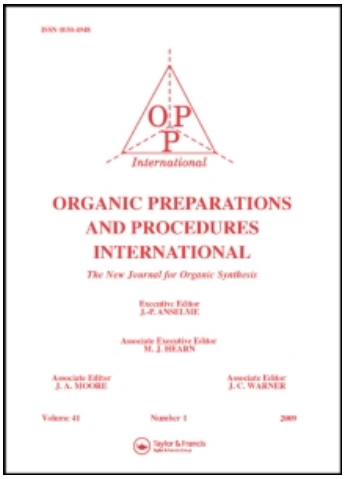

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AN EFFICIENT SYNTHESIS OF ENANTIOPURE 3-CHLOROSTYRENE OXIDE *via* OXAZABOROLIDINE-CATALYZED REDUCTION

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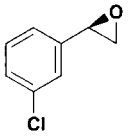
Optically pure styrene oxide derivatives are important chiral building blocks for the synthesis of a variety of chiral drugs.[1] In particular, (*R*)-3-chlorostyrene oxide (**1**) is a key intermediate for the preparation of several β_3-adrenergic agonists that exhibit antiobesity and antidiabetic activities.[2] Several different methods for the synthesis of optically active (*R*)-**1** have been reported. Asymmetric dihydroxylation of 3-chlorostyrene followed by chemical transformation to (*R*)-**1** afforded 98% ee in good yield.[2a] Enzymatic resolution of racemic 3-chlorostyrene bromohydrin followed by the treatment of base[3] and hydrolytic kinetic resolution of racemic **1** using salen catalyst[4] provide enantiomerically pure (*R*)-**1**.

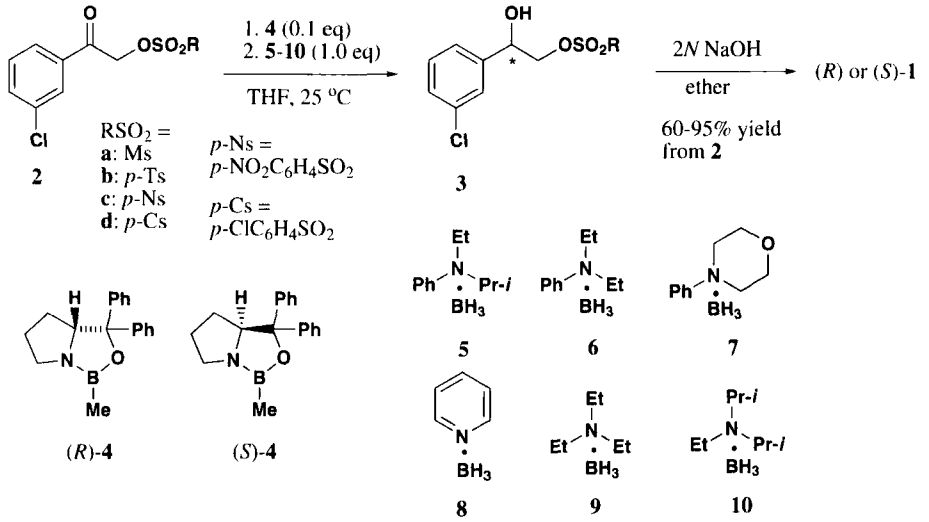


(*R*)-**1**

However, these methods suffer from the fact that the theoretical yield is limited to 50%. Although asymmetric borane reduction of 1-(3-chlorophenyl)-2-chloroethanone using (*R*)-CBS oxazaborolidine reagent as catalyst afforded the chlorohydrin precursor to (*R*)-**1** in 85% ee,[2b] this procedure is not free from disadvantages for large-scale applications, because of severe irritation to skin eyes of the α-haloketone used as a starting material. In contrast, 1-(3-chlorophenyl)-2-sulfonyloxyethanone derivatives (**2**) can be used as substrates more readily because they are not only stable and non-irritant, but also sulfonyloxy groups appear to be much better leaving groups than halogens. Recently we reported practical syntheses of oxazaborolidine-catalyzed asymmetric reduction of α-functionalized ketones using amine-borane complexes which can be more advantageously used as the hydride source than borane-tetrahydrofuran or borane-dimethyl sulfide.[5] In connection with our continuing interest in asymmetric reduction of α-functionalized ketones,[6] we describe here a simple and convenient method for preparing enantiomerically pure **1** in both enantiomeric forms by employing oxazaborolidine-catalyzed asymmetric reduction of **2**.

