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L-CYSTEINE-DERIVATIVES IN ASYMMETRIC SYNTHESIS: PREPARATION OF TWO NEW CHIRAL β-AMINO ALCOHOLS AND THEIR APPLICATION IN THE ENANTIOSELECTIVE CATALYTIC REDUCTION OF PROCHIRAL AROMATIC KETONES WITH BORANE

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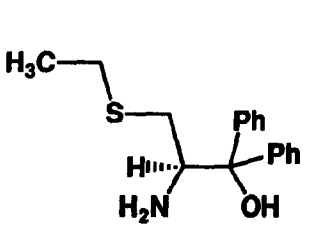
Summary : The optically active β-amino alcohols **1** and **2** derived from *S*-alkylated L-cysteine **3** and **4** respectively catalyze the enantioselective reduction of unsymmetrical ketones with borane. The resulting chiral secondary alcohols are obtained in high optical yields up to 100% under mild reaction conditions.

Amino acid-based optically active auxiliaries have often been applied successfully in stereoselective synthesis.[1] While chiral ligands prepared from proline have been well studied over the last decade, cysteine derivatives[2] have been relatively neglected.
The asymmetric reduction of prochiral ketones and imines[3] has recently achieved great interest in organic chemistry. One of the more successful methods has been based on the use of borane chirally modified by an optically active 1,2-amino alcohol (often derived from α-amino acids).



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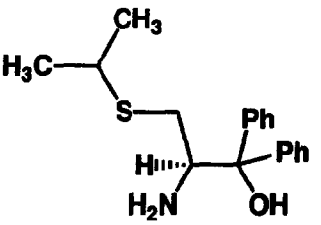

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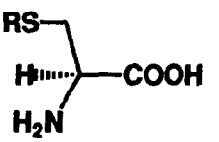
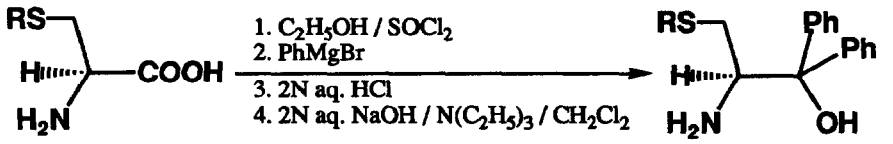


3 (R = Et)
4 (R = *i*-Prop)

Since the pioneering work of *Itsuno et al.*[4] many other groups[5] improved this efficient method.

In the course of our study on the synthesis and application of new chiral auxiliaries derived from proteinogenic and non proteinogenic amino acids[6], we prepared two new reduction catalyst precursors starting with the sulfur-containing amino acid L-cysteine.

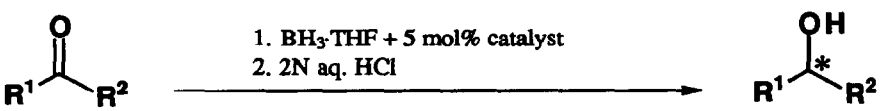


3 (R = Et)
4 (R = *i*-Prop)

1 (R = Et)
2 (R = *i*-Prop)

The new optically active ligands (*R*)-2-amino-1,1-diphenyl-3-(ethylmercapto)-1-propanol[7] **1** and (*R*)-2-amino-1,1-diphenyl-3-(isopropylmercapto)-1-propanol[8] **2** were synthesized starting from *S*-ethyl-L-cysteine[9] **3** and *S*-isopropyl-L-cysteine[10] **4** respectively in a threestep procedure. First, **3** and **4** were converted into the corresponding ethylester hydrochlorides with ethanol/thionylchloride. These ethyl carboxylates were added in small portions to the *Grignard* reagent prepared from phenylbromide (6 equiv. in dry ether, 0 °C, than 12h reflux). The crystalline tertiary β-amino alcohols **1** and **2** were obtained after usual extractive workup in 60-70% overall yield.

