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The Steric Effect and Enantioselectivity of Chiral 2,2-Disubstituted Thiaprolinol Derivatives as Ligands for Borane Reduction of Aromatic Ketones and for Diethylzinc Addition to Aromatic Aldehydes

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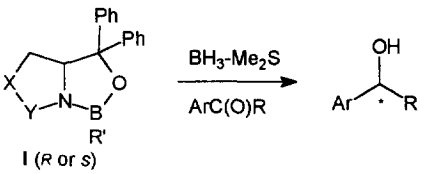
Abstract: A new series of chiral amino alcohols **3a-e** has been prepared from natural amino acid L-cysteine. These compounds have been used as chiral ligands for borane reduction of ketones and for diethylzinc addition to aldehydes. In the reduction of ketones, **3b-e** have been used as the substitute of (*R*)-prolinol to provide (*S*)-alcohols in good yields and modest enantioselectivity (30-50% ee). In the diethylzinc addition to aldehydes, **3b-e** promoted the formation of (*S*)-alcohols in excellent yields and medium to good enantioselectivities (60-80% ee).

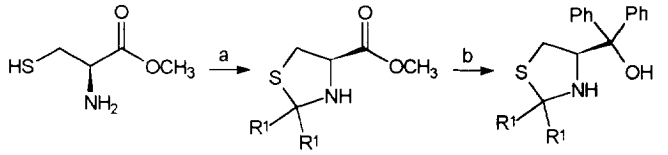
Chiral amino alcohol catalyzed enantioselective reduction of ketones and alkylation of aldehydes have been recognized as two of the most efficient methods for the preparation of enantiomerically pure alcohols. Various amino alcohols have been prepared and utilized as chiral ligands in the catalytic enantioselective reactions.[1,2] The absolute configuration of the major products is effected by the stereochemistry of these chiral amino alcohols and the transition state of the reaction. For example, in the presence of the (*S*)-prolinol derivative (X = Y = CH_2, **I**), borane reduces acetophenone to the (*R*)-alcohol.[1,3,4] However, the required (*R*)-prolinol ligand to give the (*S*)-alcohol must be prepared from the expensive D-proline. It would be very convenient and economical if an analogue of (*R*)-prolinol derivative (**I**) could be prepared from a natural amino acid and be used as a ligand for the reduction of ketones to the (*S*)-alcohols. It seems that this goal could be achieved if the substructures of X and Y of **I** are adequately modified. In this communication, we report our investigations in the preparation of chiral thiazolidinemethanols (X = S, Y = CR_2, **I**) derived from L-cysteine and their applications as ligands for the reduction of aromatic ketones and for the addition of diethylzinc to aromatic aldehydes.



I (*R* or *S*)

2,2-Disubstituted-1,3-thiazolidine-α,α-diphenylmethanol **3a-e** were prepared from L-cysteine methyl ester via two steps (Scheme 1).[5] The free amine ester **1** was converted to the thiazolidine derivatives **2** by heating with various ketones and catalytic amount of trifluoroacetic acid. Compounds **2** were then treated with excess amount of phenylmagnesium chloride to give the corresponding amino alcohols **3b-e** in 60-80% overall yield.[6] However, the yield of compound **3a** is very low due to formation of side products.

Scheme 1



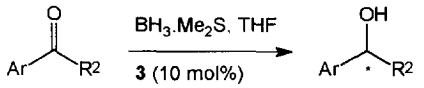
1 **2** **3**

	R^1, R^1		R^1, R^1
a	H, H		
b	CH_3, CH_3	**d**	$-(CH_2)_4-$
c	C_2H_5, C_2H_5	**e**	$-(CH_2)_5-$

Reagents and conditions: (a) $R^1C(O)R^1$ (excess), 2-3 drops of CF_3COOH, 80-100 °C oil bath, 2-4 hr; (b) PhMgCl (3.5 equiv), THF, 0-25 °C, 16 hr, 60-80% overall yield.

