressure 12 psi, He flow 1.5 mL/min, split ratio 100/1, oven temperature 150 °C]; $[\alpha]^{20}_D = +198.7$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.13 (d, *J* = 5.5 Hz, 3 H), 3.57 (q, *J* = 5.5 Hz, 1 H), 7.24−7.56 (m, 8 H), 8.03 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz) δ 13.4, 59.2, 68.6, 126.8, 128.3, 129.7, 129.8, 130.0, 133.2, 133.5, 134.2, 195.6; GC−MS (70 eV) *m*/*z* 238 (63, M^+), 223 (7), 165 (55), 194 (2), 165 (55), 133 (20), 105 (100), 77 (57), 51 (15); FT-IR (film, cm^{-1}) 3340, 3029, 2969, 1682, 1598, 1494, 1448, 1276, 1210, 971, 832, 700.

(1*S*,2*R*,3*S*)-1-Phenyl-2,3-epoxybutan-1-ol (3i): colorless oil; 52% yield; convn 67%, er 98:2 ascertained by ^{1}H NMR (500 MHz, CCl_4 with $CDCl_3$ as external standard) in the presence of the chiral solvating agent (CSA) (*R*)-(−)-1-phenyl-2,2,2-trifluoroethanol (CSA/epoxide molar ratio = 3/1) δ 1.84 (d_{major}, *J* = 6.0 Hz, 3 H, CHCH_3), 1.85 (d_{minor}, *J* = 6.0 Hz, 3 H, CHCH_3); $[\alpha]^{20}_D = +69.4$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz) δ: 1.72 (d, *J* = 6.0 Hz, 3 H), 2.35 (d, *J* = 4.0 Hz, 1 H, exchanges with D_2O), 3.24 (q, *J* = 6.0 Hz, 1 H), 5.01 (d, *J* = 4.0 Hz, 1 H), 6.99−7.36 (m, 10 H); ^{13}C NMR (125 MHz) δ: 14.9, 61.8, 68.2, 74.3, 126.1, 127.3, 127.5, 127.6, 128.1, 128.3, 136.7, 139.8; GC−MS (70 eV) *m*/*z* 222 [M^+-H_2O] (3), 196 (55), 167 (26), 152 (15), 134 (62), 133 (54), 105 (100), 91 (18), 77 (53), 51 (14), 43 (6); FT-IR (film, cm^{-1}) 3445, 3031, 1496, 1448, 1027, 756, 712.

(1*R*,2*R*,3*S*)-1-Phenyl-2,3-epoxybutan-1-ol (3j): colorless oil; 52% yield; convn 67%, er 98:2 ascertained by ^{1}H NMR (500 MHz, CCl_4 with $CDCl_3$ as external standard) in the presence of the chiral solvating agent (CSA) (*R*)-(−)-1-phenyl-2,2,2-trifluoroethanol (CSA/epoxide molar ratio = 3/1) δ 1.81 (d_{major}, *J* = 5.5 Hz, 3 H, CHCH_3), 1.82 (d_{minor}, *J* = 5.5 Hz, 3 H, CHCH_3); $[\alpha]^{20}_D = -44.6$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.69 (d, *J* = 6.0 Hz, 3 H), 2.32 (d, *J* = 3.0 Hz, 1 H, exchanges with D_2O), 3.20 (q, *J* = 6.0 Hz, 1 H), 4.99 (d, *J* = 3.0 Hz, 1 H), 7.11−7.24 (m, 10 H); ^{13}C NMR (125 MHz) δ 13.9, 61.1, 66.4, 74.4, 126.5, 127.4, 127.5, 127.7, 127.8, 137.8, 139.9; GC−MS (70 eV) *m*/*z* 222 [$M^+ - H_2O$] (2), 196 (61), 167 (30), 165 (31), 152 (18), 134 (69), 133 (60), 105 (100), 91 (15), 77(53), 51 (13), 43 (3); FT-IR (film, cm^{-1}) 3445, 3032, 1495, 1447, 1059, 756, 711.

(1*S*,2*R*,3*R*)-1-Phenyl-2,3-epoxybutan-1-ol (3k): white solid; mp 147−148 °C (hexane); 85% yield; convn >98%, er 98:2 ascertained by ^{1}H NMR (500 MHz, CCl_4 with $CDCl_3$ as external standard) in the presence of the chiral solvating agent (CSA) (*R*)-(−)-1-phenyl-2,2,2-trifluoroethanol (CSA/epoxide molar ratio = 3/1) δ 1.14 (d_{minor}, *J* = 5.5 Hz, 3 H, CHCH_3), 1.15 (d_{minor}, *J* = 5.5 Hz, 3 H, CHCH_3); $[\alpha]^{20}_D = +20.6$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz) δ 0.99 (d, *J* = 5.5 Hz, 3 H), 3.67 (q, *J* = 5.5 Hz, 1 H), 4.93 (s, 1 H), 7.01−7.28 (m, 10 H); ^{13}C NMR (125 MHz) δ 14.7, 57.2, 68.5, 76.0, 126.9, 127.4, 127.7, 127.8, 127.9, 128.1, 135.0, 140.1; GC−MS (70 eV) *m*/*z* 222 [$M^+ - H_2O$] (4), 196 (22), 165 (16), 134 (70), 133 (64), 105 (100), 91 (13), 77 (51), 51 (12); FT-IR (KBr, cm^{-1}) 3467, 2927, 1447, 1134, 1069, 758, 709. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.22; H, 6.70.

(1*R*,2*R*,3*R*)-1-Phenyl-2,3-epoxybutan-1-ol (3l): white solid; mp 95−96 °C (hexane); 85% yield; convn >98%, er 98:2 ascertained by ^{1}H NMR (500 MHz, CCl_4 with $CDCl_3$ as external standard) in the presence of the chiral solvating agent (CSA) (*R*)-(−)-1-phenyl-2,2,2-trifluoroethanol (CSA/epoxide molar ratio = 3/1) δ 1.17 (d_{minor}, *J* = 5.5 Hz, 3 H, CHCH_3), 1.18 (d_{major}, *J* = 5.5 Hz, 3 H, CHCH_3); $[\alpha]^{20}_D = +53.7$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.03 (d, *J* = 5.5 Hz, 3 H), 3.62 (q, *J* = 5.5 Hz, 1 H), 4.85 (s, 1 H), 6.96−7.28 (m, 10 H); ^{13}C NMR (125 MHz) δ 14.8, 56.4, 68.5, 76.1, 127.6, 127.7, 128.0, 128.1, 128.3, 135.0, 139.0; GC−MS (70 eV) *m*/*z* 222 [$M^+ - H_2O$] (4), 196 (19), 178 (9), 167 (48), 134 (100), 133 (90), 105 (97), 91 (14), 77 (57), 51 (14), 43 (5); FT-IR (KBr, cm^{-1}) 3415, 1456, 995, 926,

712, 696. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.36; H, 6.63.

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Supporting Information Available: General experimental paragraph, copies of the ^{1}H or ^{13}C NMR spectra of compounds **3a**,**e** (S3), **3b**,**c** (S4), **3d**,**f** (S5), **3g**-**j** (S6−S7), and an ORTEP view of (±)-**3j** (Figures S1). This material is available free of charge via the Internet at http://pubs.acs.org.

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