Facile Synthesis of Optically Active Styrene Oxide Derivatives by Asymmetric Reduction of Substituted 2-Sulfonyloxyacetophenones with (−)-*B*-Chlorodiisopinocampheylborane (^{d}Ipc$_2$BCl)

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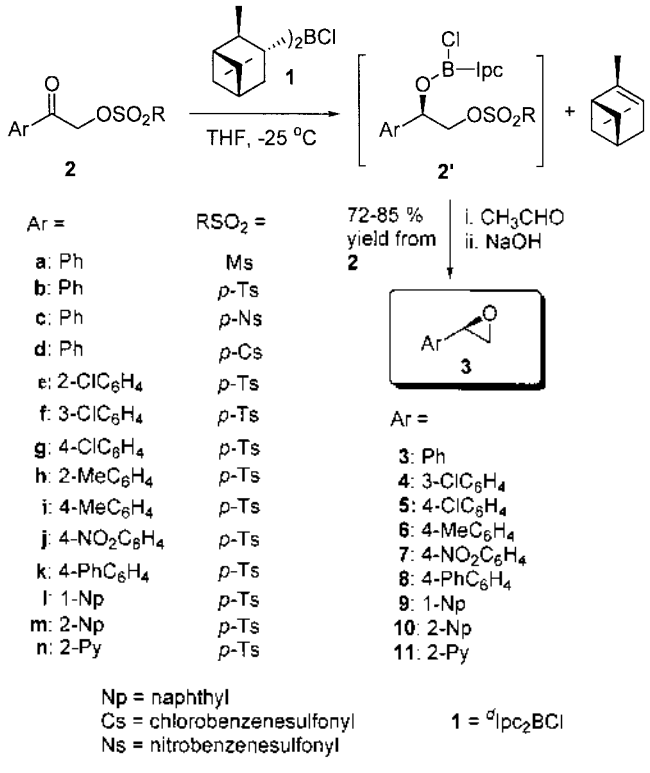
Optically active styrene oxide derivatives are extremely useful chiral building blocks for the synthesis of a variety of pharmaceutical products[1] and can be used as key intermediates[2] for the synthesis of more complex chiral organic compounds. In recent years, many chemical and biological methods for the synthesis of epoxides, such as asymmetric epoxidation of olefins,[3-5] resolution of racemic epoxides[6,7] and indirect chemical transformation[8,9] have been reported. Very recently we reported a practical synthesis of chiral terminal epoxides with high optical purity by employing oxazaborolidine-catalyzed reduction of α-sulfonyloxyketones to be more readily available for a large-scale applications.[10] On the other hand, (−)-*B*-chlorodiisopinocampheylborane (^{d}Ipc$_2$BCl, **1**) is a commercially available and highly effective asymmetric reducing agent for the asymmetric reduction of various prochiral ketones.[11] Herein we wish to report a convenient synthesis of optically active styrene oxide derivatives **3** with high enantiomeric excess by asymmetric reduction of substituted 2-sulfonyloxyacetophenone derivatives **2** with this reagent.



Scheme 1

The starting materials **2** were prepared by sulfonyloxylation of substituted acetophenones with [hydroxy(aryl or methylsulfonyloxy)iodo]benzenes in 72-87% yields according to the literature procedure.[12]

We initially compared the reduction **2b** using a 10% excess of the reagent in THF at various temperature. The reductions

Table 1. Asymmetric reduction of substituted 2-sulfonyloxyacetophenones **2** with ^{d}Ipc$_2$BCl (**1**) in THF at -25 °C[a]

Entry	Cpd	Time (h)	Epoxide	Yield[b] (%)	$[\alpha]^{22}_D$ (*c*, solvent)	% ee	confg
1	**2a**	48	**3**	76	+42.2 (1.20, C_6H_6)	92[g](94)[p]	R[h]
2	**2b**	48	**3**	82	+42.3 (1.15, C_6H_6)	92[g]	R[h]
3	**2b**	24	**3**	88[c]	f	88[g]	R[h]
4	**2b**	18	**3**	92[d]	f	85[g]	R[h]
5	**2c**	48	**3**	72	f	90[g]	R[h]
6	**2d**	48	**3**	75	f	92[g]	R[h]
7	**2e**			e			
8	**2f**	48	**4**	86	-10.5 (1.1, $CHCl_3$)	93[g](95)[r]	R[t]
9	**2g**	48	**5**	83	-24.70 (1.2, $CHCl_3$)	93[r](98)[s]	R[k]
10	**2h**			e			
11	**2i**	48	**6**	78	+25.8 (1.0, C_6H_6)	94[t](99)[m]	R[m]
12	**2j**	48	**7**	85	-36.6 (2.1, $CHCl_3$)	93[t](97)[n]	R[n]
13	**2k**	48	**8**	80	-29.2 (1.1, $CHCl_3$)	97[t]	R[o]
14	**2l**	48	**9**	78	-63.51 (1.2, $CHCl_3$)	(65)[p]	R[p]
15	**2m**	48	**10**	83	-7.2 (1.1, $CHCl_3$)	(72)[q]	R[q]
16	**2n**	24	**11**	80	+7.9 (1.1, $CHCl_3$)	52[r] (56)[s]	R[s]

