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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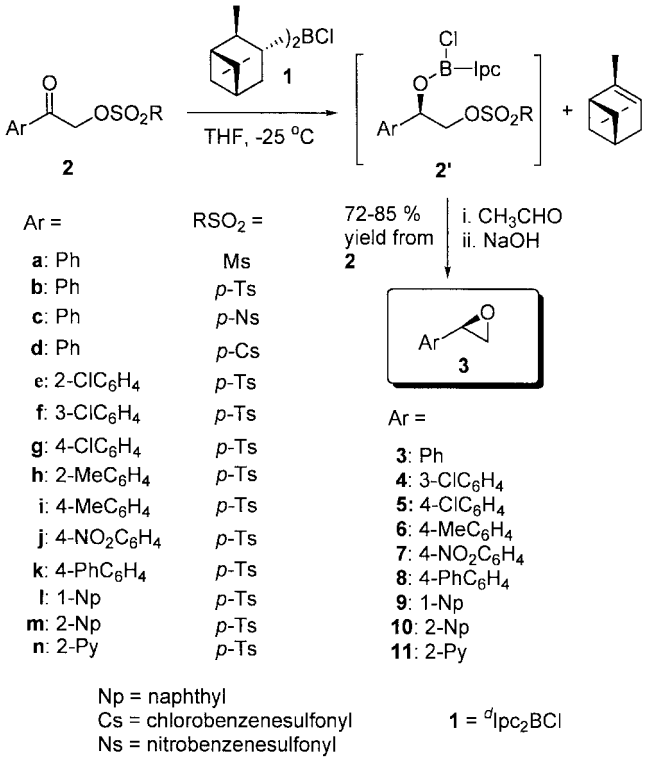
Received March 2, 2001

Keywords : Chiral epoxide, Asymmetric reduction, (–)-Ipc$_2$BCl.

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)[h]	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)[i]	R[i]
9	**2g**	48	**5**	83	-24.70 (1.2, $CHCl_3$)	93[j](98)[k]	R[k]
10	**2h**			e			
11	**2i**	48	**6**	78	+25.8 (1.0, C_6H_6)	94[j](99)[m]	R[m]
12	**2j**	48	**7**	85	-36.6 (2.1, $CHCl_3$)	93[j](97)[n]	R[n]
13	**2k**	48	**8**	80	-29.2 (1.1, $CHCl_3$)	97[l]	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 $^{d}Ipc_2BCl$ **1**. Using this methodology, we are currently investigating its application for syntheses of chiral synthons such as chiral azido alcohols, cyanohydrins and halohydrins.

Acknowledgment. This study was financially supported by the Hallym Academy of Sciences (2000), Hallym University.

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