

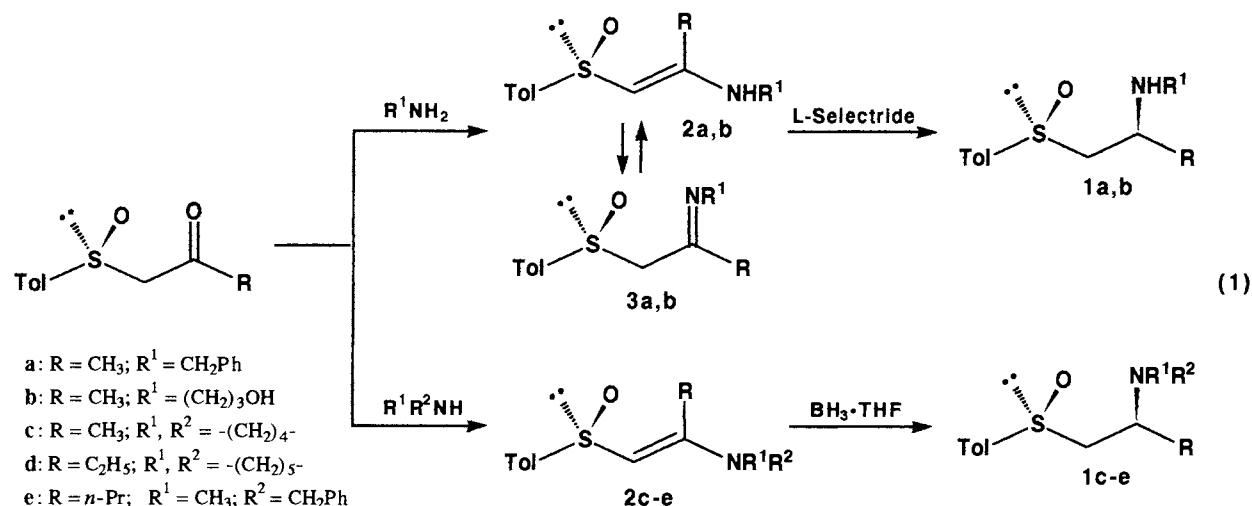
Stereoselective Reduction of Enamino Sulfoxides

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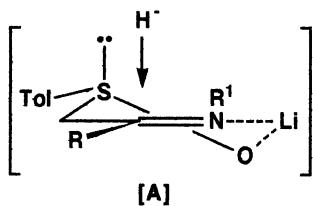
Enamino sulfoxides, *p*-TolS(O)CH=C(NR¹R²)R (where R¹ = alkyl, R² = H or alkyl), were reduced with lithium tri(*s*-butyl)borohydride or borane-THF, respectively, to give β -amino sulfoxides of *R*^{*},*R*^{*} configuration with high stereoselectivity.

β -Amino sulfoxides **1** have been shown to be good synthetic precursors for optically active amines.¹⁾ Although **1** was prepared by the addition of (*p*-tolylsulfinylmethyl)lithium to imines, only aromatic amines were available in this method. Another approach to **1** is reduction of enamino sulfoxide **2** or its tautomer, α -sulfinyl imine **3**. However little attention has been paid to this reaction as compared with many reports on stereoselective reduction of α -sulfinyl ketones.²⁾ There are only a few literatures on the reduction of cyclic enamino sulfoxides with NaBH₃(CN)³⁾ or NaBH₄,⁴⁾ but we found that these hydrides reduced acyclic **2** with poor selectivity. We report here that lithium tri(*s*-butyl)borohydride (L-Selectride) or borane-THF reduces **2** with high stereoselectivity (Eq. 1).

