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Enantioselective reduction of prochiral ketones catalyzed by new (*R*)-4-(phenylmercapto)methyl-5,5-diphenyl-1,3,2-oxazaborolidine and bis-[(*R*,*R*)-5,5-diphenyl-1,3,2-oxazaborolidine methyl]disulfide from L-cystine †

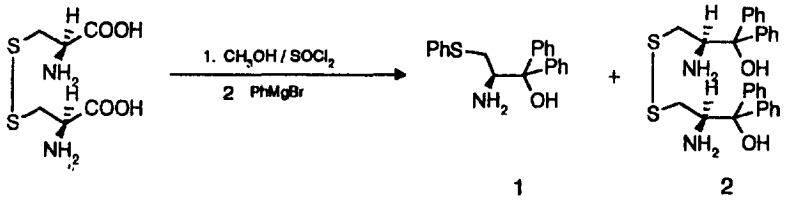
Xingshu Li and Rugang Xie *
Department of Chemistry, Sichuan University, Chengdu, 610064, P. R. China

Abstract: Two new optically active β-amino alcohols **1** and **2** were prepared from L-cystine. The *in situ* formed chiral oxazaborolidines have been used in the enantioselective catalytic homogeneous borane reduction of prochiral ketones and diketones. The chiral secondary alcohols are obtained with moderate to good enantiomeric excess. © 1997 Elsevier Science Ltd

The enantioselective synthesis of chiral alcohols which play an important role as intermediates in organic chemistry is a stimulating subject. One of the most successful methods is based on the use of chiral 1,3,2-oxazaborolidines (prepared from β-amino alcohols which are usually derived from α-amino acids) as catalysts, methods developed by Itsuno[1,2] and then improved by Corey.[3,4] During the last decade, many amino acids such as L-valine, L-proline, L-cysteine[5] and L-methionine[6] have been used in preparing 1,3,2-oxazaborolidine catalysts, but L-cystine derivatives have been relatively neglected.

We have investigated L-cysteine derivatives (*R*)-4-thiazolidinecarboxylic acid or (*R*)-4-thiazolidine methanol[7] and chiral bis-amino alcohols[8] in enantioselective reductions of prochiral ketones with borane. Now, we report two new chiral oxazaborolidines formed *in situ* with borane and β-amino alcohols derived from L-cystine, as the catalysts for the enantioselective reduction of aromatic ketones.

The two new chiral β-amino alcohols (*R*)-2-amino-1,1-diphenyl-3-(phenylmercapto)-1-propanol[9] **1** and bis-[(*R*)-2-amino-3-hydroxyl-3,3-diphenyl propyl]disulfide[10] **2** were synthesised as shown in Scheme 1.



Scheme 1.

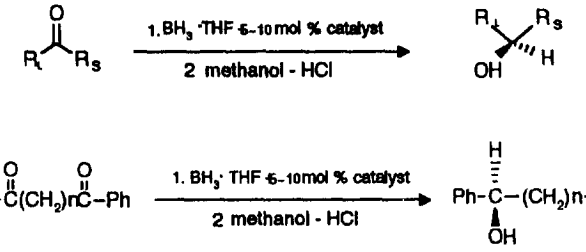
(*R*,*R*)-Cystine was treated with methanol and thionylchloride. Then, the methyl ester hydrochloride was suspended in dry diethyl ether and the Grignard reagent (8 equivalent) prepared from phenyl bromide in dry ether was added dropwise over 30 min at a temperature of 0°C under argon.

The mixture was stirring at the room temperature for 24 h. The amino alcohols **1** and **2** were obtained after extractive work-up and column chromatography on silica gel using petroleum ether

† Dedicated to Professor Zhao Huaming on the occasion of his 80th birthday.
* Corresponding author.

(b.p. 60–90°C):ethylacetate:methanol (10:5:1) as eluent. The yields of **1** and **2** were 40% and 10%, respectively.

The homogeneous catalytic reduction of prochiral ketones or diketones with borane and the *in situ* prepared 1,3,2-oxazaborolidine catalysts from **1** and **2** has been investigated.



In a typical procedure under argon atmosphere the amino alcohol **1** (1 mmol) or **2** (0.5 mmol) was put in a flask and 1 ml (1.3 mmol) of a THF solution of $BH_3 \cdot THF$ complex added at room temperature. The mixture was stirred for at least 12 h and then heated to 50–60°C. The appropriate aromatic ketone or diketone (10 mmol or 5 mmol) in 15 ml dry THF was added dropwise over 30 min, before addition of 7.5 ml (10 mmol) $BH_3 \cdot THF$ complex in the same manner over 60 min. After stirring for another 1–3 hours, the reaction mixture was cooled to room temperature. Methanol (1 ml) was added dropwise at 0°C and stirring was continued. Methanol–HCl (1 ml) was added after 5 min. The mixture was stirred for another 30 min and the solvents evaporated at reduced pressure. The residue was extracted with diethyl ether and the liquid phase was washed with 2 M NaOH and brine, dried ($MgSO_4$) and concentrated under reduced pressure. (The solid phase was treated to retrieve the amino alcohol for use in further enantioselective reduction as catalyst.) The crude alcohol was purified by column chromatography on silica gel using petroleum ether:ethyl acetate (4:1, v/v) as eluent to afford the secondary alcohol or diol. The enantiomeric excess was determined by specific rotation analysis. The results are given in Table 1.