[a] [**2**] : [**1**] = 1 : 0 : 1.1. [**2**] = 0.8 M. [b] Isolated and purified yields of the corresponding epoxides converted by the direct treatment of 2 N-NaOH to the reaction mixture obtained after treating reduction products **2** with acetaldehyde. [c] at 0 °C. [d] at 25 °C. [e] No reduction even at 25 °C for 24 h. [f] Not measured. [g] Determined by a capillary GC analysis using a β-DEX 120 chiral column (Supelco). [h] Based on $[\alpha]^{23}_D$ -44.9 (*c* 1.02, C_6H_6). *S*; ref. 14. [i] Based on $[\alpha]_D$ -11.1 (*c* 1.23, $CHCl_3$), 100% ee, *R*; ref. 15. [j] Determined by HPLC analysis using a Daicel Chiralpak OT; hexane/*i*-PrOH = 99/1. [k] Based on $[\alpha]^{20}_D$ -24.0 (*c* 1.08, $CHCl_3$), >97% ee. *S*; ref. 6b. [l] Determined by HPLC analysis using a Daicel Chiralpak OD; hexane/*i*-PrOH = 99.8/0.2. [m] Based on $[\alpha]^{20}_D$ −25.5 (*c* 1.3, C_6H_6), 98% ee. *R*; ref. 16. [n] Based on $[\alpha]^{25}_D$ −36.0 (*c* 1.25, $CHCl_3$), 95% ee. *S*; ref. 1h. [o] Based on the sign of optical rotation value, (*R*)-(−); ref. 2c. [p] Compared to optical rotation value, $[\alpha]^{22}_D$ −67.4 (*c*1.2, $CHCl_3$), of (*S*)-1-naphthyloxirane obtained from (*S*)-1-naphthylethane-1,2-diol, 69 %ee. [q] Based on $[\alpha]_D$ -9 (*c* 1.2, $CHCl_3$), 92% ee. *R*; ref. 1f. [r] Determined by a capillary GC analysis using a G-TA chiral column (Astec). [s] Based on $[\alpha]^{19}_D$ +14 (*c* 0.56, $CHCl_3$), 99% ee, *R*; ref. 17.

occur at a convenient rate even at -25 °C. The reaction mixture was treated with 2 equiv of acetaldehyde at room temperature for 4 h and then concentrated under reduced pressure.[13] The residue was diluted in ether and treated with 2 N NaOH at 0 °C for 6 h to give the product epoxide **3** in 76% yield (Scheme 1). As shown in Table 1, the reduction of **2b** provided **3** in 92 %ee at -25 °C. The reactions were faster at 0 and 25 °C, but the %ees of **3** were lower (entries 2-4). The influence of different sulfonyl groups on the enantioselectivity of the same reduction was not observed (entries 1, 2 and 5, 6). The reduction of other substituted acetophenone analogues **2b-k** having 3-chloro, 4-chloro, 4-methyl, 4-nitro and 4-phenyl groups provided the corresponding epoxides **4-8** with high enantioselectivity in good yields. The ketones bearing *o*-substituents such as **2e** and **2h** were not reduced even at room temperature for 24 h. For the sulfonyloxy ketones (**2l-n**) containing naphthyl and pyridyl groups, the reduction afforded somewhat lower enantioselectivity. All the product epoxides obtained are consistently enriched in the *R*-enantiomers. In summary, we have established an efficient synthesis of optical active styrene oxide derivatives **3** with high enantiomeric excess by asymmetric reduction of 2-sulfonyloxyacetophenone derivatives **2** using a commercially available ^{d}Ipc$_2$BCl **1**. Using this methodology, we are currently investigating its application for syntheses of chiral synthons such as chiral azido alcohols, cyanohydrins and halohydrins.

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