Tetrahedron: Asymmetry Vol. 4, No. 9, pp. 1983-1986, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

ENANTIOSELECTIVE CATALYTIC BORANE REDUCTIONS OF ACHIRAL KETONES: SYNTHESIS AND APPLICATION OF NEW CHIRAL β-AMINO ALCOHOLS FROM L-METHIONINE

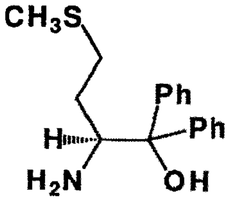
Thomas Mehler and Jürgen Martens*

Fachbereich Chemie der Universität Oldenburg
Ammerländer Heerstraße 114-118, D-26129 Oldenburg i.O.

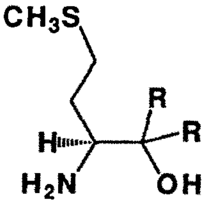
(*Received in UK* 23 *July* 1993)

Summary : The *in situ* formed chiral oxazaborolidine catalysts from optically active β-amino alcohols **1**-**3** from L-methionine ethyl carboxylate **4** have been used successfully in the enantioselective catalytic homogenous borane reductions of various aromatic ketones. The corresponding optically active alcohols are obtained in high optical purity (up to 100% *ee*).

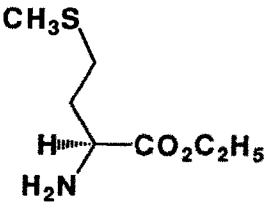
The developement of efficient asymmetric transformation reactions is still a stimulating subject in organic chemistry. Especially noteworthy is the stereoselective synthesis of optically active alcohols which play an important role as synthetic intermediates, e.g. in drug design. Besides the application of microbial processes[1] or heterogenous metal catalysts[2] the enantiocontrolled homogenous catalytic reduction using chirally modified hydride reagents[3] has been intensively investigated in recent years.



1



2 (R=p-C_6H_4-CH_3)
3 (R=p-C_6H_4-OCH_3)



4

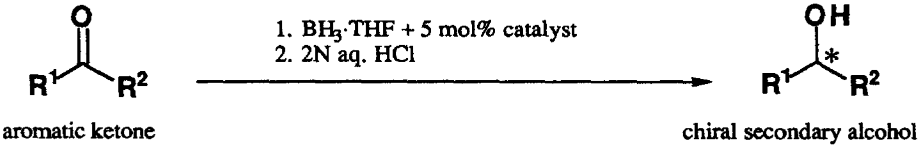
Itsuno et al. introduced the 1,3,2-oxazaborolidines as a new generation of reducing reagents[4] and later other groups improved this method[5].

In the course of our study on the preparation of new chiral auxiliaries prepared from proteinogenic and non proteinogenic amino acids[6] we wish to report herein the synthesis and application of new reduction catalyst precursors based on the sulfur-containing amino acid L-methionine.

L-Methionine as chiral source is a cheap commercially available starting material. The application of derivatives of the sulfur-containing α-amino acid L-methionine as enantioselective substoichiometric catalysts in stereoselective reactions is described in this paper for the first time.

The optically active ligand (*S*)-2-amino-1,1-diphenyl-4-(methylmercapto)-1-butanol[7] **1** was prepared from L-methionine according to the literature[4f] procedure. The synthesis of the new chiral ligands (*S*)-2-amino-1,1-di(4-methylphenyl)-4-(methylmercapto)-1-butanol[8] **2** and (*S*)-2-amino-1,1-di(4-methoxyphenyl)-4-(methylmercapto)-1-butanol[9] **3** was accomplished in the same manner starting from L-methionine ethyl carboxylate **4**. Thus, **4** was added in small portions to the respective *Grignard* reagent (in dry ether, 22 °C, than 12h reflux). The crystalline β-amino alcohols **1**, **2** and **3** were obtained after usual extractive workup in 50-60% overall yield.

