# CsF in Organic Synthesis. Regioselective Nucleophilic Reactions of Phenols with Oxiranes Leading to Enantiopure β-Blockers

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**Abstract:** The two modes of the paths in the reaction of oxiranes with phenols are completely controlled by CsF. Glycidyl nosylate undergoes exclusive substitution at the $C_1$ position whereas the ring-opening (C-3 attack) occurs with epichlorohydrin, glycidol, and 1,2-epoxyalkanes. These reactions provide convenient access to enantiopure β-blockers. © 1999 Elsevier Science Ltd. All rights reserved.

## INTRODUCTION

β-Blockers which are in great commercial demand are still sold mostly as racemates despite the intense desire to change into enantiopure forms.[1] Of particular significance, therefore, is the generation of β-amino alcohol moiety involving substituted phenol, the core of the β-blockers, in enantiopure forms. Among various methods reported so far, the most simple and promising one is the protocol which makes use of nucleophilic attack of phenols to oxiranes.

The reactions of oxiranes with nucleophiles are constituted basically by two types of transformations, ring-opening and substitution (Scheme 1). In the former reaction, the rigorous regiocontrol of the nucleophilic attack on the oxirane ring is required for selective synthesis when oxiranes derived from terminal olefins are employed. Another versatile reaction is the substitution at the $C_1$ position when X is a good leaving group like in epichlorohydrin or glycidyl ethers, yet this reaction is frequently accompanied by the ring-opening (C-3 attack). The substitution leads to the retention of the chiral center while the chirality sense is reversed upon the ring-opening. Accordingly, suppression of the ring-opening is crucial for attaining the high enantiopurity in the substitution reaction.
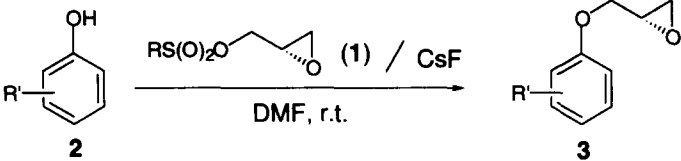
**Scheme 1**
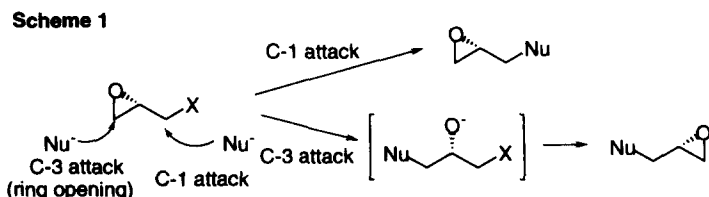
In contrast to extensive studies on the ring-opening by aliphatic alcohols,[2] only a limited number of reactions using phenols has been reported. The competition between the C-1 and C-3 attacks was first systematically studied under basic conditions (phenol/K$_2$CO$_3$ or NaH) by McClure et al.[3] Epichlorohydrin and glycidyl mesylate exhibited the varying ratio (from 5/95 to 95/5) of C-1/C-3 attack while glycidyl triflate constantly underwent the exclusive C-1 attack. We also observed the decrease of the %ee in some degree in the ring-opening of epichlorohydrin with phenol under analogous conditions in the synthesis of atenolol.[4] Sharpless and his coworkers found that the selectivity is improved by use of Ti(OR)$_4$ catalyst.[5] Thus, the ring-opening of glycidol obtained by the Sharpless oxidation of allyl alcohol with sodium 1-naphthoxide gave 3-naphthoxy-1,2-propanediol in 90% ee. On the other hand, glycidyl 3-nitrobenzenesulfonate (nosylate) underwent the C-1 attack exclusively.[6] The ring-opening of 2,3-epoxy esters by phenol was effected by AlPO$_4$-Al$_2$O$_3$.[7] The similar reaction using various substituted phenols was conducted in the presence of catalytic Et$_3$N.[8] In general, the desired 1,2-diols were obtained with slight decrease in the enantiopurity (from 89% ee of glycidol to 86-87% ee of the products) together with 1,3-diol by-products (3-4% yield).

In our project on the synthetic applications of CsF, we disclosed that this reagent worked for the SN2 reaction of tosylates and mesylates[9] and for intramolecular ring-opening of oxirane by malonate ion.[10,11] These precedents led us to postulate that the effective switching of C-1/C-3 attack on oxiranes is feasible with CsF. We report herein that highly selective C-1 and C-3 nucleophilic reactions that provide convenient access to a variety of enantiopure β-blockers and related compounds.[12,13]

## RESULTS AND DISCUSSION

First, glycidyl tosylate (**1a**) was exposed to various phenols **2** in the presence of CsF (3.0 equiv.) at room temperature (Table 1). The nucleophilic attack occurred mainly on the C$_1$ position but the %ee varied extensively depending on the *para*-substituents, yet no rule was sorted out for the electronic effects of the substituents (entries 1-12). Since the decrease in %ee is caused by the competing C-3 attack, glycidyl nosylate (**1b**) was employed in the hope of increasing the C-1 attack due to the enhanced leaving character (entries 13-24). As expected, the yields were dramatically improved and no decrease in %ee was observed irrespective of the *para*-substituents. Notably, KF afforded only a 28% yield even after 126 h (entry 25). Other conventional methods employing K$_2$CO$_3$ or NaH resulted in decreased yields or %ee's (entries 26-28). Apparently, CsF is crucial for such excellent outcomes in terms of both yield and %ee.

