Chiral β-Sulfinylamines as Ligands for Enantioselective Addition of Diethylzinc to Benzaldehyde†

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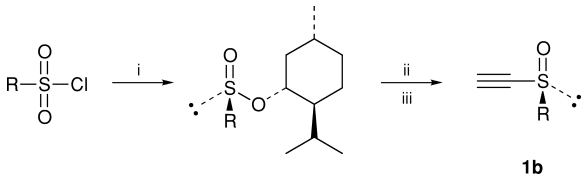
Chiral β-sulfinylamines **4a**, **6a**, **6b**, **8a**, **8b** and **9b** were synthesized and assessed in the enantioselective addition of diethylzinc to benzaldehyde.

Enantioselective carbon–carbon bond formation has continued to be one of the most extensively studied areas in catalytic asymmetric synthesis over the past ten years. In particular, the catalytic enantioselective addition of diethylzinc to aldehydes has drawn much attention because of its simplicity and its effectiveness in the preparation of a variety of useful chiral alcohols.[1] In order to serve as efficient catalysts to complex and activate organozinc reagents for addition reactions, the presence of two basic centers in the catalysts appears to be essential. Noticeable examples of catalysts exhibiting good results include chiral β-amino alcohols,[2] 1,2-diols and sulfonamides.[3–4] On this point, β-sulfinylpyridines possessing one basic oxygen and one nitrogen have been recently used as chiral bidentated ligands to promote enantioselective addition reactions.[5] This report prompted us to reveal our findings in utilizing chiral β-sulfinylamines as ligands for enantioselective addition of diethylzinc to benzaldehyde.

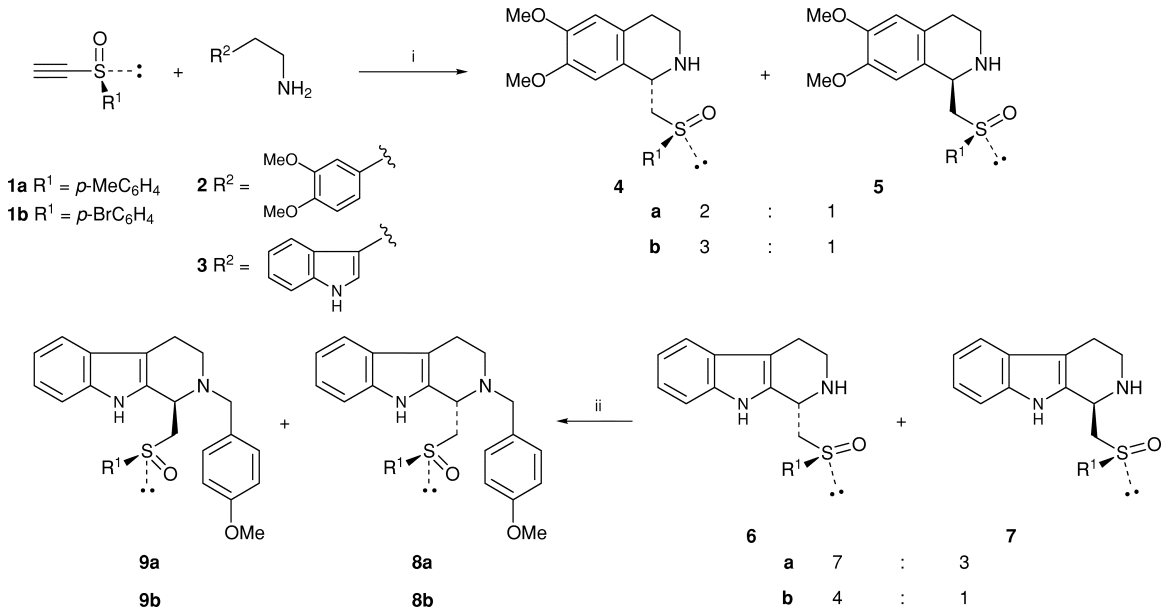
Based on the two-step synthetic protocol as shown in Scheme 1, Michael addition of amine **2** or **3** to chiral acetylenic sulfoxide **1a** followed by acid induced cyclization gave a diastereomeric mixture of **4a**/**5a** (2:1) and **6a**/**7a** (7:3) in 45 and 91% yield, respectively.[6] The diastereomeric mixtures could easily be separated into optically pure compounds by column chromatography on silica gel. However, the starting acetylenic sulfoxide **1a** was found to be quite labile and gradually decomposed on standing.