We initially compared the asymmetric reduction of 1-(3-chlorophenyl)-2-p-toluene-sulfonyloxyethanone **2b** catalyzed by proline-based oxazaborolidines (Corey's CBS reagents, **4**[7]) using commercially available amine-borane reagents, such as *N*-ethyl-*N*-isopropyaniline-borane **5**, *N*,*N*-diethylaniline-borane **6**, *N*-phenylmorpholine-borane **7**, pyridine-borane **8**, triethylamine-borane **9** and diisopropylethylamine-borane **10** as the hydride source under the same reaction conditions. The reaction was carried out by slow addition of THF solution of **2b** over 1 h to a solution of 1.0 equiv of each

amine-borane reagent in the presence of 10 mol% of **4** in THF at 25° (*Scheme 1*). As shown in Table 1, the reduction using *N*-phenylamine-borane reagents **5-7** was complete within 10 min to provide 1-(3-chlorophenyl)-2-*p*-toluenesulfonyloxyethanol **3b** in better than 90% yields. The reduction with **10**



Scheme 1

Table 1. Preparation of Optically Active 3-Chlorostyrene oxide (**1**)[a]

Entry	Cmpd	cat.	Amine-borane	Yield (%)[b]	% ee of **1**[c]	config.[d]
1	**2a**	(*R*)-**4**	**5**	95	97	*R*
2	**2b**	(*R*)-**4**	**5**	95	>99	*R*
3	**2b**	(*S*)-**4**	**5**	93	>99	*S*
4	**2c**	(*R*)-**4**	**5**	94	98	*R*
5	**2d**	(*R*)-**4**	**5**	95	96	*R*
6	**2b**	(*R*)-**4**	**6**	95	89	*R*
7	**2b**	(*R*)-**4**	**7**	94	80	*R*
8	**2b**	(*R*)-**4**	**8**	e	g	
9	**2b**	(*R*)-**4**	**9**	e	g	
10	**2b**	(*R*)-**4**	**10**	60[f]	21	*R*

[a] [**2**] : [cat] : [amine-borane] = 1 : 0.1 : 1. [**2**] = 0.5 M. The reaction was complete within 10 min to give α-sulfonyloxyalcohols (**3**) in almost quantitative yield, unless otherwise indicated. [b] Isolated yield of **1** obtained by the direct treatment of **3** with 2*N* NaOH. [c] Determined by chiral GC analysis using a 20m G-TA column (Astec). [d] Based on the sign of optical rotation value of the known compound: ref. 3. [e] No reaction in 24 h. [f] In 3 h. [g] Not determined.

provided 60% yield in 3 h. No reactions with **8** and **9** were observed in 24 h. The sulfonyloxyalcohol **3b** obtained was easily converted to **1** by the treatment of 2*N* NaOH at room temperature in nearly quantitative yields. The enantiomeric excess of **1** was determined by chiral GC analysis using a 20*m* G-TA column (Astec). Among the amine-borane complexes examined, reagent **5** provided the best enantioselectivity approaching 100% ee (Table 1, entries 2 and 3). The results showed that the present procedure is quite superior to the same reduction[2h] of 1-(3-chlorophenyl)-2-chloroethanone using borane-THF as the hydride source to afford **1** in 85% ee. Other amine-borane reagents **6**, **7** and **10** afforded **1** with 89% ee, 80% ee and 21% ee, respectively (entries 6-7 and 10). In this reaction, the influence of different sulfonyl groups of the compound **2** on the enantioselectivity was not significant (entries 1-5).