The homogenous catalytic reduction of aromatic ketones with the *in situ* formed oxazaborolidine catalysts from **1** and **2** has been investigated.



aromatic ketone

chiral secondary alcohol

In a typical procedure a mixture of the respective ketone in dry THF was slowly added within 45 min to a solution of the catalyst **1** or **2** (5 mol%) and borane-THF complex in dry THF at 30°C. After stirring for 3 hours at 30°C the reaction mixture was hydrolyzed with 2N HCl and extracted with diethyl ether. The combined organic layers were sucessively washed with 2N NaOH and water, dried ($MgSO_4$) and concentrated under reduced pressure. The obtained crude

product was distilled under *vacuo* (Kugelrohr) to afford the corresponding chiral secondary alcohol. The optical yields were determined by optical rotation analysis.

As can be seen from Table 1, the chiral catalysts **1** and **2** show a high ability to induce chirality in the target molecules. Especially ω-haloacetophenones were reduced to the corresponding carbinols in excellent *ee*'s up to 100% (entries 2, 3, 6 und 7). These 2-halo-1-phenylethanols could easily converted into optically active phenyloxirane in high optical purity. In comparison, the bulkiness of the sulfur-substituent in **1** (Et) respectively **2** (*i*-Prop) show no significant influence on the enantioselectivity of the reaction.

Table 1. Enantioselective reduction of aromatic ketones with **1** (5 mol%) and **2** (5 mol%) respectively and excess borane in THF.

			chiral secondary alcohol[a]	
entry	ketone	catalyst	*ee*[b] [%]	configuration
1	acetophenone	**1**	83	*R*
2	ω-chloroacetophenone	**1**	97	*S*
3	ω-bromoacetophenone	**1**	100	*S*
4	methyl-2-naphthylketone	**1**	88	*R*
5	acetophenone	**2**	70	*R*
6	ω-chloroacetophenone	**2**	100	*S*
7	ω-bromoacetophenone	**2**	100	*S*
8	methyl-2-naphthylketone	**2**	83	*R*

[a] The isolated yields of the chiral alcohols were 80–95%.– [b] The *ee*-values of chiral secondary alcohols obtained were calculated from specific rotations based on the following maximum rotations of each alcohol: $[\alpha]_D^{20} = +43.1$ ($c = 7.19$, cyclopentane) for (*R*)-1-phenylethanol[11], $[\alpha]_D^{20} = -48.1$ ($c = 1.73$, cyclohexane) for (*R*)-2-chloro-1-phenylethanol[12], $[\alpha]_D^{20} = -39.0$ ($c = 8$, $CHCl_3$) for (*R*)-2-bromo-1-phenylethanol[13], $[\alpha]_D^{20} = +55.8$ ($c = 4.8$, $CHCl_3$) for (*R*)-1-(naphth-2-yl)ethanol[14].

In summary, the *in situ* prepared chiral 1,3,2-oxazaborolidines from the L-cysteine derivatives **1** and **2** catalyze the enantoselective reduction of prochiral ketones and allow efficient aymmetric synthesis of secondary alcohol with high optical purity and predictable configuration.
Further studies on the preparation and application of new auxiliaries from natural sulfur-containing α-amino acids are in progress.

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References and Notes

1 (a) J. Martens, *Top. Curr. Chem.* **1984**, *125*, 165. (b) K. Drauz, A. Kleemann, J. Martens, *Angew. Chem.* **1982**, *94*, 590; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 584. (c) M. Coppola, H. F. Schuster, *Asymmetric Synthesis*, John Whiley & Sons Inc., **1987**.

2 (a) H. Brunner, R. Becker, G. Riepl, *Organomet.* **1984**, *3*, 1354. (b) K. Soai, T. Yamanoi, H. Oyamada, *Chem. Lett.* **1984**, 251. (c) J. H. Griffin, R. M. Kollegg, *J. Org. Chem.* **1985**, *50*, 3261.