Then, for the purpose of gaining the catalytic version of this reaction, the reaction of 2-allyloxyphenol **2e** with **1b** was screened. As shown in Table 2, an excellent outcome was obtained with 1.5 equiv. of CsF (entry 1) but reduction of the amount of CsF to 0.2 equiv. failed to give the satisfactory yield (entry 2). However, addition of K$_2$CO$_3$ (1.3 equiv.) dramatically improved the yield without decrease of %ee (entry 3).

Table 1. CsF-promoted reaction of glycidyl sulfonate with phenols.[a]



| entry | 1[b] | 2 (R') | Reaction time /h | 3 Yield/% | % Ee |
|---|---|---|---|---|---|
| 1 | 1a (tosyl) | 2a (p-CH₂CONH₂) | 12 | 3a, 68 | 98.5 |
| 2 | | 2b (p-CN) | 12 | 3b, 88 | 98.0 |
| 3 | | 2c (p-Br) | 12 | 3c, 98 | 97.9 |
| 4 | | 2d (p-Cl) | 12 | 3d, 85 | 94.3 |
| 5 | | 2e (o-allyloxy) | 24 | 3e, 89 | 92.3 |
| 6 | | 2f (p-MeO) | 16 | 3f, 78 | 89.6 |
| 7 | | 2g (p-NO₂) | 30 | 3g, 58 | 88.1 |
| 8 | | 2h (p-H) | 30 | 3h, 42 | 84.5 |
| 9 | | 2i (p-CO₂Me) | 12 | 2i, 92 | 82.3 |
| 10 | | 2j (p-CH₂CN) | 30 | 3j, 53 | 59.6 |
| 11 | | 2k (p-CH₃) | 24 | 3k, 34 | 58.7 |
| 12 | | 2l (p-CHO) | 30 | 3l, 58 | 57.6 |
| 13 | 1b (nosyl) | 2a (p-CH₂CONH₂) | 14 | 3a, 95 | 98.8 |
| 14 | | 2b (p-CN) | 16 | 3b, 98 | 98.8 |
| 15 | | 2c (p-Br) | 14 | 3c, 98 | 98.8 |
| 16 | | 2d (p-Cl) | 14 | 3d, 93 | 98.6 |
| 17 | | 2e (o-allyloxy) | 12 | 3e, 95 | 98.8 |
| 18 | | 2f (p-MeO) | 16 | 3f, 92 | 98.5 |
| 19 | | 2g (p-NO₂) | 24 | 3g, 80 | 98.5 |
| 20 | | 2h (p-H) | 24 | 3h, 85 | 98.5 |
| 21 | | 2i (p-CO₂Me) | 14 | 3i, 97 | 98.4 |
| 22 | | 2j (p-CH₂CN | 30 | 3j, 84 | 98.3 |
| 23 | | 2k (p-CH₃) | 24 | 3k, 83 | 98.5 |
| 24 | | 2l (p-CHO) | 24 | 3l, 89 | 98.8 |
| 25 | 1b (nosyl) | 2e (o-allyloxy)[c] | 126 | 3b, 28 | 98.8 |
| 26 | | 2e (o-allyloxy)[d] | 30 | 3b, 63 | 89.6 |
| 27 | | 2e (o-allyloxy)[e] | 24 | 3b, 92 | 92.0 |
| 28 | | 2e (o-allyloxy)[f] | 6 | 3b, 68 | 97.4 |

[a] Reaction conditions: 2:3:CsF = 1.0:1.0:3.0;  DMF; r.t.  [b] %Ee: 2a, 98.5; 2b, 98.8.
[c] KF (3 equiv.) was used in place of CsF.  [d] K₂CO₃ (3 equiv)/acetone; 50 °C.
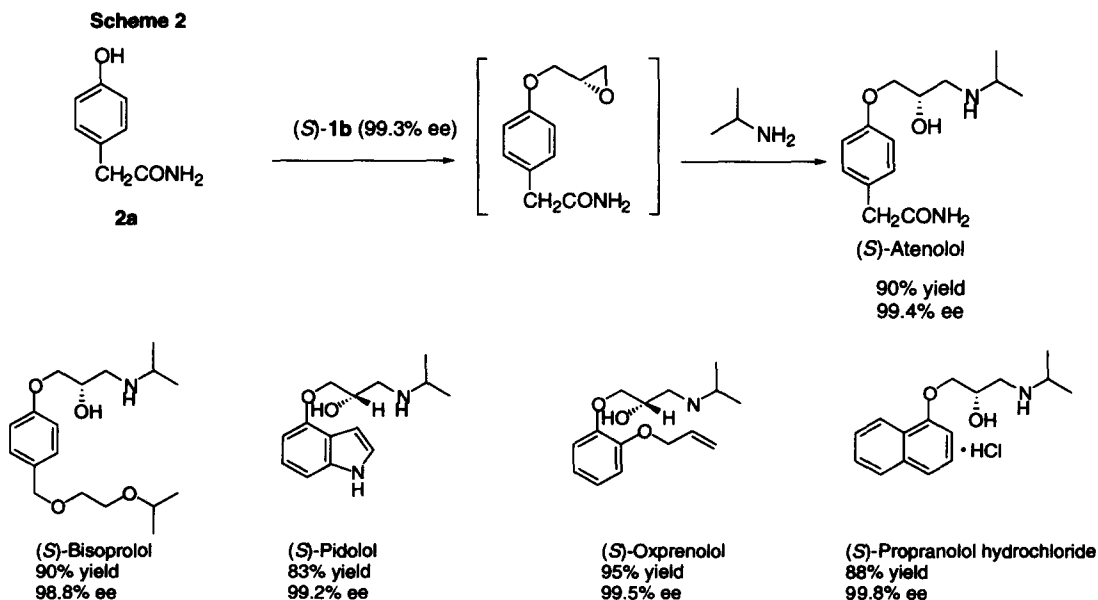[e] K₂CO₃ (3 equiv)/DMF;50 °C.  [f] NaH/DMF; rt.

