Pergamon

Tetrahedron Letters 40 (1999) 5379–5382

TETRAHEDRON LETTERS

Enantiomerically Pure 2-Piperazinemethanols as Novel Chiral Ligands of Oxazaborolidine Catalysts in Enantioselective Borane Reductions

Tsutomu Inoue,[a] Daisuke Sato,[a] Kenichi Komura,[b] and Shinichi Itsuno[b]*

[a]*Research & Planning Laboratory, Odawara Research Center, Nippon Soda Co., Ltd., 345 Takada, Odawara, Kanagawa 250-0280, Japan*

[b]*Department of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi 441-8580, Japan*

Received 21 April 1999; revised 20 May 1999; accepted 21 May 1999

Abstract: Novel enantiomerically pure 2-piperazinemethanols (**3-5**) were synthesized from 2-piperazinecarboxylic acid **1**. The asymmetric reduction of aromatic ketones, ketimine and oxime ether has been performed with reagents prepared from 2-piprazinemethanol and borane to yield enantiomerically enriched alcohols and amines, respectively. The preferred absolute configuration of the product was dependent on the structure of the sulfonyl substituent in the chiral ligand.

Keywords: asymmetric reduction; piperazinemethanol; ketones; oxime ethers

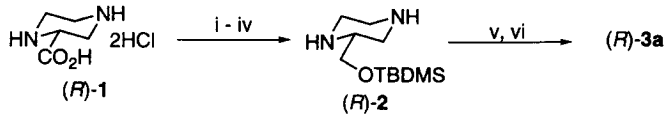
Asymmetric reduction of C=O and C=N double bonds is an important route for obtaining enantioenriched alcohols and amines. Although various methodologies have been developed for the asymmetric reduction, one most important and useful reducing system is the oxazaborolidine catalyzed borane reduction.[1] A number of chiral oxazaborolidine catalysts have been prepared from various kinds of enantiopure amino alcohols and utilized in the borane reduction of ketones.[1] Since we have developed the synthesis of both enantiomers of 2-piperazinecarboxylic acid **1**,[2] several novel enantiopure amino alcohols (**3-5**) were prepared from **1**, which could be used as a chiral ligand in the oxazaborolidine catalyst. In enantioselective reactions, it is always desired to obtain both enantiomers of the product from the same reaction. Easy availability of both enantiomers of the chiral ligands makes it possible to lead to both enantiomers. More interestingly, we have found that the structure of the sulfonyl substituent at N-4 in 2-piperazinemethanol influenced the sense of the enantioface selection. Only a slight modification of the sulfonyl group caused a dramatic effect on the face selection. This paper reports the preparation of novel enantiopure piperazinemethanols and their use in oxazaborolidine-catalyzed borane reduction of prochiral

* Corresponding author. E-mail: itsuno@tutms.tut.ac.jp

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01031-X

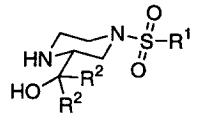
ketones and oxime ether.

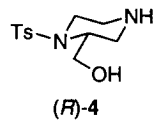
We have synthesized enantiopure 2-piperazinemethanols (**3**) having various 4-sulfonyl substituents by a route that permits selective introduction of the 4-sulfonyl group as shown in Scheme 1. Both enantiomers of **3** could be obtained from each enantiomer of 2-piperazinecarboxylic acid **1**[2] that is readily available by optical resolution of its *tert*-butylamide. From *O*-protected 2-piperazinemethanol **2**, γ-amino alcohol **4** and bis(piperazinemethanol) **5** were also prepared in good yield.



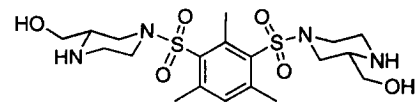
Reagents and conditions: i, BnCl, TEA, 78%; ii, $LiAlH_4$, THF, 82%; iii, TBDMSCl, 93%; iv, H_2/Pd-C, 100%; v, TsCl, TEA, $CHCl_3$, 71%; vi, TBAF, THF, 68%

Scheme 1



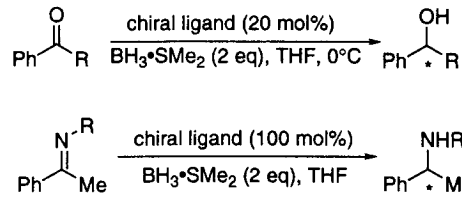


(*R*)-**4**



(*S*, *S*)-**5**

3a: R^1 = Tolyl, R^2 = H
3b: R^1 = Tolyl, R^2 = Ph
3c: R^1 = 2,4,6-Triisopropylphenyl (=tripyl), R^2 = H
3d: R^1 = 1-Naphthyl, R^2 = H
3e: R^1 = 2-Naphthyl, R^2 = H
3f: R^1 = Me, R^2 = H
3g: R^1 = Octyl, R^2 = H



