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CsF in Organic Synthesis. The First and Convenient Synthesis of Enantiopure Bisoprolol by Use of Glycidyl Nosylate

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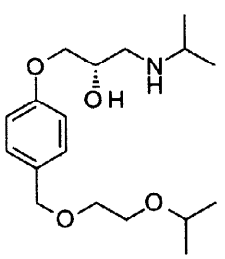
Abstract: The regioselective substitution of glycidyl nosylate with phenols is catalyzed by CsF in the presence of K_2CO_3 in DMF; this reaction enables the first and convenient synthesis of enantiopure bisoprolol.

The replacement of so far approved racemic drugs with the single enantiomers (racemic switches) is currently in strong need.[1] Bisoprolol (**1**) is one of those species that are desired to undergo the racemic switch on earliest possible occasion.[2] Bisoprolol hemifumarate is a highly β-1 selective adrenoceptor blocking agent without membrane-stabilizing activity or intrinsic sympathomimetic activity and thus used in the treatment of hypertension, angina pectoris, cardiac arrhythmias, glaucoma, and prevention of migraine attacks.[3] The (*S*)-enantiomer of **1** exhibits the activity to block β-adrenergic receptors 30-80 times as large as that of the (*R*)-enantiomer.[4] The area under the curve of concentration versus time of (*S*)-**1** is 1.5 times higher than that of (*R*)-**1** and the elimination half-life of the former is 1.4 times longer than that of the latter.[5] As such, enantiopure (*S*)-**1** is greatly desired, yet only the racemate is commercially available at present and the optical resolution should be invoked to obtain the enantiomers.



(*S*)-bisoprolol (**1**)

One of the most promising ways to arrive at this goal is to start from glycidyl derivatives that are now readily accessible in enantiopure form.[6] Two reaction paths are generally possible in the reaction of glycidyl ethers with nucleophile (Scheme 1). The simple nucleophilic substitution (path A) results in the retention of the center of chirality while the inversion is induced by the ring-opening (path B). The high regioselectivity was achieved to a considerable degree under basic conditions using NaH or K_2CO_3.[7]

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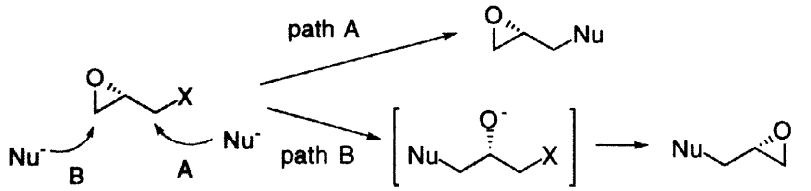
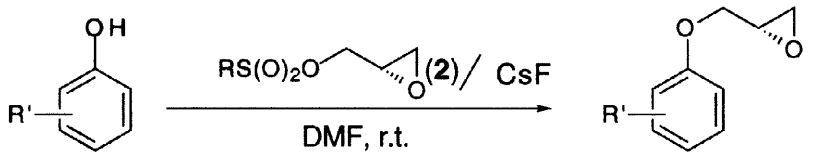
Scheme 1



Previously, we disclosed that nucleophilic substitution of secondary mesylates and tosylates was promoted by CsF under extremely mild conditions.[8] In this reaction, however, an equivalent amount of CsF or more was usually employed. This is a quite general propensity: few catalytic uses of this reagent were reported in precedent CsF-promoted reactions.[9] We have now found that glycidyl 3-nitrobenzenesulfonate (nosylate) undergoes substitution by phenols to give aryl glycidyl ethers with perfect regioselectivity even *by use of the catalytic amount of CsF* when K_2CO_3 coexists. This reaction has been applied to the first synthesis of enantiopure bisoprolol.

Since we already disclosed that tosylates are more prone to undergo nucleophilic substitution than the corresponding mesylates,[8c] glycidyl tosylates **2a** was employed at first. When **2a** (1.0 equiv.) was exposed to phenols **3** (1.0 equiv.) in the presence of 3.0 equiv. of CsF at room temperature, the %ee's of the product aryl glycidyl ethers **4** varied extensively as given in Table 1 (entries 1-5). Apparently, the ring-opening competed with the nucleophilic substitution to some extent although the effect of the *para*-substituents of the phenol is not

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



3 **4**

entry	**2**[b]	**3** (R')	Reaction time [h]	Yield [%]	% Ee
1	**2a** (tosyl)	**3a** (*p*-CH_2CONH_2)	12	68	98.5
2		**3b** (*o*-allyloxy)	24	89	92.3
3		**3i** (*p*-CO_2Me)	12	92	82.3
4		**3d** (*p*-CH_3)	24	34	58.7
5		**3e** (*p*-CHO)	30	58	57.6
6	**2b** (nosyl)	**3a** (*p*-CH_2CONH_2)	14	95	98.8
7		**3b** (*o*-allyloxy)	12	95	98.8
8		**3i** (*p*-CO_2Me)	14	97	98.4
9		**3d** (*p*-CH_3)	24	83	98.5
10		**3e** (*p*-CHO)	24	89	98.8
11	**2b** (nosyl)	**3b** (*o*-allyloxy)[c]	126	28	98.8
12		**3b** (*o*-allyloxy)[d]	30	63	89.6
13		**3b** (*o*-allyloxy)[e]	24	92	92.0
14		**3b** (*o*-allyloxy)[f]	6	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]K_2CO_3 (3 equiv)/acetone; 50 °C.
[e]K_2CO_3 (3 equiv)/DMF;50 °C. [f]NaH/DMF; rt.

simple in terms of the electronic effect. We expected that this problem could be overcome by use of glycidyl nosylate (**2b**) due to its enhanced leaving character.[7a] This is indeed the case as shown in the same table (entries 6-10). Virtually, the complete enantioselectivities were attained in all cases carried out in this study. Notably, the yields are constantly high and various functional groups remain intact. It should be noted that KF afforded only a 28% yield even after the prolonged reaction time (entry 11). Moreover, other conventional methods employing K_2CO_3 or NaH resulted in decreased yields or %ee's (entries 12-14). Apparently, the combination of CsF and **2b** is superior to any other precedent ones.