NaHCO$_3$ also exhibited a similar effect but a higher reaction temperature as well as a longer reaction time was required (entry 4). When KF (0.2 equiv.) was employed in place of CsF under the same conditions, no reaction occurred at room temperature (entry 5). The reaction at 50 °C afforded a 92% yield but with a decreased %ee (entry 6). The less reactivity of KF indicates that this species is not formed from CsF and K$_2$CO$_3$ in the catalytic reaction. Conceivably, the nucleophilic substitution is promoted by CsF, and K$_2$CO$_3$ serves to trap the resulting 3-nitrobenzenesulfonic acid. It is reasonably understood that more than one equivalent of CsF is necessary in the absence of K$_2$CO$_3$ since CsF should work twofold as a promoter as well as a captor of the acid.[14]

Table 2. CsF-catalyzed reaction of glycidyl nosylate (1b) with 2e.[a]

| entry | Catalyst | Reaction temp/°C | time/h | Yield /% | % ee |
|-------|----------|------------------|--------|----------|------|
| 1 | CsF (1.5 equiv.) | rt | 12 | 95 | 99.3 |
| 2 | CsF (0.2 equiv.) | rt | 12 | 25 | 99.3 |
| 3 | CsF (0.2 equiv.)/K$_2$CO$_3$ (1.3 equiv.) | rt | 24 | 95 | 99.3 |
| 4 | CsF (0.2 equiv.)/NaHCO$_3$ (1.3 equiv.) | 40 | 26 | 92 | 99.2 |
| 5 | KF (0.2 equiv.)/K$_2$CO$_3$ (1.3 equiv.) | rt | 24 | No reaction | |
| 6 | KF (0.2 equiv.)/K$_2$CO$_3$ (1.3 equiv.) | 50 | 24 | 92 | 88.1 |

[a]Reaction conditions: 1b (99.3% ee):2e = 1.0:1.0; DMF.

With these results in hand, we addressed ourselves to the one-pot synthesis of enantiopure β-blockers (Scheme 2). Phenol 2a was exposed to (S)-1b (99.3 %ee) as desribed above. The resulting glycidyl ether, without isolation, was treated with isopropylamine. (S)-Atenolol (99.4% ee)[4,12f] was obtained in 90% overall yield. Moreover, (S)-bisoprolol,[13] (S)-pindolol,[12,c,e,g,i,j] (S)-oxprenolol,[12,b,f] and (S)-propranolol hydrochloride[12c,d,f,h,k] were synthesized in enantiopure forms as shown below.

**Scheme 2**



(S)-1b (99.3% ee)

(S)-Atenolol
90% yield
99.4% ee

(S)-Bisoprolol
90% yield
98.8% ee

(S)-Pidolol
83% yield
99.2% ee

(S)-Oxprenolol
95% yield
99.5% ee

(S)-Propranolol hydrochloride
88% yield
99.8% ee

Next, we turned our attention to the exclusive ring-opening (C-3 attack). Treatment of (R)-epichlorohydrin (98.4% ee) with **2a** in the presence of 3 equiv. of CsF at 50 °C afforded glycidyl ether **3a** (75% yield, 98.4% ee) and halohydrin **4** (19% yield) (eq. 1). The exclusive C-3 attack is evident from the S configuration of **3a** without decrease of %ee.



(1)
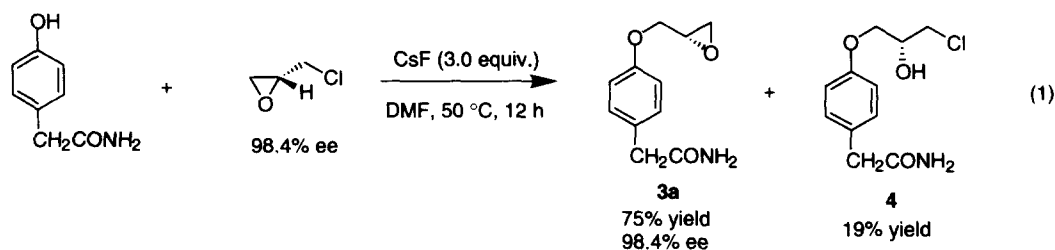
The reaction of glycidol took place much more efficiently. Treatment of (S)-glycidol with various phenols in the presence of 2 mol% of CsF provided the desired (R)-3-aryloxy-1,2-propanediols **5** in excellent yields (Table 3, entries 1-5). In this reaction, the decrease of %ee and the formation of 1,3-propandiols that were the by-products in Et₃N-catalyzed reaction[8] were not detected at all. Thus, this is a convenient and efficient route to arrive at mephenesin (**5b**)[8,12a,h] and guaifenesin (**5c**).[8,12a,h] It should be further noted that heating glycidol in methanol or benzyl alcohol solvent furnished the corresponding 3-alkoxy-1,2-propanediol in excellent yields with high enantiopurities (entries 6 and 7).