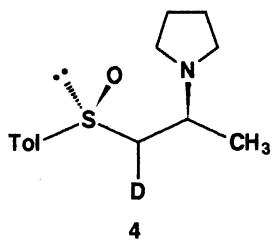
The enamino sulfoxides **2** were easily prepared by the condensation of readily available α -sulfinyl ketones^{5,6)} with primary or secondary amines.^{7,8)} Stereochemistry of **2** was determined to be *E* by NOE.⁹⁾ We found that highly stereocontrolled reduction of **2a,b** was performed with L-Selectride (97-98%.



selectivity). Typically, a THF solution of L-Selectride (1.5 mol equiv.) was added dropwise to a CH_2Cl_2 solution of **2a** at -20°C . After 6 h at -20°C , the mixture was quenched with methanol. The usual workup and purification by preparative TLC (silica-gel, AcOEt - methanol 10 : 1) gave the amino sulfoxide **1a** (57%) along with *p*-tolylsulfinylacetone derived from the unreacted **2a** (43%). The diastereomeric ratio ($R^*,R^* : R^*,S^*$) of **1a** was determined to be 97 : 3 by HPLC analysis after acetylation. Lowering the reaction temperature to -78°C brought about little enhancement of the selectivity (Table 1). The reduction proceeds probably via the imine form **3** since **2c-e** are not reduced under the same reaction conditions.^{8,10} Thus the high selectivity is ascribed to a chelation model [A].¹¹



Stereoselective reduction of **2c-e** was achieved with borane-THF complex.¹² For example, a THF solution of borane-THF complex (1.0 M, 0.44 mmol) was added to a CH_2Cl_2 (4 mL) solution of **2c** (0.20 mmol) over 3 min. After 3 h at -78°C , water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4 , and concentrated. The residue was dissolved in THF (2 mL) and treated with 1,4-diazabicyclo[2.2.2]octane (0.4 mL) to decompose **1c**-borane complex. After the usual workup, the crude product was subjected to preparative TLC to give **1c** (95%) as colorless crystals. The ratio of (R^*,R^*)-**1c** : (R^*,S^*)-**1c** was 87 : 13 (^1H NMR). Other results are summarized in Table 1. Polar solvents were less effective. The reaction involves direct hydroboration to the C=C bonds of **2c-e**. This is confirmed by a deuterating experiment: quenching the reaction of **2c** with D_2O gave an α -deutero- β -amino sulfoxide **4**, that was identified by ^1H NMR.



The relative stereochemistry of **1** was estimated as follows. Desulfurization of the major isomer derived from (*S*)-**2d** with Raney Ni afforded (*R*)-1-(*s*-butyl)-piperidine¹³ (86%) (Eq. 2). Thus, the major isomer of **1d** must have *S,S* configuration. The same relative stereochemistry was assigned to the major isomers of **1a-c** and **1e** since they showed good similarity in their spectroscopic behavior.¹⁵ It is noteworthy that the transformation of Eq. 2 demonstrates the utility of the present reaction for a facile synthesis of optically active amines.

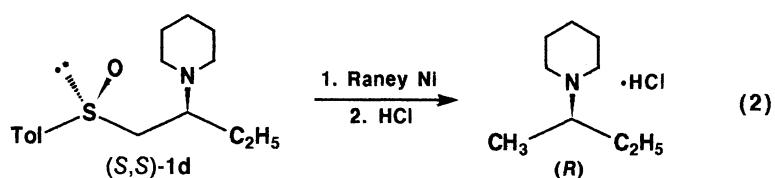


Table 1. Stereoselective reduction of 2

Enamino sulfoxide (2)	Reagent (mol equiv.)	Solvent	Temp/°C, Time/h	Product ^{a)}	Yield/% ^{b,c)}	$R^*,R^* : R^*,S^*$
	L-Selectride (1.5)	CH ₂ Cl ₂	-20, 6		57 [43]	97 : 3
2a	L-Selectride (2.5)	CH ₂ Cl ₂	-20, 48	1a	62 [37]	97 : 3
2a	L-Selectride (1.5)	CH ₂ Cl ₂	-78, 6	1a	14 [80]	98 : 2
	L-Selectride (3.0)	CH ₂ Cl ₂	-20, 5		41 [45]	98 : 2
	BH ₃ ·THF (2.2)	CH ₂ Cl ₂	-78, 3		95	87 : 13
2c	BH ₃ ·THF (2.4)	THF	-78, 2	1c	81	81 : 19
2c	BH ₃ ·THF (2.2)	DME ^{d)}	-78, 3	1c	77	63 : 37
	BH ₃ ·THF (2.2)	CH ₂ Cl ₂	-78, 3		73	73 : 27 ^{e)}
	BH ₃ ·THF (3.4)	CH ₂ Cl ₂	-78, 7		82	85 : 15

a) Only major (R^*,R^*) isomers are shown. b) Total yield of both R^*,R^* and R^*,S^* isomers. c) Values in the brackets are the yields of the recovered *p*-tolylsulfinylacetone. d) 1,2-Dimethoxyethane. e) $S_s, S_c : S_s, R_c$.