Scheme 2 *Reagents and conditions*: i, $(EtO)_3P$–NEt_3, (1*R*,2*S*,5*R*)-menthol; ii, $Me_3SiC{\equiv}CMgBr$; iii, KF/MeCN. R = *p*-BrC_6H_4

The crystalline chiral *p*-bromophenylethynyl sulfoxide **1b** which exhibited outstanding stability was thus prepared in 34% overall yield over a three-step sequence (Scheme 2). Repeating the synthetic manipulations described in Scheme 1, **4b**/**5b** (3:1) and **6b**/**7b** (4:1) were obtained, again as separable diastereomeric mixtures in 48 and 66% yield, respectively. To extend our collection in the chiral pool, tertiary amines **8a**, **8b** and **9b** were prepared from the corresponding amines *via* reductive amination. In addition, (*S*)-(4-methylphenyl)pyrrol-2-yl sulfoxide **10** was also prepared and was used as a catalyst.[8]

With these homochiral materials in our disposal, their performance as new ligands for catalyzing enantioselective addition to benzaldehyde was evaluated and results are summarized in Table 1. The majority of the reactions were conducted in hexane–toluene solution (1:1) in the presence



Scheme 1 *Reagents and conditions*: i, $CHCl_3$, TsOH or TFA, 0 to –30 °C; ii, *p*-$MeOC_6H_4CHO$, $NaCNBH_3$, MeCN

of 5 mol% of ligands at room temperature. In general, in the presence of the catalyst, the rate of reaction was only marginally accelerated as compared with the control reac-

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Table 1 Enantioselective addition of diethylzinc to benzaldehyde catalyzed by chiral β-sulfinylamines

	Ligand[a]	Reaction temperature (time/h)	Ee(%) (config.)[d]	Yield (%)
1	**4a**	r.t. (20)	3 (*S*)	53
2	**6a**	r.t. (20)	4 (*S*)	50
3	**6a**[b]	r.t. (20)	4.3 (*S*)	50
4	**6a**[c]	0 °C (5)	5 (*S*)	60
5	**6b**[c]	0 °C to r.t. (20)	2.2 (*S*)	92
6	**8a**	0 °C to r.t. (20)	8.6 (*S*)	56
7	**8b**	r.t. (20)	11 (*S*)	80
8	**9b**	0 °C to r.t. (22)	2.5 (*R*)	62
9	**10**	0 °C to r.t. (22)	14 (*R*)	63
10	**10**	0 °C	6 (*R*)	75

[a]5 mol% of ligand was used for each reaction. [b]THF–hexane (1:1) used as solvent. [c]1.5 mol% of BuLi was added to the ligand prior to the addition of diethylzinc. [d]Determined by both optical rotation measurement in comparison with the known chiral ethyl phenyl alcohol and the chiral HPLC method.

tion. Most of the catalysts gave (*S*)-1-phenylpropan-1-ol in satisfactory yield but with low enantioselectively. The catalytic systems resulting from the amide anion of **6a** or **6b** and diethylzinc accelerated the reaction substantially, but gave the same level of enantioselectivity (Table 1, entry 4 and 5). By converting the secondary β-sulfinylamines **6** and **7** into tertiary amines **8** and **9** seemed to increase the solubility of the ligands in the mixed solvent system and resulted in improvement in the ee of the reaction (Table 1, entry 6 and 7). An attempt to shorten the distance of the chelating centers by using ligand **10** for the asymmetric reaction did not result in any substantial improvement in the ee (Table 1, entry 9 and 10). Our present findings together with those reported indicated that bidentate ligands comprising a sulfinyl group and a basic nitrogen either in pyridine or pyrrole or cyclic secondary or tertiary amine form are not efficient in catalyzing enantioselective addition.