As can be seen from Table 1, the chiral oxazaborolidines formed *in situ* with **1** and **2** as catalysts for enantioselective borane reduction of aromatic ketones and diketones provide moderate to good results. Catalyst **2** which has two catalytic centers seems especially good at catalyzing the enantioselective reduction of prochiral diketones. The CPK model suggests that cooperation of the two catalytic centers of **2** occurs when they catalyze the reduction of diketones. Further studies on the enantioselective reduction of diketones catalyzed by other bis-chiral oxazaborolidines are in progress.

Acknowledgements

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9. (*R*)-2-Amino-1,1-diphenyl-3-(phenylmercapto)-1-propanol **1**: m.p.: 93–94°C; $[\alpha]_D = -124.8$ (1.05, $CHCl_3$). Elemental analysis: found, C, 75.78, H, 6.31, N, 4.44; calculated, C, 75.18, H, 6.31, N, 4.18. ^{1}H-NMR ($CDCl_3$) δ in ppm, 2.69–2.73 (d, 1H, H4), 2.97–3.02 (d, 1H, H4), 3.94–3.99 (tr, 1H, H2), 7.14–7.52 (m, 15H, ArH). Ms: 336 (M^++1, 100%). 318 ($MH^+ - H_2O$, 42%), 183 (Ph_2C^+OH, 18%), 152 ($PhSCH_2C^+HNH_2$, 69%), 123 ($PhS\,CH_2^+$, 20%).

Table 1. Enantioselective reduction of prochiral aromatic ketones or diketones with **1** and **2** respectively and borane in THF[11,12]

catalyst (mol%)	ketone	chiral secondary alcohol[a]	
		$[\alpha]_D$(c,solvent)	e. e. % (R or S)
1(5)	$PhCOCH_3$	+37.50(1.3,CH_2Cl_2)	71.4(R)[b]
1(10)	$PhCOCH_3$	+39.13(0.9,CH_2Cl_2)	74.5(R)[b]
1(5)	$PhCOCH_2Br$	+36.46(2.0,$CHCl_3$)	87.0(S)[b]
1(10)	$PhCOCH_2Br$	+38.73(2.0,$CHCl_3$)	92.4(S)[b]
2(2.5)	$PhCOCH_3$	+38.10(1.5,CH_2Cl_2)	72.6(R)[b]
2(2.5)	$PhCOCH_2Br$	+36.58(2.1,$CHCl_3$)	87.2(S)[b]
1(10)	$PhCO(CH_2)_3COPh$	+20.40(1.0,CH_3OH)	89.5(R,R)[c]
1(10)	$PhCO(CH_2)_4COPh$	+10.30(1.0,CH_3OH)	81.7(R,R)[c]
2(5)	$PhCO(CH_2)_3COPh$	+21.50(1.0,CH_3OH)	94.3(R,R)[c]
2(5)	$PhCO(CH_2)_4COPh$	+12.41(1.0,CH_3OH)	98.4(R,R)[c]

a. The isolated yields of the chiral secondary alcohols were 80-90%.

b. The e. e. values of chiral secondary alcohols were calculated from specific rotations based on the following maximum rotations $[\alpha]_D^{25} = -52.5$ (2.27, CH_2Cl_2, S) for (S)-1-phenylethanol[11a] and $[\alpha]_D^{25} = -39.0$ (8.00, $CHCl_3$, R) for (R)-α-bromo-1-phenylethanol, 93% e. e.[11b]

c. The e. e. values of chiral diols were calculated from specific rotations based on the maximum rotations $[\alpha]_D = -22.8$ (c = 1, MeOH) for (S,S) − 1,5-diphenyl-1.5-dihydroxyl pentane[12], 99% e. e. and $[\alpha]_D = -12.6$ (c = 1, MeOH) for (S,S)-1.5-diphenyl-1,6-dihydroxyl hexane[12] 99% e. e. without considering the content of meso isomer. The determination of the amounts meso, (R,R) and (S,S) isomers is in progress.

10. Bis[(*R*)-2-amino-3-hydroxyl-3,3-diphenylpropyl]disulfide **2**: m.p.: 56–58°C; $[\alpha]_D$=395.6 (1.15, $CHCl_3$). Elemental analysis: found, C, 69.79, H, 6.24, N, 5.47; calculated, C, 69.73, H, 6.24, N, 5.42. ^{1}H-NMR ($CDCl_3$) δ in ppm, 2.3–2.7 (m, 4H, H4), 4.1–4.3 (tr, 2H, H2), 7.1–7.6 (m, 20H, ArH). Ms: 517 (M^+, 50%), 334 (M^+-183.38%), 240 ($M^+/2$-H_2O, 18%), 183 ($(Ph)_2C^+OH$, 40%).
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