Scheme 2

In the first place, we applied 2-piperazinemethanol **3** to the enantioselective borane reduction of acetophenone (Scheme 2). The borane reduction proceeded smoothly in the presence of 20 mol% of chiral ligand (*R*)-**3a** to afford (*S*)-1-phenylethanol in high yield with 68% ee (Table 1, run 1).[3] The same reaction using (*S*)-**3a** led to (*R*)-alcohol with the same degree of enantioselectivity as expected (run 3). Higher enantioselectivity (81% ee) was attained when α-chloroacetophenone was reduced in this system (run 4). Interestingly, the use of relatively bulky sulfonamides such as tripyl (**3c**), naphthyl (**3d**, **3e**) or octyl (**3g**) derivatives showed the opposite face selection in the reduction of acetophenone (run 6-8, 10). In these cases (*S*)-alcohol was obtained from (*S*)-piperazinemethanol. In particular, the use of 1-naphthyl derivative ((*S*)-**3d**) resulted in completely opposite selectivity to that from (*S*)-**3a** (run 3, 7). Stable conformation of the bicyclo[4.3.0]nonane structure of the oxazaborolidines derived from **3** would be critically dependent on the structure of the sulfonamide substituent, which may determine the course of the stereoselection.[4] It is obvious that γ-amino alcohol **4** is not an effective chiral ligand in the borane reduction (run 11). Bis(piperazinemethanol) (*S*, *S*)-**5** is considered to possess a bulky sulfonamide group, which led to (*S*)-alcohol with 71% ee.

Table 1. Enantioselective reduction of aromatic ketones and imines

Run	Ketone or imine	Chiral ligand	Reaction time / h	Reaction temp. ℃	Yield / %	% ee	*Config.*
1[a]	PhCOMe	(*R*)-**3a**	18	0	97	68	*S*
2[b]	PhCOMe	(*R*)-**3a**	2	0	60	54	*S*
3[a]	PhCOMe	(*S*)-**3a**	18	0	97	68	*R*
4[a]	$PhCOCH_2Cl$	(*S*)-**3a**	4	0	100	81	*S*
5[c]	PhCOMe	(*R*)-**3b**	5 min	0	100	15	*S*
6[a]	PhCOMe	(*S*)-**3c**	18	0	100	31	*S*
7[a]	PhCOMe	(*S*)-**3d**	4	0	100	67	*S*
8[a]	PhCOMe	(*S*)-**3e**	4	0	76	23	*S*
9[a]	PhCOMe	(*S*)-**3f**	18	0	100	59	*R*
10[a]	PhCOMe	(*S*)-**3g**	18	0	96	46	*S*
11[a]	PhCOMe	(*S*)-**4**	18	0	100	9	*S*
12[d]	PhCOMe	(*S,S*)-**5**	4	0	100	71	*S*
13[e]	PhC(=NBn)Me	(*S*)-**3a**	0.5	rt	39	4	*S*
14[c]	PhC(=NOMe)Me	(*S*)-**3a**	6	50	61	84	*S*
15[c]	PhC(=NOMe)Me	(*S*)-**3d**	3	50	31	84	*R*

[a]Chiral ligand : BH_3•SMe_2 : Ketone = 0.20 : 2.0 : 1.0 (mmol), THF. [b]BH_3•THF (0.6 eq) was used. [c]BH_3•THF (1.0 eq) was used. [d]Chiral ligand : BH_3•SMe_2 : Ketone = 0.10 : 2.0 : 1.0 (mmol), [e]Chiral ligand : BH_3•SMe_2 : C=N = 1.0 : 2.0 : 1.0 (mmol), THF. [f]BH_3•THF (2.0 eq) was used.

