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ENANTIOSELECTIVE CATALYTIC REDUCTIONS OF KETONES: SYNTHESIS AND APPLICATION OF A NEW STRUCTURALLY RIGID BICYCLIC CATALYST

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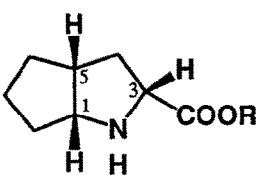
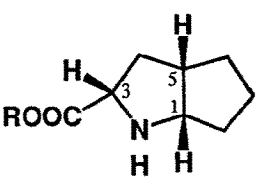
Abstract : The oxazaborolidine catalyst from (1*R*,3*R*,5*R*)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]-octane (1*R*,3*R*,5*R*)-**3** has been used in the enantioselective homogenous reductions of prochiral ketones with borane.

Amino acid-based chiral auxiliaries have attracted much attention over the last decade.[1] In particular structurally rigid pyrrolidine derivatives often lead to very high asymmetric inductions in organic syntheses.[2] Among various asymmetric reactions enantioselective reductions of prochiral ketones to optically active alcohols have achieved great interest. Beside the use of microbial processes[3] or heterogenous metal catalysts[4] the enantioselective homogenous catalytic reduction using chirally modified hydride reagents[5] is a challenging task. *Itsuno et al.* developed the oxazaborolidines as a new generation of reduction reagents.[6] Later other groups improved this new method.[7]



(1*R*,3*R*,5*R*)-**1** (R=H)
(1*R*,3*R*,5*R*)-**2** (R=CH_2Ph)



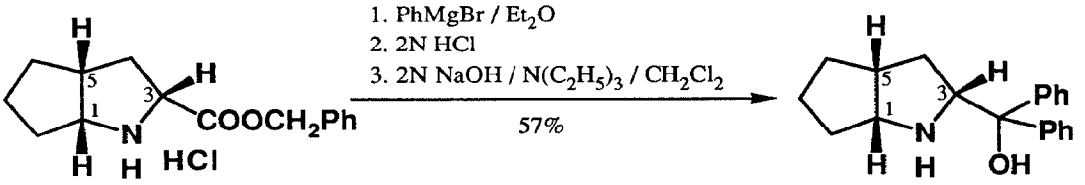
(1*S*,3*S*,5*S*)-**1** (R=H)
(1*S*,3*S*,5*S*)-**2** (R=CH_2Ph)

We envisioned that a bicyclic analogue of proline (1*R*,3*R*,5*R*)-2-azabicyclo[3.3.0]octane carboxylic acid (1*R*,3*R*,5*R*)-**1** and its enantiomer[8] would encompass the structural requirements necessary for efficient catalytic asymmetric reductions of prochiral ketones.
The nonproteinogenic amino acid (1*S*,3*S*,5*S*)-**1** has been used as an intermediate in the synthesis of the highly potent angiotensin converting enzyme (ACE) inhibitor Ramipril.[9] The industrial production of (1*S*,3*S*,5*S*)-**1**

is based on the optical resolution of the racemic benzyl ester derivatives (1*RS*,3*RS*,5*RS*)-**2** *via* diastereomeric salts with an enantiomerically pure chiral carboxylic acid. Thus, the unnatural amino acid **1** is advantageously accessible in both enantiomeric forms. The ester (1*R*,3*R*,5*R*)-**2**-HCl with (all-*R*)-configuration is recovered from waste streams of the resolution step in the industrial production of Ramipril.

Some new chiral auxiliaries based on (1*S*,3*S*,5*S*)-**1** and its enantiomeric form were synthesized in our laboratory.[10]

(1*R*,3*R*,5*R*)-3-(Diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane (1*R*,3*R*,5*R*)-**3** is obtained *via* an efficient simple two-step procedure from the ester (1*R*,3*R*,5*R*)-**2**-HCl.



(1*R*,3*R*,5*R*)-**2**-HCl (1*R*,3*R*,5*R*)-**3**

The synthesis of (1*R*,3*R*,5*R*)-**3** was accomplished starting from (1*R*,3*R*,5*R*)-**2**-HCl which was added in small portions to the Grignard reagent from phenylbromide (8 equiv. in ether, −15°C than 4 h reflux) to give after usual acidic work up and recrystallisation from methanol/ether colourless needles of (1*R*,3*R*,5*R*)-**3**-HCl[11] in 57% overall yield. The free base (1*R*,3*R*,5*R*)-**3**[12] was obtained quantitavely from the hydrochloride by treatment with 2N NaOH, triethylamine and extraction with dichloromethane as a colourless solid.

