Pergamon

Tetrahedron Letters 39 (1998) 5195–5198

TETRAHEDRON LETTERS

Stereoselective Synthesis of 1,2-Amino Alcohols by Asymmetric Borane Reduction of α-Oxoketoxime Ethers

Moriyasu Masui [a*] and Takayuki Shioiri [b]

[a] Aburahi Laboratories, Shionogi & Co., Ltd., Koka-cho, Koka-gun, Shiga 520-3423, Japan

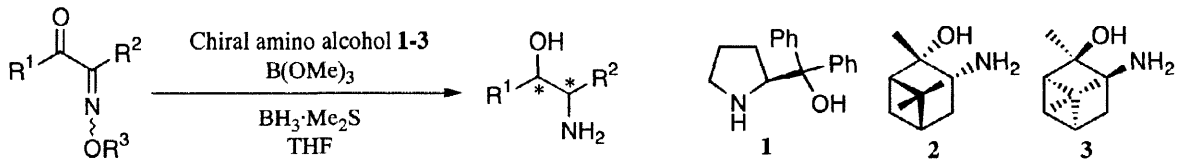
[b] Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

Received 3 March 1998; revised 11 May 1998; accepted 13 May 1998

Abstract: Asymmetric reduction of α-oxoketoxime ethers with the reagents prepared *in situ* from trimethyl borate and chiral amino alcohols derived from either L-proline or α-pinene was investigated. Both cyclic and acyclic α-oxoketoxime ethers were reduced to afford the corresponding chiral 1,2-amino alcohols with high enantioselectivities.

Keywords: Asymmetric reactions; Ketones; Oximes; Reduction

Chiral 1,2-amino alcohols are found in many biologically active compounds as important structural units. In addition they have been widely used in asymmetric reactions as chiral auxiliaries[1] and chiral sources.[2,3] Thus, the development of practical synthetic routes for the preparation of chiral 1,2-amino alcohols is of great importance. We have previously reported a practical and efficient method for the asymmetric borane reduction of prochiral ketones using reagents prepared *in situ* from trimethyl borate and chiral amino alcohols **1-3**.[4] The new method yielded successful results especially for the reduction of nitrogen containing prochiral ketones such as acetylpyridines. Therefore, it should be applicable to the asymmetric borane reduction of α-oxoketoxime ethers which have been used as precursors of 1,2-amino alcohols.[5,6] We describe here a stereoselective reduction of α-oxoketoxime ethers using our new method for the asymmetric borane reduction.



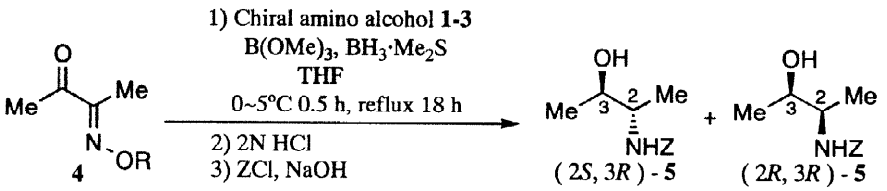
Scheme 1

We initially investigated the asymmetric reduction of 2,3-butadione monoxime ethers **4**.[7] The reaction was performed with the catalysts generated *in situ* from 0.12 equivalent (eq) of trimethyl borate and 0.1 eq of chiral amino alcohols **1-3** by using 4 eq of borane-dimethyl sulfide complex as a reducing agent in dry THF.[8] The resulting 3-amino-2-butanol was isolated as carbamate **5** by treatment with benzyloxycarbonyl chloride in alkaline solution,[9] and then it was analyzed by chiral HPLC to determine the *anti/syn* ratio along with the respective enantiomeric excess. The absolute configuration of the product was assigned by comparison of its specific rotation with the literature value.[10] The results are summarized in Table 1.

The reduction of methyl, benzyl, *tert*-butyldimethylsilyl, and *tert*-butyldiphenylsilyl ethers of 2,3-butadione monoxime **4a-d** with amino alcohol **1** gave the desired compound **5** in good yields, though the enantioselectivities were unsatisfactory (Runs 1-4). On the other hand, the reduction of triphenylmethyl (trityl) ether **4e** proceeded with excellent enantioselectivity to afford *anti*-(2*S*, 3*R*)-**5** and *syn*-(2*R*, 3*R*)-**5** at the ratio of 86:14 with 99 and 97 % ee, respectively (Run 5).