Table 3. CsF-catalyzed reaction of (S)-glycidol with phenols and alcohols.[a]



| entry | R | Reaction time/h | Yield /% | % ee |
|-------|---|-----------------|----------|------|
| 1 | $C_6H_5$ | 5 | **5a**, 90 | 98.9 |
| 2 | $o$-$CH_3C_6H_4$ | 6 | **5b**, 92 | 99.2 |
| 3 | $o$-$CH_3OC_6H_4$ | 9 | **5c**, 91 | 99.4 |
| 4 | $o$-$CH_2$=$CHCH_2OC_6H_4$ | 8 | **5d**, 93 | 99.4 |
| 5 | $p$-$ClC_6H_4$ | 18 | **5f**, 94 | 99.4 |
| 6 | $CH_3$[b] | 5 | **5g**, >99 | 99.4 |
| 7 | $C_6H_5CH_2$[b] | 6 | **5h**, >99 | 98.6 |

[a] Reaction conditions: glycidol:ROH:CsF = 1.0:0.0:0.02; DMF, 80°C unless otherwise noted.
[b] In the alcohol solvent at 120 °C.

Finally, simple oxiranes derived from terminal olefins were subjected to the reacion. As shown in Table 4, the exclusive ring-opening took place and no decrease of %ee was observed for (R)-1,2-epoxyoctane.

Table 4. CsF-catalyzed reaction of 1,2-epoxyalkanes with phenol.[a]



| entry | R | Reaction time/h | Yield /% | % ee |
|-------|---|-----------------|----------|------|
| 1 | $C_4H_9$ | 10 | 6a, 89 | ------- |
| 2 | $(R)$-$C_6H_{13}$[b] | 11 | 6b, 96 | 87.8 |

[a]Reaction conditions: oxirane:ROH:CsF = 1.0:0.0:0.02; DMF, 130°C.
[b] 88% ee.

In summary, CsF enables the C-1 or C-3 nucleophilic attack of phenols to be tuned in an exclusive manner by proper choice of oxiranes. Glycidyl nosylate undergoes C-1 attack due to the strong leaving character of the nosyl group whereas the exclusive C-3 ring-opening occurs with epichlorohydrin, glycidol, and 1,2-epoxyalkanes. Remarkably, the %ee of the starting materials is preserved perfectly and, hence, these reactions provide convenient access to enantiopure β-blockers.

## EXPERIMENTAL SECTION

Melting points were determined with a Mettler FP-61 melting point apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on a JEOL JNM-GSX-270 NMR spectrometer with tetramethylsilane as an internal standard. HRMS were recorded on a JEOL JMS-AX505W spectrometer. Optical rotations were measured on JASCO DIP-370 at 21°C. All reactions were monitored by HPLC. HPLC analyses were performed on a DAISO PACK SP-120-5-ODS-AP column (4.6 mm i.d. x 150 mm) using a Shimadzu LC-10A system equipped with an SPD-10A UV detector (eluent, MeOH-H₂O, 7:3, v/v; flow rate, 1.0 ml/min; detection, UV at 228nm; temperature, 40°C). Enantiomeric excesses were determined by HPLC on a Chiralcel OD column (4.6 mm i.d. x 250mm, eluent, hexane-EtOH-Et₂NH, 90:10:0.1 v/v; flow rate, 1.0 ml/min; UV at 228nm; temperature, 40°C).

***Preparation of (S)-p-Carbamoymethylphenyl Glycidyl Ether (3a)***: To a solution of **2a** (1.0 g, 6.6 mmol) in anhydrous DMF (5 ml) was added CsF (3.02 g, 19.9 mmol). The reaction mixture was stirred for 1 h and (S)-**1b** (1.76 g, 6.6 mmol, 98.8% ee) was added. The reaction mixture was stirred at 25 °C for 12 h under an inert atmosphere. After water (150 ml) was added, the solution was extracted with EtOAc (100 ml X 2). The organic phase was dried (MgSO₄) and evaporated. The residue was purified by column chromatography on silica gel (1:1, hexane/ EtOAc ) to give (S)-**3a** (1.30 g, 95%, 98.8% ee, based on chiral HPLC with Chiralcel OD) as a colorless prisms. m.p. 167.3-168.6 °C. $[\alpha]_D^{21}$=+10.9 ° (c 1.0, MeOH). $^1$H-NMR (DMSO-d₆) δ 2.69 (m, 1H), 2.83 (dt, 1H, J = 1.1, 5.1 Hz), 3.29 (s, 2H), 3.33 (m, 1H), 3.80 (ddd, 1H, J = -11.4, 1.1, 6.6 Hz), 4.29 (ddd, 1H, J = -11.4, 1.1, 2.6 Hz), 6.82 (br s, 1H), 6.89 (d, 2H, J = 7.7 Hz), 7.17 (d, 2H, J = 7.7 Hz), 7.39 (br s, 1H). $^{13}$C-NMR (DMSO-d₆) δ 41.33, 43.74, 49.75, 68.90, 114.20, 130.06, 156.81, 172.51. HR-MS m/z: 207.0895 (Calcd for C₁₁H₁₃NO₃: 207.0894).