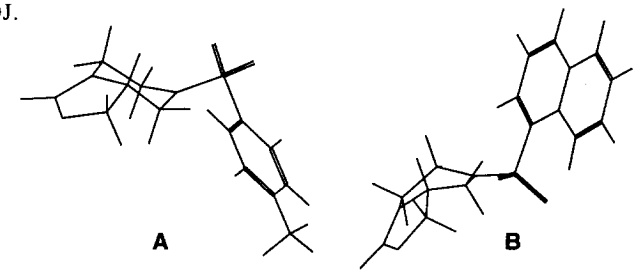
The stereoselective synthesis of optically active amines remains a topic of considerable interest, since these compounds are useful starting materials for biologically active compounds.[5] Enantioselective reduction of C=N compounds is a convenient method to obtain such amines.[6] Since the oxazaborolidine-catalyzed borane reduction could be applied to ketimines[7] and oxime ethers[8] to give enantioenriched amines, we next extended our investigation to the reduction of ketimine derivatives. Borane reduction of *N*-benzyl imine afforded the racemic secondary amine (run 13). On the contrary, acetophenone *O*-methyloxime was reduced smoothly to give the corresponding primary amine with high enantioselectivity (run 14,15).[9] In this case, again choice of the chiral ligand determined the preferred configuration of the amine produced. The completely opposite face of the C=N double bond of the oxime ether was selectively attacked by the choice of the chiral ligand. To our knowledge, this is the first example that both enantiomers of primary amines were obtained by a slight modification of the substituent in the chiral ligand of the catalyst.

In summary, 4-sulfonyl substituted 2-piperazinemethanols (**3**, **5**) were easily prepared from enantiomerically pure **1**. They are excellent chiral ligands in the enantioselective borane reduction of ketones and oxime ethers. The sulfonyl substituents of chiral ligands affected markedly the sense of enantioface selection in these reductions. Although the precise reaction mechanism of how different face selection occurs is not clear, the present method

provides the preparation of both enantiomers of enantioenriched alcohols and amines by oxazaborolidine-catalyzed borane reduction.

References and notes

1. S. Itsuno, *Organic Reactions*, John Wiley & Sons., **1998**, *52*, Chapter 2, 395. S. Itsuno, *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz and H. Yamamoto, eds., Chapter 6, Springer, in press. E. J. Corey and C. J. Helal, *Angew. Chem. Int. Ed.*, **1998**, *37*, 1986.
2. Both enantiomers and racemate of **1** are available from Nippon Soda Co. Ltd. (Fax: +81-3-3245-6059)
3. A typical experimental procedure for the enantioselective reduction of acetophenone: To a solution of amino alcohol **3** (0.74 mmol) in THF (4 ml) was added a THF solution of borane dimethylsulfide (7.32 mmol) at 0 °C, and the mixture was refluxed for 1 h to complete the formation of the chiral oxazaborolidine. Then THF (1 ml) solution of acetophenone (3.66 mmol) was added dropwise to the above solution at 0 °C. The reaction mixture was stirred for 18 h at 0 °C and quenched with 3M HCl aqueous solution. After usual workup, the crude product was chromatographed on silica gel to afford 1-phenylethanol. Enantioselectivity was determined by HPLC analysis using CHIRALCEL OJ.
4. Stable conformations (**A**, **B**) of the oxazaborolidines derived from (*R*)-**3a** and (*R*)-**3d** were estimated by MOPAC-AM1 calculation. The toluene (**A**) and naphthalene (**B**) moieties seem to shield the opposite approach of the substrate effectively.



5. D. Enders and U. Reinhold, *Tetrahedron: Asymmetry*, **1997**, *8*, 1895. S. E. Denmark and O. J. -C. Nicaise, *Chem. Commun.*, **1996**, 999.
6. S. R. Landor, Y. M. Chan, O. O. Sonola and A. R. Tatchell, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 493. S. Itsuno, Y. Sakurai, K. Shimizu and K. Ito, *J. Chem. Soc., Perkin 1*, **1990**, 1859. J. T. Dougherty, J. R. Flisak, J. Hayes, I. Lantos, L. Liu and L. Tucker, *Tetrahedron: Asymmetry*, **1997**, *8*, 497. C. Bolm and M. Felder, *Synlett*, **1994**, 655. M. Masui and T. Shioiri, *Tetrahedron Lett.*, **1998**, *39*, 5195.
7. B. T. Cho and Y. S. Chun, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 3200.
8. S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao and S. Nakahama, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2039. S. Itsuno, Y. Sakurai, K. Ito, A. Hirao and S. Nakahama, *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 395.
9. A typical experimental procedure for the enantioselective reduction of acetophenone *O*-methyloxime: To a solution of amino alcohol **3** (1.36 mmol) in THF (7 ml) was added a THF solution of borane dimethylsulfide (2.72 mmol) at 0 °C, and the mixture was refluxed for 10 min to complete the formation of the chiral oxazaborolidine. Then THF (1 ml) solution of acetophenone *O*-methyloxime (1.36 mmol) was added dropwise to the above solution. The reaction mixture was stirred for 6 h at 50 °C and quenched with 3M HCl aqueous solution. After usual workup, the crude product was chromatographed on silica gel to afford 1-phenylethylamine. Enantioselectivity was determined for its *N*-ethoxycarbonyl derivative by HPLC analysis using CHIRALCEL OJ.