The homogenous catalytic reduction of aromatic ketones with the *in situ* formed oxazaborolidine catalysts from **1**-**3** has been investigated. The effect of the reaction temperature was examined. The best enantioselectivities were realized when the reaction was carried out at 30°C.



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**-**3** (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. The chiral auxiliaries **1**-**3** could be recycled from the aqueous layer or the destillation residue and can be used in further enantioselective reductions as catalysts.

As can be seen from Table 1, the enantioselective reduction of ketones catalyzed by *in situ* prepared oxazaborolidines from **1-3** provides high enantiomeric excess (up to 100%) in the production of optically active alcohols of predictable absolute stereochemistry.

Table 1. Enantioselective reduction of aromatic ketones with (*S*)-**1-3** (5 mol%) and excess borane in THF.

			chiral secondary alcohol[a]	
entry	ketone	catalyst	*ee*[b] [%]	configuration
1	acetophenone	**1**	79	*R*
2	ω-chloroacetophenone	**1**	95	*S*
3	ω-bromoacetophenone	**1**	100	*S*
4	methyl-2-naphthylketone	**1**	77	*R*
5	acetophenone	**2**	78	*R*
6	ω-chloroacetophenone	**2**	100	*S*
7	ω-bromoacetophenone	**2**	100	*S*
8	methyl-2-naphthylketone	**2**	84	*R*
9	acetophenone	**3**	68	*R*
10	ω-chloroacetophenone	**3**	98	*S*
11	ω-bromoacetophenone	**3**	100	*S*
12	methyl-2-naphthylketone	**3**	85	*R*

[a] The isolated yields of the chiral alcohols were 80–95%.– [b] The *ee*-values of chiral secondary alcohols obtained were calculated from optical rotations based on the following maximum rotations of each alcohol: $[\alpha]_D^{20} = +43.1$ ($c = 7.19$, cyclopentane) for (*R*)-1-phenylethanol[10], $[\alpha]_D^{20} = -48.1$ ($c = 1.73$, cyclohexane) for (*R*)-2-chloro-1-phenylethanol[11], $[\alpha]_D^{20} = -39.0$ ($c = 8$, $CHCl_3$) for (*R*)-2-bromo-1-phenylethanol[12], $[\alpha]_D^{20} = +55.8$ ($c = 4.8$, $CHCl_3$) for (*R*)-1-(naphth-2-yl)ethanol[13].

Further investigation of other optically active oxazaborolidines prepared from sulfur-containing β-amino alcohols is in progress.

Acknowledgements : Thanks are due to Degussa AG and the Fonds der Chemischen Industrie for support.

References and Notes

1 (a) R. Csuk, B. I. Glänzer, *Chem. Rev.* **1991**, *91*, 49.

2 (a) S. L. Blystone, *Chem. Rev.* **1989**, *89*, 1664. (b) M. Bartok, *Stereochemistry of Heterogenous Metal Catalysts*, Wiley & Sons, Chichester, New York, Brisbane, Toronto, Singapore (1985) p. 390 and references cited therein. (c) A. Tungler, T. Tarnai, T. Máthé, J. Petró, *J. Mol. Catal.* **1991**, *67*, 277. (d) Blaser, H.-U., Tetrahedron: *Asymmetry* **1991**, *3*, 843.

3 (a) M. M. Midland, *Chem. Rev.* **1989**, *89*, 1553. (b) J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH Publishers: New York, 1991.

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. (d) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc. Chem. Commun.* **1983**, 469. (e) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J. Org. Chem.* **1983**, *49*, 555. (f) S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc. Perkin I* **1985**, 2039.

5 (a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Org. Chem.* **1988**, *53*, 2861. Reviews: (d) V. K. Singh, *Synthesis* **1992**, *7*, 605. (e) S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1992**, *3*, 1475. (f) L. Deloux, M. Screbnik, *Chem. Rev.* **1993**, *93*, 763.