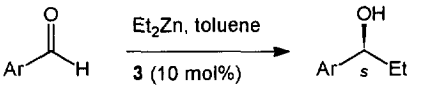
In the reduction of aromatic ketones (Scheme 2), the oxazaborolidine catalysts were prepared *in situ* from an amino alcohol **3** (10 mol%) and borane-dimethyl sulfide complex in dry tetrahydrofuran at 50 °C for 16 hr. To this solution at 50 °C was added dropwise the respective ketone **4** in tetrahydrofuran slowly.[7] The mixture was stirred for 1 hr after completion of addition, and then quenched with methanol. The product was purified by chromatography. The enantiomeric excess (ee) values of each chiral alcohol was analyzed by a chiral HPLC column (Daicel OB or OD column), and the absolute configurations were determined by their specific rotation values. We found that the configurations of the obtained alcohols **6** are dependent on the structures of ketones **5** and the amino alcohols **3**. For the reduction of acyclic aromatic ketones **4a-c** catalyzed by (*S*)-amino alcohol ligands **3b-3e**, the hydride transfers from borane to the *re* face of the C=O group to afford (*S*)-**6a-b** as well as (*R*)-**6c** as the major products. Amino alcohols **3b** and **3d** are generally more selective than their analogues (**3c**, **3e**), and chiral products **6** are obtained in modest selectivity (30-50% ee, see Table 1). This outcome of the chiral inductions is different from the cases reported in literatures and could not be interpreted by the transition state **TS2** as described before.[1,3,4b,8a] Due to the more serious steric repulsion between R^1 and R^2, the transition state **TS2** might be less favorable for acyclic ketones **4a-c**. However, transition state **TS1** should be more favorable for these acyclic ketones, and therefore, alcohols (*S*)-**6a-b** and (*R*)-**6c** are the predominated products.[8b] In a comparison experiment, (entry 1, Table 1), amino alcohol **3a** provided (*R*)-**6a** in very low selectivity (14% ee). These results demonstrate that the enantioselectivity is originated from the steric requirement of chiral amino alcohol **3b**. On the other hand, that the reduction of α-tetralone **4d** to give the (*R*)-**6d** as the major product means that the **TS2** might still be more favorable for cyclic ketones.

Scheme 2



4a $PhC(O)CH_3$ **6a-d**
4b $PhC(O)CH_2CH_3$
4c $PhC(O)CH_2Cl$
4d α-tetralone

Scheme 3



5a PhCHO **7a-d**
5b 4-Cl-PhCHO
5c 4-F-PhCHO
5d 4-OMe-PhCHO

Table 1 Catalytic Enantioselective Borane Reduction of Ketones 4a-d

			alcohol **6**	
entry	ketone	amino alcohol[a]	yield %	ee, % (config)[c]
1	**4a**	**3a**	99	14 (*R*)
2	**4a**	**3b**	74	46 (*S*)
3	**4a**	**3c**	78	24 (*S*)
4	**4a**	**3d**	99	49 (*S*)
5	**4a**	**3e**	81	10 (*S*)
6	**4b**	**3b**	99	43 (*S*)
7	**4b**	**3c**	84	7 (*S*)
8	**4b**	**3d**	93	39 (*S*)
9	**4b**	**3e**	38	22 (*S*)
10	**4c**	**3b**	77	35 (*R*)
11	**4c**	**3c**	99	2 (*R*)
12	**4c**	**3e**	99	10 (*R*)
13	**4d**	**3b**	99	47 (*R*)
14	**4d**	**3c**	99	3 (*R*)
15	**4d**	**3d**	99	39 (*R*)
16	**4d**	**3e**	99	14 (*R*)

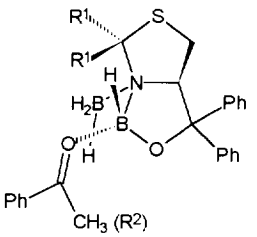
Table 2 Catalytic Enantioselective Diethylzinc Addition to Aldehydes 5a-d