In summary, we have established a simple and practical procedure for the synthesis of enantiopure (*R*)- and (*S*)-3-chlorostyrene oxide in high yields *via* CBS oxazaborolidine-catalyzed borane reduction of 3'-chloro-α-*p*-toluenesulfonyloxyacetophenone using *N*-ethyl-*N*-isopropylaniline-borane complex as the borane carrier. This procedure can be used as an excellent alternative to synthesis of such compounds. Further applications using this methodology are under current investigation.

EXPERIMENTAL SECTION

All operations with air-sensitive materials were carried out under a nitrogen atmosphere with oven-dried glassware. Liquid materials were transferred with a double-ended needle. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230-400 mesh). NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$. Optical rotations were measured with a high resolution digital polarimeter. Melting points are uncorrected.

Preparation of 2. **General Procedure**.- Compounds **2** were prepared according to the literature,[8] by refluxing aryl methyl ketones with phenyliodohydroxyaryl (or alkyl)sulfonates in acetonitrile, dioxane, toluene or diglyme.

1-(3-Chlorophenyl)-2-methanesulfonyloxyethanone (2a), mp 94-96°; yield: 81%; IR (KBr, cm^{-1}): 1710, 1365, 1169; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (s, 3 H), 5.47 (s, 2 H), 7.47 (m, 1 H), 7.62 (m, 1 H), 7.76 (m, 1 H), 7.88 (m, 1 H); ^{13}C NMR (100 MHz) δ 39.31, 69.96, 125.91, 127.99, 130.47, 134.47, 134.93, 135.61, 190.10.

Anal. Calcd for $C_9H_9ClO_4S$: C, 43.47; H, 3.65; S, 12.89. Found: C, 43.51; H, 3.62; S, 12.92

1-(3-Chlorophenyl)-2-*p*-toluenesulfonyloxyethanone (2b), mp 54-56°; yield: 76%; IR (KBr, cm^{-1}): 1718, 1362, 1191, 987, 771; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 5.22 (s, 2 H), 7.35 (d, 2 H, J = 8.19 Hz), 7.42 (m, 1 H), 7.57-7.59 (m, 1 H), 7.71-7.73 (m, 1 H), 7.79 (m, 1 H), 7.83-7.85 (m, 2 H); ^{13}C NMR (100 MHz) δ 21.72, 69.85, 126.15, 128.17, 129.98, 130.26, 132.48, 134.12, 135.25, 135.34, 145.49, 189.50.

Anal. Calcd for $C_{15}H_{13}ClO_4S$: C, 55.47; H, 4.03; S, 9.87. Found: C, 55.42; H, 4.01; S, 9.83

1-(3-Chlorophenyl)-2-*p*-chlorobenzenesulfonyloxyethanone (2c), mp 93-95°; yield: 80%; IR (KBr,

cm^{-1}): 1711, 1362, 1185, 1001, 790; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 2 H), 7.44 (t, 1 H, J = 7.92 Hz), 7.53-7.56 (m, 2 H), 7.59-7.61 (m, 1 H), 7.71-7.73 (m, 1 H), 7.81 (m, 1 H), 7.90-7.93 (m 2 H); ^{13}C NMR (100 MHz) δ 70.03, 126.03, 128.08, 129.56, 129.68, 130.36, 134.19, 134.31, 135.04, 135.47, 141.07, 189.10.