***Preparation of (S)-p-Cyanophenyl Glycidyl Ether (3b)***: (S)-**3b**, colorless oil, was synthesized from (S)-**1b** (98.8% ee) and **2b** in 98% yield by a procedure similar to that used for (S)-**3a**. $^1$H-NMR (CDCl₃) δ 2.77 (m, 1H), 2.93 (m, 1H), 3.37 (m, 1H), 3.96 (m, 1H), 4.33 (m, 1H), 6.98 (d, 2H, J = 8.8 Hz), 7.59 (d, 2H, J = 8.8 Hz). $^{13}$C-NMR (CDCl₃) δ 44.3, 49.7, 69.0, 104.5, 115.3, 134.0, 161.6. HR-MS m/z: 175.0634 (Calcd for C₁₀H₉NO₂: 175.0633).

**Preparation of (S)-p-Bromophenyl Glycidyl Ether (3c):** (S)-**3c**, colorless oil, was synthesized from (S)-**1b** (98.8% ee) and **2c** in 98% yield by a procedure similar to that used for (S)-**3a**. $^1$H-NMR (CDCl$_3$) δ 2.74 (m, 1H), 2.90 (m, 1H), 3.21 (m, 1H), 3.88 (m, 1H), 4.20 (m, 1H), 6.79 (d, 2H, $J$ = 8.9 Hz), 7.36 (d, 2H, $J$ = 8.9 Hz). $^{13}$C-NMR (CDCl$_3$) δ 44.3, 50.0, 68.9, 113.4, 116.4, 132.2, 157.5. HR-MS $m/z$: 227.9786 (Calcd for C$_9$H$_9$BrO$_2$: 227.9785).

**Preparation of (S)-p-Chrolophenyl Glycidyl Ether (3d):** (S)-**3d**, colorless oil was synthesized from (S)-**1b** (98.8% ee) and **2d** in 93% yield by a procedure similar to that used for (S)-**3a**. $^1$H-NMR (CDCl$_3$) δ 2.75 (m, 1H), 2.91 (m, 1H), 3.35 (m, 1H), 3.90 (m, 1H), 4.13 (m, 1H), 6.85 (d, 2H, $J$ = 8.9 Hz), 7.24 (d, 2H, $J$ = 8.9 Hz). $^{13}$C-NMR (CDCl$_3$) δ: 44.5, 50.0, 69.0, 114.6, 115.9, 129.3, 157.0. HR-MS $m/z$: 184.0291 (Calcd for C$_9$H$_9$ClO$_2$: 184.0291).

**Preparation of (S)-o-Allyloxyphenyl Glycidyl Ether (3e):** (S)-**3e**, colorless oil, was synthesized from (S)-**1b** (98.8% ee) and **2e** in 95% yield by a procedure similar to that used for (S)-**3a**. $[\alpha]_D^{21}$=+15.0 ° (c 1.0, MeOH). $^1$H-NMR (CDCl$_3$) δ 2.75 (q, 1H, $J$ = 2.7, 4.2, 5.0 Hz), 2.87 (q, 1H, $J$ = 2.7, 4.2, 5.0 Hz), 3.34 (m, 1H), 4.03 (q, 1H, $J$ = 3.7, 5.0, 11.3 Hz), 4.25 (q, 1H, $J$ = 3.7, 5.0, 11.3 Hz), 4.59 (m, 2H), 5.27 (m, 2H), 5.41 (m, 2H), 6.08 (q, 1H, $J$ = 10.1, 17.2Hz), 6.93 (m, 4H). $^{13}$C-NMR (CDCl$_3$) δ: 44.8, 50.3, 69.9, 70.3, 114.4, 115.1, 117.4, 121.3, 121.9, 133.3, 148.7. HR-MS $m/z$: 206.0943 (Calcd for C$_{12}$H$_{14}$O$_3$: 206.0943).

**Preparation of (S)-Glycidyl p-Methoxyphenyl Ether (3f):** (S)-**3f**, colorless oil, was synthesized from (S)-**1b** (98.8% ee) and **2f** in 92% yield by a procedure similar to that used for (S)-**3a**. $^1$H-NMR (CDCl$_3$) δ 2.75 (m, 1H), 2.93 (m, 1H), 3.36 (m, 1H), 3.73 (s, 3H), 3.92 (m, 1H), 4.16 (m, 1H), 6.82 (d, 2H, $J$ = 8.7 Hz), 7.39 (d, 2H, $J$ = 8.7 Hz). $^{13}$C-NMR (CDCl$_3$) δ 44.3, 49.9, 55.8, 69.0, 115.2, 130.1, 158.3. HR-MS $m/z$: 180.0788 (Calcd for C$_{10}$H$_{12}$O$_3$: 180.0786).

**Preparation of (S)-Glycidyl p-Nitrophenyl Ether (3g):** (S)-**3g**, colorless oil, was synthesized from (S)-**1b** (98.8% ee) and **2g** in 80% yield by a procedure similar to that used for (S)-**3a**. $^1$H-NMR (CDCl$_3$) δ 2.79 (dd, 1H, $J$ = 2.6, 4.9 Hz), 2.95 (m, 1H), 3.39 (m, 1H), 4.00 (dd, 1H, $J$ = 5.9, 11.2 Hz), 4.37 (d, 1H, $J$ = 2.6 Hz), 4.44 (d, 1H, $J$ = 2.6 Hz), 7.00 (d, 2H, $J$ = 9.2 Hz), 8.20 (d, 2H, $J$ = 9.2 Hz). $^{13}$C-NMR (CDCl$_3$) δ 44.5, 49.7, 69.5, 114.7, 125.9, 141.9, 163.4. HR-MS $m/z$: 195.0530 (Calcd for C$_9$H$_9$NO$_4$: 195.0531).