			alcohol **7**	
entry	aldehyde	amino alcohol[b]	yield %	ee, % (config)[c]
1	**5a**	**3a**	30	15 (*S*)
2	**5a**	**3b**	96	73 (*S*)
3	**5a**	**3b**	99	81 (*S*)[d]
4	**5a**	**3c**	84	64 (*S*)
5	**5a**	**3d**	99	69 (*S*)
6	**5a**	**3e**	90	67 (*S*)
7	**5b**	**3b**	73	75 (*S*)
8	**5b**	**3c**	95	66 (*S*)
9	**5b**	**3d**	99	70 (*S*)
10	**5b**	**3e**	99	69 (*S*)
11	**5c**	**3b**	33	76 (*S*)
12	**5c**	**3c**	99	65 (*S*)
13	**5c**	**3d**	99	68 (*S*)
14	**5c**	**3e**	99	69 (*S*)
15	**5d**	**3b**	99	64 (*S*)
16	**5d**	**3c**	99	25 (*S*)
17	**5d**	**3d**	99	30 (*S*)
18	**5d**	**3e**	15	0.5 (*S*)

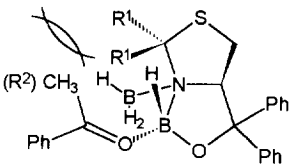
(a) BH_3/**3**/ketone molar ratio = 2.0/0.1/1.0. (b) $ZnEt_2$/**3**/aldehyde molar ratio = 3.0/0.1/1.0. (c) The enantiomeric excess (ee) was measured by a chiral Daicel OB or OD column. The absolute configuration was determined by comparison of the specific rotation with the value in the literature.[3,4,8,9] (d) The reaction was run at 4 °C for 5 days.

These chiral amino alcohols **3a-e** are also able to catalyze the addition of diethylzinc to aldehydes (Scheme 3). Respective aldehyde **5** was added to a solution of diethylzinc and an amino alcohol ligand **3** (10 mol%), and the mixture was stirred at room temperature overnight. The (*S*)-alcohols **7a-d** were obtained in good to excellent yields and 60-80% ee (Table 2). Evidently, these chiral ligands are more enantioselective for diethylzinc addition to aldehydes than for borane reduction of ketones, and the amino alcohol **3b** is the most selective ligand in this series. Some enhancement in enantioselectivity (8% ee, entry 2 and 3, Table 2) was observed when the reaction was run at 4 °C for 5 days. The *S* configuration of the chiral alcohols is consistent with the mechanism **TS3** as reported in the literature.[2,9]

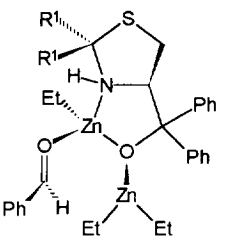
In conclusion, we have prepared a series of chiral amino alcohols **3a-e** derived from natural amino acid L-cysteine. These compounds have been successfully used as chiral ligands in the borane reduction of ketones and diethylzinc addition to aldehydes to provide chiral alcohols.



TS1
no R^1/R^2 repulsion
C=O *re* face reduced



TS2
R^1/R^2 repulsion
C=O *si* face reduced



TS3
no R^1/R^2 repulsion
C=O *si* face alkylated

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(1) Recent reviews of chiral reducing agents: (a) Singh, V. K. *Synthesis* **1992**, 605. (b) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475. (c) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763.

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(6) **3b**: mp 98.5-99.5 °C; $[\alpha]_D^{25}$ = -113 (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.62-7.20 (m, 10 H), 4.45 (dd, *J* = 5.8, 9.8 Hz, 1 H), 3.32 (bs, 1 H), 3.02 (dd, *J* = 9.8, 10.8 Hz, 1 H), 2.64 (dd, *J* = 5.0, 11.0 Hz, 1 H), 2.11 (bs, 1 H), 1.69 (s, 3 H), 1.65 (s, 3 H). **3c**: $[\alpha]_D^{25}$ = -78 (c 1.0, $CHCl_3$). **3d**: $[\alpha]_D^{25}$ = -78 (c 1.0, $CHCl_3$). **3e**: $[\alpha]_D^{25}$ = -70 (c 1.0, $CHCl_3$).

(7) We found no significant enantioselectivity if the reduction was performed at lower temperature, also see: Jiang, Y.; Qin, Y.; Mi, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1211.

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(10) We thank Ms. Ying Chen for operating NMR spectrometers.

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