The homogenous reduction of aromatic ketones with the oxazaborolidine catalyst (1mol%) prepared from (1*R*,3*R*,5*R*)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane (1*R*,3*R*,5*R*)-**3** and borane·THF *in situ* has been investigated (Table 1).

In a typical procedure to a solution of the catalyst (1*R*,3*R*,5*R*)-**3** (0.3 mmol) and borane-THF complex (30.3 mmol) in dry THF was slowly added within 1 h a mixture of the respective ketone (30 mmol) in dry THF at 35° C. After stirring for two hours at 35° C the reaction mixture was hydrolyzed with 2N HCl and extracted with ether. The combined organic layers were sucessively washed with 2N NaOH and brine, dried and concentrated under reduced pressure. The obtained crude product was distilled through a *Vigreaux* column under vacuo to afford the respective optically active alcohol in 69-81% isolated yield. The optical yields were determined by optical rotation analysis. The β-amino alcohol (1*R*,3*R*,5*R*)-**3** could be recycled from the distillation residue and can be used in further enantioselective reductions as chiral catalyst.

As can be seen from Table 1, the optically active β-amino alcohol (1*R*,3*R*,5*R*)-**3** is indeed suitable for use as a precursor for a new oxazaborolidine catalyst for the enantioselective reduction of prochiral ketones with borane. The optical yields are in the order of 48-61%. In each case the (*S*)-enantiomer of the secondary alcohol was formed preferentially. This result follows the expected pattern as observed with other catalysts.[6,7]

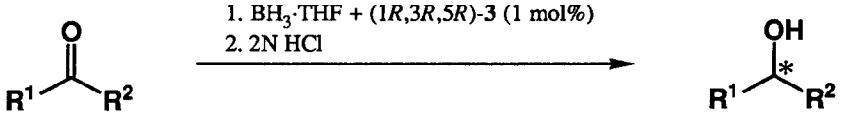


Table 1. Enantioselective reduction of aromatic ketones with (1*R*,3*R*,5*R*)-**3** (1 mol%) and BH_3·THF.

	Chiral alcohol obtained		
Ketone	Isolated yield[a] [%]	Optical yield[b][%]	Absolute configuration
Acetophenone	78	61	(*S*)
Propiophenone	81	59	(*S*)
α-Tetralone	69	48	(*S*)

[a] The chemical yield of the chiral alcohol was > 99% in each case (controled by TLC), isolated yield after distillation.

[b] Optical yield was calculated from optical rotation based on the following maximum rotations of each alcohol: $[\alpha]_D^{20} = -43.1$ ($c = 7.19$, cyclopentane) for (*S*)-1-phenylethanol[13], $[\alpha]_D^{\pi} = -45.45$ ($c = 5.15$, $CHCl_3$) for (*S*)-1-phenyl-1-propanol[14], $[\alpha]_D^{17} = +32.65$ ($c = 2.5$, $CHCl_3$) for (*S*)-1,2,3,4-tetrahydro-1-naphthol[15].

Further studies investigating the influence of *B*-substituents and a reagent prepared from the epimeric amino acid (1*R*,3*S*,5*R*)-**1** on the enantioselectivity of catalytic reductions will be forthcoming.

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References and Notes

1 J. Martens, *Top. Curr. Chem.* **1984**, *125*, 165.

2 (a) J. Martens, *Chem. Ztg.* **1986**, *110*, 169. (b) K. Drauz, A. Kleemann, J. Martens, *Angew. Chem.* **1982**, *94*, 590; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 584. (c) D. Enders, H. Eichenhauer, *Chem. Ber.* **1979**, *112*, 2933. (d) M. Asami, H. Ohno, S. Kobayashi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1869. (e) S. Terashima, S. Jew, K. Koga, *Chem. Lett.*, **1977**, 1109.

3 (a) R. Csuk, B. I. Glänzer, *Chem. Rev.* **1991**, *91*, 49. (b) K. Nakamura, Y. Kawai, T. Kitayama, T. Miyai, M. Ogawa, Y. Mikata, M. Higaki, A. Ohno, *Bull. Inst. Chem. Res., Kyoto Univ.* **1989**, *67*, 156. (c) T. Kitazume, N. Ishikawa, *Chem. Lett.* **1983**, 237. (d) C. Fuganti, P. Grasselli, S. Servi, *J. Chem. Soc. Perkin Trans. I* **1983**, 241. (e) R. F. Newton, J. Paton, D. P. Reynolds, S. Young, *J. Chem. Soc.* **1979**, 908. (f) M. Bucciarelli, A. Farni, I. Moretti, G. Tarre, *J. Chem. Soc. Chem. Commun.* **1978**, 456.