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- 2) Stereoselective reduction of α -sulfinyl ketones: G. Solladie, G. Demaillly, and C. Greck, *Tetrahedron Lett.*, **26**, 435 (1985); H. Kosugi, M. Kitaoka, A. Takahashi, and H. Uda, *J. Chem. Soc., Chem. Commun.*, **1986**, 1268; G. Solladie, G. Demaillly, and C.

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3) M. E. Price and N. E. Schore, *J. Org. Chem.*, **54**, 5662 (1989).

4) D. H. Hua, S. N. Bharatih, P. D. Robinson, and A. Tsujimoto, *J. Org. Chem.*, **55**, 2128 (1990).

5) Preparation of optically active α -sulfinyl ketones: N. Kunieda, J. Nokami, and M. Kinoshita, *Chem. Lett.*, **1974**, 369; K. Ogura, M. Ishida, H. Tomori, and M. Fujita, *Bull. Chem. Soc. Jpn.*, **62**, 3531 (1989). Also see Ref. 2.

6) Racemates were employed throughout this work unless otherwise noted.

7) For example, a mixture of 1-(*p*-tolylsulfinyl)propan-2-one (5.0 mmol) and benzylamine (5.5 mmol) was allowed to stand for 0.5 h at room temperature, and the resulting solid was recrystallized from methanol to give **2a** (94%) as colorless crystals (mp 149 - 150 °C dec).⁸⁾ Similarly, **2c** (mp 108 - 110 °C) was prepared in a quantitative yield. Since **2b,d,e** were obtained as viscous oils, they were employed in the following reduction without purification.

8) ¹H NMR showed that **2a** was stereochemically pure and was in equilibrium with the imine form **3a** (**2a** : **3a** = 73 : 27 in CDCl₃ at 27 °C) though only **2a** exists in a crystalline form as shown by the IR spectrum.

9) An NOE (12%) was observed between the olefinic and the benzylic protons of **2a**.

10) Since employment of large excess L-Selectride (3.0 mol equiv.) and elongation of reaction period (48 h) did not affect the yield of **1a** significantly, the recovery of *p*-tolylsulfinylacetone is attributable to unfavorable formation of the azaenolate, *p*-TolS(O)CH=C(NR¹Li)R, which no longer participates in the reduction.

11) The attack of the hydride from the upper side leads to a chair-like transition state. See: P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry," Pergamon Press, Oxford (1983), Chap. 6.

12) Borane-THF reduction of **2a**, however, showed poor selectivity (*R*,R** : *R*,S** = 59 : 41), possibly owing to a different pathway via the imine form rather than the enamine form.

13) (*R*)-1-(*s*-Butyl)piperidine-hydrochloride: mp >270 °C; [α]_D +3.82° (c 0.50, H₂O) (lit.¹⁴⁾ for the *R* enantiomer (the ee is unknown) +0.96° (c 4.4, H₂O)).

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15) Kagan et al. assigned the stereochemistry of **1** based on the spectroscopic similarity.^{1a)} For the methylene protons of -CH_aH_b-S(O)-, we also found the similarity that $|\delta H_a - \delta H_b| > 0.4$ ppm for all of the *R*,R** isomers while $|\delta H_a - \delta H_b| < 0.13$ ppm for all of the *R*,S** isomers. Similar behavior was reported in the ¹H NMR of 1-substituted 2-(*p*-tolylsulfinyl)ethanols: G. Solladie, C. Greck, G. Demailly, and A. Cavallo, *Tetrahedron Lett.*, **23**, 504 (1982).

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