Anal. Calcd for $C_{14}H_{10}Cl_2O_4S$: C, 48.71; H, 2.92; S, 9.29. Found: C, 48.65; H, 2.87; S, 9.25

1-(3-Chlorophenyl)-2-*p*-nitrobenzenesulfonyloxyethanone (2d), mp 110-114°; yield: 86%; IR (KBr, cm^{-1}): 1715, 1530, 1361, 1184, 1059, 977, 792; ^1H NMR (400 MHz, $CDCl_3$) δ 5.49 (s, 2 H), 7.48-7.52 (m, 2 H), 7.64 (m, 1 H), 7.82-7.84 (m, 2 H), 8.18-8.21 (m 2 H), 8.39-8.42 (m, 2 H); ^{13}C NMR (100 MHz) d 70.89, 124.36, 127.85, 129.12, 129.47, 133.29, 134.60, 143.94, 150.86, 189.72.

Anal. Calcd for $C_{14}H_{10}ClNO_6S$: C, 47.27; H, 2.83; N, 3.94; S, 9.01.

Found: C, 47.32; H, 2.87; N, 3.96; S, 9.08

Representative Procedure for Preparation of 1 *via* Asymmetric Reduction of 2.- The following procedure is representative. To a stirred solution of (*R*)-**4** (0.2 mmol; 0.2 M, 1 mL) in dry THF was added **5** (2 mmol, 2 M, 1 mL) in an atmosphere of nitrogen. To this was added slowly 2 mL of THF solution of **2b** (2 mmol; 0.65 g) over 1 h using a syringe pump at 25°. The reaction mixture was stirred for 10 min at the same temperature and then quenched cautiously with methanol (0.5 mL). After solvent was evaporated under reduced pressure, the product (*R*)-**3b** was obtained by a flash column chromatography on silica gel using ethyl acetate/hexane (1:1) as eluent: 99% yield; oil (R_f 0.65); $[\alpha]^{22}_D$ –39.13 (*c* 1.42, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.86, 1H, J = 3.1), 4.02 (dd, 1H, J = 8.22, 10.42), 4.12 (dd, 1H, J = 3.43, 10.42), 4.95 (m, 1H), 7.17-7.34 (m, 6H), 7.74 (m, 2H); ^{13}C NMR (100 MHz) δ 21.68, 71.26, 73.03, 124.41, 125.88, 126.36, 127.92, 128.15, 128.58, 129,92, 129.99, 132.39, 134.60, 140.40, 145.24.

Anal. Calcd for $C_{15}H_{15}ClO_4S$: C, 53.13; H, 4.63; S, 9.81. Found: C, 53.34; H, 4.59; S, 9.67

The sulfonyloxyalcohol **3b** (2 mmol) was dissolved in ether (5 mL) and treated with 2*N*-NaOH (2 mL) at 0° for 3 h. Water layer was extracted with ether (3 x 10 mL). The combined ether extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The epoxide product **1** was further purified by a flash column chromatography on silica gel using ethyl acetate/hexane (1:2) as eluent to give (*R*)-3-chlorostyrene oxide (oil; R_f 0.72; 294 mg, 95 % yield): ^1H NMR (400 MHz, $CDCl_3$) δ 2.76 (dd, 1H, J = 2.52, 5.45), 3.15 (dd, 1H, J = 4.08, 5.45), 3.84 (dd, 1H, J = 2.57, 3.96), 7.16-7.29 (m, 4H); ^{13}C NMR (100 MHz) δ 51.24, 51.70, 123.72, 125.50, 129.78, 134.59, 139.82.

Anal. Calcd for C_8H_7ClO: C, 62.15; H, 4.56.

Found: C, 62.16; H, 4.59; $[\alpha]^{22}_D$ –11.15 (*c* 1.56, $CHCl_3$) {$[\alpha]^{20}_D$ –11.1 (*c* 1.23, $CHCl_3$), *R*}.[3]

Enantiomeric excess was measured by capillary GC analysis using G-TA column (Astec) [oven temperature: 120° (isothermal); t_R (*R*): 9.34 min; t_R (*S*): 6.97 min]. GC analysis showed a composition of 99.65 (*R*) and 0.35 (*S*) (i.e., 99.3% ee).

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