4 (a) A. Tungler, T. Tarnai, T. Máthé, J. Petró, *J. Mol. Catal.* **1991**, *67*, 277. (b) S. L. Blystone, *Chem. Rev.* **1989**, *89*, 1664. (c) M. Bartok, *Stereochemistry of heterogenous metal catalysts*, Wiley & Sons, Chichester, New York, Brisbane, Toronto, Singapore (1985) p. 390 and references cited therein.

5 Lithiumaluminiumhydride reagents : (a) E. R. Grandbois, S. I. Howard, J. D. Morrison, *Asymmetric Synthesis, Vol. 2*, Academic Press, New York (1983) p. 71. (b) T. Mukaiyama, M. Asami, *Top. Curr. Chem. 127*, 133. Borohydride reagents : (c) M. M. Midland, *Chem. Rev.* **1989**, *89*, 1553. (d) H. C. Brown, W. S. Park, B. T. Cho, P. V. Ramachandran, *J. Org. Chem.* **1987**, *52*, 5406. (e) M. M. Midland, *Asymmetric Synthesis, Vol. 2*, Academic Press, New York (1983), p. 45. (f) H. C. Brown, P. K. Jadhav, A. K. Mandal, *Tetrahedron* **1981**, *37*, 3547. Tinhydride reagents : (g) T. Oriyama, T. Mukaiyama, *Chem. Lett.*, **1984**, 2071. (h) M. Falorni, L. Lardicci, A. M. Piroddi, G. Giacomelli, *Gazz. Chim. Ital.* **1989**, *119*, 511. (i) M. Falorni, L. Lardicci, *Tetrahedron Lett.* **1989**, *30*, 3551.

6 (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 Trans. 1* **1983**, 1673. (c) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc. Perkin Trans. 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.

7 (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.

8 (a) V. Teetz, R. Geiger, H. Gaul, *Tetrahedron Lett.* **1984**, *25*, 4479.

9 (a) H. Metzger, R. Maier, C. Sitter, H. O. Stern, *Arzneim.-Forsch./Drug Res.* **1984**, *34 (II)*, 1402. (b) H. H. Donaubauer, D. Mayer, *Arzneim.-Forsch./Drug Res.* **1988**, *38 (I)*, 14. (c) R. Henning, U. Lerch, H. Urbach, *Synthesis* **1989**, 265. (d) H. Urbach, R. Henning, *Heterocycles* **1989**, *28*, 957.

10 (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.

11 (1*R*,3*R*,5*R*)-3-(Diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane hydrochloride (1*R*,3*R*,5*R*)-**3**-HCl $[\alpha]_D^{20}$ = +47.6 (*c*=0.70, methanol); m.p. 261°C (dec.); ^{1}H-NMR (MeOD): ∂ in ppm =1.52-1.86(m, 7H, H4, H5, 2xH6, 2xH7, 2xH8), 2.04 (m, 1H, H4), 2.22 (m, 1H, H4),2.96 (m, 1H, H1), 4.09 (m, 1H, H3), 7.21-7.39 (m, 6H, Ar-H), 7.53-7.56 (m, 2H, Ar-H), 7.64-7.67 (m, 2H, Ar-H).

12 (1*R*,3*R*,5*R*)-3-(Diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane (1*R*,3*R*,5*R*)-**3** : $[\alpha]_D^{20}$ = +107.1 (*c*= 0.94, dichloromethane); m.p. 104°C; ^{1}H-NMR ($CDCl_3$): ∂ in ppm =1.28-1.78 (m, 8H, H4, H5, 2xH6, 2xH7, 2xH8), 2.53 (m, 1H, H4), 3.72 (m, 1H, H1),4.17 (dd, J=5.8 and 10.2 Hz, 1H, H3), 7.11-7.31 (m, 6H, Ar-H), 7.42 (m, 2H, Ar-H), 7.60 (m, 2H, Ar-H).

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

14 R. H. Pickard, J. Kenyon, *J. Chem. Soc.* **1914**, *105*, 1115.

15 A. G. Davies, A. M. White, *J. Chem. Soc.* **1952**, 3300.