**Preparation of (S)-Glycidyl Phenyl Ether (3h):** (S)-**3h**, colorless oil, was synthesized from (S)-**1b** (98.8% ee) and **2h** in 85% yield by a procedure similar to that used for (S)-**3a**. $^1$H-NMR (CDCl$_3$) δ 3.59 (m, 2H), 4.01 (m, 2H), 4.17 (m, 1H), 6.94 (m, 3H), 7.28 (m, 2H). $^{13}$C-NMR (CDCl$_3$) δ 44.8, 50.2, 69.1, 114.6, 121.3, 129.5, 158.6. HR-MS $m/z$: 150.0681 (Calcd for C$_9$H$_{10}$O$_2$: 150.0681).

**Preparation of (S)-Glycidyl p-Methoxylcarbonylphenyl Ether (3i):** (S)-**3i**, colorless oil, was synthesized from (S)-**1b** (98.8% ee) and **2i** in 97% yield by a procedure similar to that used for (S)-**3a**. $^1$H-NMR (CDCl$_3$) δ 2.77 (dd, 1H, $J$ = 2.6, 4.6 Hz), 2.92 (m, 1H), 3.37 (m, 1H), 3.88 (s, 3H), 3.98 (m, 1H), 4.30 (m, 1H), 4.30 (m, 1H), 6.94 (d, 2H, $J$ = 8.9 Hz), 7.99 (d, 2H, $J$ = 8.9 Hz). $^{13}$C-NMR (CDCl$_3$) δ 44.5, 49.8, 51.8, 68.7, 114.0, 122.9, 131.4, 161.9, 166.5. HR-MS $m/z$: 208.0735 (Calcd for C$_{11}$H$_{12}$O$_4$: 208.0735).

**Preparation of (S)-p-Cyanomethylphenyl Glycidyl Ether (3j):** (S)-**3j**, colorless prisms, was synthesized from (S)-**1b** (98.8% ee) and **2j** in 84% yield by a procedure similar to that used for (S)-**3a**. m.p. 114.6-117.8 °C. $^1$H-NMR (CDCl$_3$) δ 2.77 (dd, 1H, $J$ = 2.6, 4.6 Hz), 2.91 (t, 1H, $J$ = 4.6 Hz), 3.35 (m, 1H), 3.68 (s, 2H), 3.94 (dd, 1H, $J$ = 5.6, 11.2 Hz), 4.24 (dd, 1H, $J$ = 2.9, 112 Hz), 6.92 (d, 2H, $J$ = 8.6 Hz), 7.23 (d, 2H, $J$ = 8.6 Hz). $^{13}$C-NMR (CDCl$_3$) δ 22.8, 44.6, 50.1, 68.9, 115.2, 118.0, 122.3, 129.0, 158.1. HR-MS $m/z$: 189.0789 (Calcd for C$_{11}$H$_{11}$NO$_2$: 189.0790).

**Preparation of (S)-Glycidyl p-Methylphenyl Ether (3k):** (S)-**3k**, colorless oil, was synthesized from (S)-**1b** (98.8% ee) and **2k** in 83% yield by a procedure similar to that used for (S)-**3a**. $^1$H-NMR (CDCl$_3$) δ 2.28 (s, 3H), 2.75 (m, 1H), 2.89 (m, 1H), 3.34 (m, 1H), 3.94 (m, 1H), 4.18 (m, 1H), 6.95 (d, 2H, $J$ = 8.7 Hz), 7.08 (d,

2H, $J$ = 8.7 Hz). $^{13}$C-NMR (CDCl$_3$) δ 20.4, 44.7, 50.2, 68.7, 114.4, 129.9, 156.3. HR-MS $m/z$: 164.0837 (Calcd for C$_{10}$H$_{12}$O$_2$: 164.0837).

***Preparation of (S)-p-Formylphenyl Glycidyl Ether (3l)***: (S)-3l, colorless oil, was synthesized from (S)-1b (98.8% ee) and 2l in 89% yield by a procedure similar to that used for (S)-3a. $^1$H-NMR (CDCl$_3$) δ 3.30 – 4.11 (m, 5H), 6.95 (d, 2H, $J$ = 8.9 Hz), 7.78 (d, 2H, $J$ = 8.9 Hz), 9.82 (s, 1H). $^{13}$C-NMR (CDCl$_3$) δ 63.4, 68.8, 70.1, 114.3, 130.1, 131.6, 163.4, 190.8. HR-MS $m/z$: 178.0631 (Calcd for C$_{10}$H$_{10}$O$_3$: 178.0630).

***Synthesis of (S)-Atenolol***:[4,12f] To a solution of 2a (5 g, 33.1 mmol) in anhydrous DMF (100ml) was added CsF (g, 1.01g, 6.6 mmol) and dried K$_2$CO$_3$ (5.95 g, 43.1 mmol). After the mixture was stirred for 1h, (S)-1b (8.58 g, 33.1 mmol, 99.3% ee) was added. The reaction mixture was stirred at 25°C for 24h under inert atmosphere. The reaction mixture was added dropwise to isopropylamine (47.0 g, 795.1 mmol), and the solution was stirred at 5°C for 6h, then distilled under reduced pressure to remove isopropylamine. After water (100 ml) was added, the solution was extracted with EtOAc (100 ml X 2). The organic layer was dried (MgSO$_4$) and evaporated. The residue was purified by column chromatography on silica gel (1:1, hexane/ EtOAc ) to give (S)-Atenolol (8.58 g, 90 %, 99.4% ee, based on chiral HPLC with Chiralcel OD) as a colorless prisms. m.p. 155.4-156.0 °C.