6 (a) J. Martens, *Top. Curr. Chem.* **1984**, *125*, 165. (b) J. Martens, S. Lübben, R. Bhushan, *Tetrahedron Lett.* **1989**, *30*, 7181. (c) J. Martens, S. Lübben, *Arch. Pharm. (Weinheim)* **1991**, *324*, 59. (d) J. Martens, S. Lübben, *Liebigs Ann. Chem.* **1990**, 949. (e) J. Martens, S. Lübben, *Tetrahedron* **1991**, *47*, 1205. (f) S. Wallbaum; J. Martens; *Tetrahedron: Asymmetry* **1991**, *2*, 1093. (g) J. Martens; Ch. Dauelsberg; W. Behnen; S. Wallbaum; *Tetrahedron: Asymmetry* **1992**, *3*, 347. (h) K. Stingl; J. Martens; *Synth. Comm.* **1992**, *22*, 2745. (i) S. Wallbaum; J. Martens; *Tetrahedron: Asymmetry* **1993**, *4*, 637. (j) W. Behnen; T. Mehler; J. Martens; *Tetrahedron: Asymmetry* **1993**, *4*, 1413.

7 (*S*)-2-Amino-1,1-diphenyl-4-(methylmercapto)-1-butanol (*S*)-**1**: mp.: 95-97°C; $[\alpha]_D^{20}$ = −108.1 (*c*=0.90, CHCl$_3$) [ref.4f: mp.: 96-98°C; $[\alpha]_D^{20}$ = −108.57 (*c*=0.986, CHCl$_3$)].

8 (*S*)-2-Amino-1,1-di(4-methylphenyl)-4-(methylmercapto)-1-butanol (*S*)-**2**: mp.: 69-71°C; $[\alpha]_D^{20}$ = −83.5 (*c*=0.65, CHCl$_3$); ^{1}H-NMR (CDCl$_3$): δ in ppm = 1.41-1.53 (m, 1H, H4), 1.63-1.74 (m, 1H, H4), 1.95 (s, 3H, SC*H*$_3$), 2.25, 2.26 (2s, 6H, 2xPhC*H*$_3$), 2.39-2.59 (m, 2H, 2xH3), 3.98-4.02 (m, 1H, H2), 7.04-7.46 (m, 8H, Ar-H); ^{13}C-NMR (CDCl$_3$): δ in ppm = 15.15 (C3), 20.82 (2xPhCH$_3$), 29.49 (C4), 31.92 (*C*H$_3$S), 55.58 (C2), 79.12 (C1), 125.31-143.71 (Ar-C); MS (CI, *i*-Butane): 316 (MH$^+$, 100%), 298 (MH$^+$-H$_2$O, 34%).

9 (*S*)-2-Amino-1,1-di(4-methoxyphenyl)-4-(methylmercapto)-1-butanol (*S*)-**3**: mp.: 82-85°C; $[\alpha]_D^{20}$ = −95.5 (*c*=0.48, CHCl$_3$); ^{1}H-NMR (CDCl$_3$): δ in ppm = 1.40-1.52 (m, 2H, OH, H4), 1.64-1.75 (m, 1H, H4), 1.96 (s, 3H, SC*H*$_3$), 2.41-2.60 (m, 2H, 2xH3), 3.73, 3.74 (2s, 6H, 2xPhOC*H*$_3$), 3.93-3.97 (m, 1H, H2), 6.78-6.86 (m, 4H, Ar-H), 7.35-7.49 (m, 4H, Ar-H); ^{13}C-NMR (CDCl$_3$): δ in ppm = 15.02 (C3), 29.46 (C4), 31.77 (*C*H$_3$S), 54.94 (2xPhO*C*H$_3$), 55.55 (C2), 78.61 (C1), 113.19-138.68 (Ar-C); MS (CI, *i*-Butane): 348 (MH$^+$, 100%), 330 (MH$^+$-H$_2$O, 88%).

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

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

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

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