Experimental

Melting points are uncorrected. Optical rotation was determined using a Jusco Dip 1000 Digital polarimeter. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EI) or fast atomic bombardment (FAB) on a Finnigan MAT SSQ-710 mass spectrometer. NMR spectral in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard were measured with a JEOL EX 270 (270 MHz for ^1H and 67.8 MHz for ^{13}C) spectrometer. The enantioselectivity of the reactions was determined on a Hewlett Packed 1050 HPLC with chiralcel OD (0.46 × 25 cm) chiral column. Elemental analysis was carried out at the Shanghai Institute of Organic Chemistry.

Preparation of Compound **1b**.—To a suspension of magnesium (0.37 g, 15 mmol) in diethyl ether (30 ml) under N_2, ethyl bromide (1.1 ml, 15 mmol) was introduced and the mixture was refluxed for 1 h. After cooling to 0 °C, ethynyltrimethylsilane (2.5 ml, 18 mmol) was added and the mixture was refluxed for 2.5 h. Then, most of ether was evaporated by a N_2 flow and toluene (10 ml) was introduced. To this toluene solution at 0 °C, (1*R*, 2*S*, 5*R*)-(−)-menthyl (S_s)-4-bromobenzenesulfinate prepared according to the Sharpless procedure[7] (2.2 g, 6.2 mmol) in toluene (5 ml) was added. The mixture was stirred at 0 °C for 3 h, quenched with saturated NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 3 ml). The organic layer was dried to give the crude product. This crude product was dissolved in MeCN (30 ml) and KF (0.8 g, 13 mmol) was added. The mixture was stirred at r.t. for 30 min and the solvent was removed. Water (30 ml) was added and the product was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic layers were dried, filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate–petroleum ether (1:9), to afford **1b** as a white solid (750 mg, 53%). Mp 91–93 °C (Found: C, 41.65; H, 2.04; C_8H_5SOBr requires C, 41.75; H, 2.19%), δ_H 3.75 (1H, s), 7.70 (4H, m); δ_C 81.3, 90.7, 126.4, 126.7, 132.9, 142.1; $[\alpha]_D^{25}$ 127.14 (*c* 0.78, $CHCl_3$).

Preparation of Chiral Ligand **6b**.—Ligand **6b** was prepared in 66% yield according to the procedure described in ref. 6. Mp 118 °C (decomp.) (Found: C, 55.25; H, 4.28; N, 7.16; $C_{18}H_{17}N_2OSBr$ requires C, 55.51; H, 4.40; N, 7.19%). δ_H 2.77 (2H, m), 3.03 (1H, dd, *J* 5.40, 5.13 Hz), 3.27 (3H, m), 4.81 (1H, dd, *J* 5.40, 4.00 Hz), 7.12 (2H, m), 7.35 (1H, d, *J* 7.83 Hz), 7.47 (1H, d, *J* 8.37 Hz), 7.57 (2H, d, *J* 8.64 Hz), 7.68 (2H, d, *J* 8.64 Hz), 9.27 (1H, s); δ_C 22.48, 42.23, 49.56, 63.74, 109.3, 111.3, 118.1, 119.3, 122.0, 125.5, 126.0, 127.0, 132.8, 133.0, 135.8, 142.6. $[\alpha]_D^{20}$ 217.0 (*c* 0.095, CH_2Cl_2).

Enantioselective Addition of Diethylzinc to Benzaldehyde: General Procedure.—To a solution of the chiral ligand (5% mmol) in toluene (3 ml), diethylzinc (1 M solution, 2.5 ml, 2.5 mmol) in hexane was added at r.t. The mixture was stirred for 1 h. Then the solution was cooled to 0 °C and benzaldehyde (0.13 ml, 1.25 mmol) was introduced and the mixture stirred for 20 h. Saturated NH_4Cl solution was added to quench the reaction. After extraction with CH_2Cl_2 (3 × 30 ml), the combined organic layers were dried, filtered and evaporated. The residue was purified by flash chromatography on silica gel, eluting with hexane–ether (7:3), to afford 1-phenylethanol as a liquid. The ee values of the products were determined by rotation measurement and chiral HPLC.

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