(S)-Bisoprolol,[13] ( S)-Pindolol,[12c,e,g,i,j] ( S)-Oxprenolol1[12b,f] and ( S)-Propranolol hydrochloride[12c,d,f,h,k] were confirmed by their $^1$H-NMR spectra, $^{13}$C-NMR spectra and elemental analysis in comparison with authentic materials or literature assignments.

***Preparation of (R)-3-Phenoxypropane-1,2-diol (5a)***: To a solution of phenol (200 mg, 2.1mmol) in anhydrous DMF (5 ml) was added CsF (6.4 mg, 0.04 mmol). The reaction mixture was stirred for 1h and (R)-glycidol (156 mg, 2.1 mmol, 99.4% ee) was added. The reaction mixture was stirred at 80 °C for 5h under inert atmosphere. After water (100 ml) was added, the solution was extracted with EtOAc (100 ml X 2). The organic layer was dried (MgSO$_4$) and evaporated. The residue was purified by column chromatography on silica gel (3:1, hexane/ EtOAc ) to give (R)-5a (317.9 mg, 90%, 98.9% ee, based on chiral HPLC with Chiralcel OD) as a colorless prisms. m.p. 62.5-64.5 °C. [α]$_D^{25}$=-9.5 ° (c 0.5, MeOH). $^1$H-NMR (DMSO-d$_6$) δ 3.41(m, 2H, OH), 3.83 (m, 2H), 3.98 (m, 1H), 4.66 (t, 1H, $J$ = 5.3 Hz), 4.93 (d, 1H, $J$ = 4.3 Hz), 6.92 (m, 3H), 7.28 (m, 2H). $^{13}$C-NMR (DMSO-d$_6$) δ 62.7, 69.4, 70.0, 114.4, 120.39, 129.4, 158.7. HR-MS $m/z$: 168.0788 (Calcd for C$_9$H$_{12}$O$_3$: 168.0786).

***Preparation of (R)-3-(o-Methylphenoxy)propane-1,2-diol (5b) (Mephenesin)***: (R)-5b, colorless prisms, was synthesized from o-cresol and (R)-glycidol (99.4% ee) in 92% yield by a procedure similar to that used for (R)-5a. m.p. 90.9-92.9 °C, Lit[8] m.p. 92.9 °C. [α]$_D^{25}$=-1.9 ° (c 0.5, CHCl$_3$). $^1$H-NMR (DMSO-d$_6$) δ 2.16 (s, 3H), 3.50 (m, 2H), 3.89 (m, 3H), 4.64 (t, 1H, $J$ = 5.6 Hz), 4.90 (d, 1H, $J$ = 5.0 Hz), 6.70 (m, 2H), 7.13 (m, 2H). $^{13}$C-NMR (DMSO-d$_6$) δ 15.9, 62.8, 69.4, 70.0, 111.21, 120.1, 125.8, 126.9, 130.3, 156.7. HR-MS $m/z$: 182.0941 (Calcd for C$_{10}$H$_{14}$O$_3$: 182.0943).

***Preparation of (R)-3-(o-Methoxyphenoxy)propane-1,2-diol (5c) (Guaifenesin)***: (R)-5c, colorless prisms, was synthesized from o-guaiacol and (R)-glycidol (99.4% ee) in 91% yield by a procedure similar to that used for (R)-5a. m.p. 96.8-99.1 °C, Lit[8] m.p. 99.8 °C.. [α]$_D^{25}$=-9.4 ° (c 1.0, MeOH). $^1$H-NMR (DMSO-d$_6$) δ 3.44 (m, 2H), 3.75 (s, 3H), 3.88 (m, 3H), 4.64 (t, 1H, $J$ = 5.7 Hz), 4.90 (d, 1H, $J$ = 4.6 Hz), 6.92 (m, 4H). $^{13}$C-NMR (DMSO-d$_6$) δ 55.5, 62.9, 70.0, 70.3, 112.26, 113.26, 120.8, 120.8, 148.3, 149.1. HR-MS $m/z$: 198.0892 (Calcd for C$_{10}$H$_{14}$O$_4$: 198.0892).

***Preparation of (R)-3-(o-Allyloxyphenoxy)propane-1,2-diol (5d)***: (R)-5d, colorless prisms, was synthesized from 2e and (R)-glycidol (99.4% ee) in 93% yield by a procedure similar to that used for (R)-5a. m.p. 85.3-86.5 °C. [α]$_D^{25}$=-6.2 ° (c 1.0, MeOH). $^1$H-NMR (DMSO-d$_6$) δ 3.46 (m, 2H), 3.88 (m, 3H), 4.55 (t, 1H, $J$ = 5.2 Hz), 4.62 (t, 2H, $J$=5.4 Hz), 4.89 (d, 1H, $J$ = 4.0 Hz), 5.23 (d, 1H, $J$=10.7 Hz), 5.40 (dd, 1H, J=17.3 , 1.5 Hz), 6.92 (m, 4H). $^{13}$C-NMR (DMSO-d$_6$) δ 62.9, 69.0, 70.0, 70.4, 113.9, 114.4, 117.1, 120.9, 121.2, 134.0, 147.9, 148.8. HR-MS $m/z$: 224.1047 (Calcd for C$_{12}$H$_{16}$O$_4$: 224.1048).