Next, we turned our attention to the catalytic version. The reaction of 2-allyloxyphenol **3b** with **2b** 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 a satisfactory yield (entry 2). However, addition of K_2CO_3 (1.3 equiv.) dramatically improved the yield without decrease of %ee (entry 3). $NaHCO_3$ 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 activity of KF indicates that this species is not formed from CsF and K_2CO_3 in the catalytic reaction. Conceivably, the nucleophilic substitution is promoted by CsF, and K_2CO_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_2CO_3 since CsF should work twofold as a promoter as well as a captor of the acid.[10]

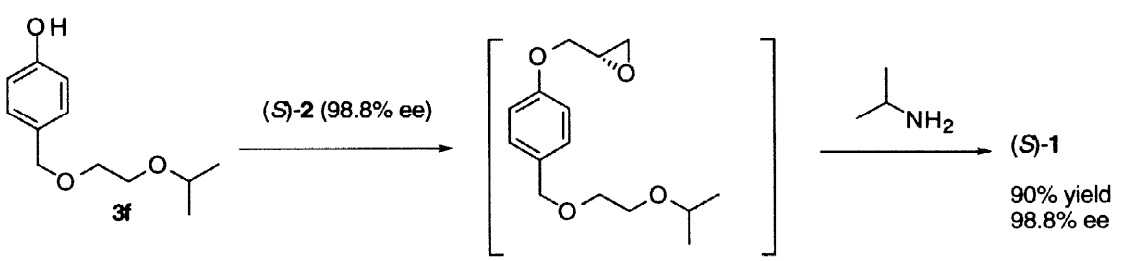
Table 2. CsF-catalyzed reaction of glycidyl nosylate (**2b**) with **3b** .[a]

entry	Catalyst	Reaction		Yield [%]	% Ee
		temp [°C]	time [h]		
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_2CO_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_2CO_3 (1.3 equiv.)	rt	24	No reaction	
6	KF (0.2 equiv.)/K_2CO_3 (1.3 equiv.)	50	24	92	88.1

[a]Reaction conditions: **2b** (99.3% ee):**3b** = 1.0:1.0; DMF.

With these results in hand, we addressed ourselves to the synthesis of enantiopure bisoprolol (Scheme 2). Phenol **3f** (1.00 equiv.) was exposed to (*S*)-**2** (98.8% ee, 1.0 equiv.) under the conditions discovered above. The resulting glycidyl ether, without isolation, was treated in one-pot with isopropylamine (24 equiv.) to give the desired (*S*)-**1** in 90% yield with 98.8% ee.[11] The hemifumarate of this compound was obtained straightforwardly in 93% yield.

Scheme 2



In summary, various aryl glycidyl ethers were obtained in highly enantio- and chemoselective fashion starting from glycidyl nosylate. The regioselective nucleophilic substitution was effected by CsF. The required amount of this rather expensive reagent was reduced by co-employment of K_2CO_3. The first synthesis of enantiopure bisoprolol was realized in a practical way by this catalytic version.

Synthesis of (S)-bisoprolol: To an anhydrous DMF solution (50 mL) of **3f** (5 g, 23.8 mmol) was added CsF (0.72 g, 4.7 mmol) and dried K_2CO_3 (4.27 g, 30.3 mmol). The mixture was stirred for 1 h and (*S*)-**2b** (6.17 g, 23.8 mmol, 98.8% ee) was added. The reaction mixture was stirred at 25 °C for 30 h and, then, added dropwise to isopropylamine (33.8 g, 571.8 mmol). The mixture was stirred for 18 h at 50 °C. The isopropylamine was removed by distillation under reduced pressure. The residue was combined with water (100 mL) and extracted with EtOAc (100 mL x 3). The organic layer was dried ($MgSO_4$) and evaporated to afford (*S*)-**1** (6.96 g, 90%, 98.8% ee based on chiral HPLC with Chiralcel OD, 98.6% chemical purity based on HPLC) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 6H, J = 6.3 Hz), 1.28 (d, 6H, J = 2.3 Hz), 3.05 (m, 3H), 3.61 (m, 5H), 3.99 (m, 2H), 4.29 (m, 1H), 4.50 (S, 2H), 7.06 (m, 4H); MS (EI) m/z 325 [M^+]; HRMS: Calcd for $C_{18}H_{31}NO_4$ 325.2251, found 325.2252.

The liquid (*S*)-**1** obtained was dissolved in MeOH (2 mL) and EtOAc (20 mL) at 50 °C. To this solution was added fumaric acid (1.24 g, 10.6 mmol). White crystals obtained were recrystallized from MeOH-EtOAc provided (*S*)-bisoprolol hemifumarate (7.56 g, 93%): mp 96.9-97.1 °C; $[\alpha]_D^{21}$ -20.6° (*c* 1.0, MeOH).

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11. The conventional method[7] using K_2CO_3 in acetone or NaH in DMF gave the aryl glycidyl ether in 38% yield (93.8 %ee) or 60% yield (97.6 %ee).