3 M. Nakagawa, T. Kawate, T. Kakikawa, H. Yamada, T. Matsui, T. Hino, *Tetrahedron* **1993**, *49*, 1739.

4 (a) A. Hirao, S. Itsuno, S. Nakahama, N. Yamazaki, *J. Chem. Soc. Chem. Commun.* **1981**, 315. (b) S. Itsuno, A. Hirao, S. Nakahama, Y. Yamazaki, *J. Chem. Soc. Perkin I* **1983**, 1673. (c) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc. Perkin I* **1984**, 2887.

5 Reviews: (a) V. K. Singh, *Synthesis* **1992**, *7*, 605. (b) S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1992**, *3*, 1475. (c) L. Deloux, M. Screbnik, *Chem. Rev.* **1993**, *93*, 763.

6 (a) J. Martens, S. Lübben, R. Bhushan, *Tetrahedron Lett.* **1989**, *30*, 7181. (b) J. Martens, S. Lübben, *Arch. Pharm. (Weinheim)* **1991**, *324*, 59. (c) J. Martens, S. Lübben, *Liebigs Ann. Chem.* **1990**, 949. (d) J. Martens, S. Lübben, *Tetrahedron* **1991**, *47*, 1205. (e) S. Wallbaum; J. Martens; *Tetrahedron: Asymmetry* **1991**, *2*, 1093. (f) J. Martens; Ch. Dauelsberg; W. Behnen; S. Wallbaum; *Tetrahedron: Asymmetry* **1992**, *3*, 347. (g) K. Stingl; J. Martens; *Synth. Comm.* **1992**, *22*, 2745. (h) S. Wallbaum; J. Martens; *Tetrahedron: Asymmetry* **1993**, *4*, 637. (i) W. Behnen; T. Mehler; J. Martens; *Tetrahedron: Asymmetry* **1993**, *4*, 1413.

7 (*R*)-2-Amino-1,1-diphenyl-3-(ethylmercapto)-1-propanol **1**: mp.: 58-59°C; $[\alpha]_D^{20}$ = –166.3 (*c*=0.44, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm = 1.18 (t, 3H, C*H*$_3$CH$_2$S), 1.69 (s, 2H, N*H*$_2$), 2.45-2.59 (m, 4H, 2xH3, CH$_3$C*H*$_2$), 4.04 (dd, *J*=2.4 and 10.8, 1H, H2), 4.53 (s, 1H, O*H*), 7.15-7.64 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm = 14.66 (*C*H$_3$CH$_2$S), 25.81 (CH$_3$*C*H$_2$S), 33.41 (C3), 55.36 (C2), 78.32 (C1), 125.23-146.73 (Ar-C).

8 (*R*)-2-Amino-1,1-diphenyl-3-(isopropylmercapto)-1-propanol **2**: mp.: 112-114°C; $[\alpha]_D^{20}$ = –160.3 (*c*=0.40, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm = 1.14 and 1.20 [2d, 6H, (C*H*$_3$)$_2$CH], 1.63 (s, 2H, N*H*$_2$), 2.36 and 2.55 (2dd, *J*=2.3, 10.8 and 13.5 Hz, 2H, 2xH3), 2.82-2.91 [m, 1H, (CH$_3$)$_2$C*H*], 4.00 (m, 1H, H2), 4.48 (s, 1H, O*H*), 7.13-7.62 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm = 23.2 and 23.17 [(*C*H$_3$)$_2$CH], 29.31 [(CH$_3$)$_2$*C*H], 33.19 (C3), 56.92 (C2), 78.43 (C1), 125.25-144.15 (Ar-C).

9 M. D. Amstrong, J. D. Davis, *J. Org. Chem.* **1951**, *16* 749.

10 A. Stoll, E. Seebeck, *Helv. Chim. Acta* **1949**, *32*, 866.

11 A. S. Yamaguchi, H. S. Mosher, *J. Org. Chem.* **1973**, *38*, 1870.

12 L. C. J. van der Lean, J. B. N. Engberts, T. J. de Boer, *Tetrahedron* **1977**, *27*, 4323.

13 M. Imuta, K. Kawai, H. Ziffer, *J. Org. Chem.* **1980**, *30*, 4091.

14 T. A. Collyer, J. Kenyon, *J. Chem. Soc.* **1940**, 676.