***Preparation of (R)-3-(p-Chlorophenoxy)propane-1,2-diol (5f)***: (R)-**5f**, colorless prisms, was synthesized from **2d** and (R)-glycidol (99.4% ee) in 94% yield by a procedure similar to that used for (R)-**5a**. m.p. 83.5-84.5 °C, Lit[8] m.p. 83.0 °C. $[\alpha]_D^{25}$=-10.2 ° (c 1.0, MeOH). $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.44 (m, 2H), 3.89 (m, 3H), 4.67 (t, 1H, J = 5.6 Hz), 4.97 (d, 1H, J=8.9 Hz), 6.94 (m, 2H), 7.30 (m, 2H). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ 62.6, 69.9, 70.0, 116.2, 124.1, 129.2, 157.6. HR-MS m/z: 202.0396 (Calcd for $C_9H_{11}ClO_3$: 202.0397).

***Preparation of (R)-3-Methoxypropane-1,2-diol (5g)***: (R)-Glycidol (2.31 g, 31.2 mmol, 99.4% ee), CsF (94.0 mg, 0.62 mmol) and MeOH (1.0 g, 31.2 mmol) were sealed under vacuum in a glass tube and heated for 5 h in an oven at 120 °C. The reaction mixture was cooled and transferred to a round-bottomed flask where the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (5:1, hexane/ EtOAc ) to give (R)-**5g** (3.29 g, >99%, 99.4% ee, based on GC with CHIRALDEX G-TA) as a colorless oil. $^1$H-NMR (CDCl$_3$) $\delta$ 3.38 (s, 3H), 3.55 (m, 2H), 3.60 (m, 2H), 3.85 (brs , 1H), 4.04 (brs, 1H), 4.24 (brs, 1H). $^{13}$C-NMR (CDCl$_3$) $\delta$ 58.8, 63.6, 70.5, 73.8. HR-MS m/z: 106.0629 (Calcd for $C_4H_{10}O_3$: 106.0630).

***Preparation of (R)-3-Benzyloxypropane-1,2-diol (5h)***: (R)-**5h**, colorless oil, was synthesized from benzyl alcohol and (R)-glycidol (99.4% ee) in >99% yield by a procedure similar to that used for (R)-**5g**. $^1$H-NMR (CDCl$_3$) $\delta$ 3.54 (m, 4H), 3.83 (m, 1H), 4.48 (s , 2H), 7.29 (m, 5H). $^{13}$C-NMR (CDCl$_3$) $\delta$ 63.8, 70.7, 71.4, 73.3, 127.6, 128.3, 137.6. HR-MS m/z: 182.0944 (Calcd for $C_{10}H_{14}O_3$: 182.0943).

***Preparation of 3-Butoxy-1-phenoxy-2-proanol (6a)***: To a solution of phenol (200 mg, 2.1mmol) in anhydrous DMF (5 ml) was added CsF (6.4 mg, 0.04 mmol). The reaction mixture was stirred for 1h and 1,2-epoxyhexane (210 mg, 2.1 mmol) was added. The reaction mixture was stirred at 130 °C for 10 h under inert atmosphere. After water (100 ml) was added, the solution was extracted with EtOAc (100 ml X 2). The organic layer was dried (MgSO$_4$) and evaporated. The residue was purified by column chromatography on silica gel (7:1, hexane/ EtOAc ) to give **6a** (363 mg, 89%) as a colorless prisms. m.p. 49.8-53.8 °C. $^1$H-NMR (CDCl$_3$) $\delta$ 0.92 (t, 3H, J = 6.6 Hz), 1.28-1.58 (m, 3.41(m, 2H, OH), 3.83 (m, 2H), 3.98 (m, 1H), 4.66 (t, 1H, J = 5.3 Hz), 4.93 (d, 1H, J = 4.3 Hz), 6.92 (m, 3H), 7.28 (m, 2H). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ 62.7, 69.4, 70.0, 114.4, 120.39, 129.4, 158.7. HR-MS m/z: 168.0788 (Calcd for $C_9H_{12}O_3$: 168.0786).

***Preparation of (R)-3-Hexyloxy-1-phenoxy-2-propanol (6b)***: (R)-**6b**, colorless prisms, was synthesized from phenol and (R)-1,2-epoxyoctane (88% ee) in 96% yield by a procedure similar to that used for **6a**. m.p. 54.9-57.2 °C. $^1$H-NMR (CDCl$_3$) $\delta$ 0.89 (t, 3H, J = 6.5 Hz), 1.30-1.60 (m, 10H), 2.30 (brs, 1H), 3.79-3.99 (m, 3H), 6.92 (m, 3H), 7.28 (m, 2H). $^{13}$C-NMR (CDCl$_3$) $\delta$ 14.1, 22.59, 25.5, 29.3, 31.8, 33.1, 70.2, 72.2, 114.6, 121.1, 129.5, 158.6. HR-MS m/z: 222.1619 (Calcd for $C_{14}H_{22}O_2$: 222.1620).

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