0040-4039/98/$19.00
PII: S0040-4039(98)01019-3

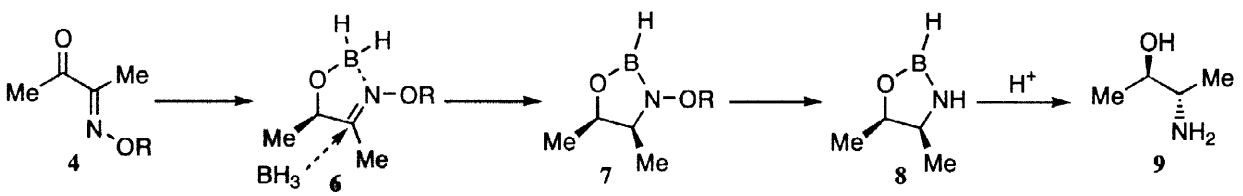
Table 1 Asymmetric Borane Reduction of 2,3-Butadione Monoxime Ethers



Run	Starting material	Amino alcohol	Yield (%)	*anti* : *syn* [a]	% ee [a] (Config.)	
					anti	*syn*
1	**4a** (R = Me)	**1**	89	72 : 28	65 (2*S*, 3*R*)	36 (2*R*, 3*R*)
2	**4b** (R = Bzl)	**1**	89	72 : 28	68 (2*S*, 3*R*)	37 (2*R*, 3*R*)
3	**4c** (R = TBDMS)	**1**	87	74 : 26	75 (2*S*, 3*R*)	50 (2*R*, 3*R*)
4	**4d** (R = TBDPS)	**1**	87	74 : 26	68 (2*S*, 3*R*)	54 (2*R*, 3*R*)
5	**4e** (R = Tr)	**1**	92	86 : 14	99 (2*S*, 3*R*)	97 (2*R*, 3*R*)
6	**4e** (R = Tr)	**2**	92	83 : 17	98 (2*R*, 3*S*)	99 (2*S*, 3*S*)
7	**4e** (R = Tr)	**3**	90	82 : 18	98 (2*S*, 3*R*)	99 (2*R*, 3*R*)

a) Determined by HPLC analysis using a Chiralcel OJ chiral column.

The difference in enantioselectivity due to the substituent of oxime ether can be rationalized as follows. The reduction of **4** would proceed according to the pathway illustrated in Scheme 2. If oxazaboloridine **8**, which should catalyze the reduction of **4** with low enantioselectivity,[11] forms before completion of the conversion from **4** to **6**, a moderate enantiomeric excess of the product results. Introducing bulky trityl group as the oxime substituent would lead to the desirable stepwise reduction where the carbonyl group is reduced at 0~5 °C and the oxime group is reduced at a higher temperature, with avoidance of the reduction catalyzed by **8**.

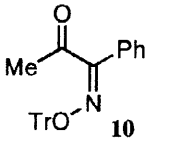
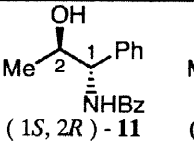
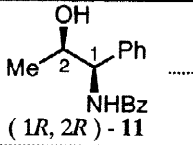
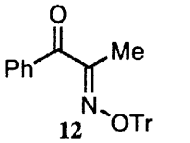
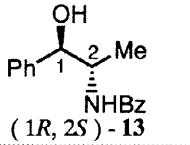
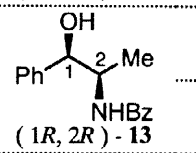
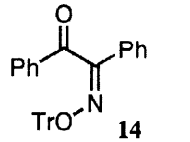
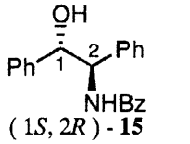
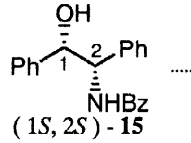
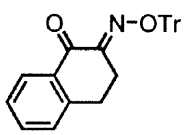
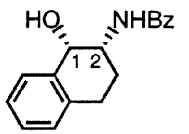
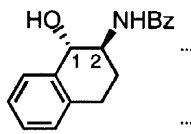
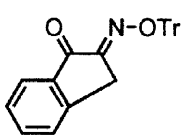
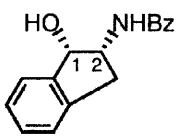
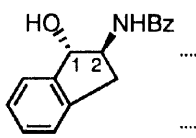


Scheme 2

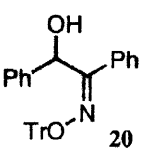
Amino alcohols **2** and **3**, derived from α-pinene,[12] were also effective for the reduction of **4e**. Both enantiomers of **5** were available from these reactions (Runs 6 and 7). Similarly to previous results for the reduction of prochiral ketones, the predominant enantiomer obtained with amino alcohol **2** was opposite that obtained with **1**.[4] In all the cases examined for the reduction of **4e**, the *anti* isomer was predominant over the *syn* isomer although there was little difference in the ratio. These data suggest that the attack by borane on the oxime group occurs from the less hindered side in the chelating intermediate **6** with little influence from the chiral catalyst.

We then extended our investigation to the reduction of other α-oxoketoxime trityl ethers. The starting materials could be readily prepared by the reaction of α-diketone and hydroxylamine hydrochloride[13] or by α-nitrosation of ketone,[14] followed by *O*-tritylation.[7e] The borane reduction was conducted according to the procedure for the reduction of 2,3-butadione momoxime ethers **4**, except for the reaction time. The resulting amino alcohols were isolated as their *N*-benzoyl derivatives by treatment with benzoyl chloride.[15] The absolute configurations of the products were assigned by comparison of the retention time on HPLC with authentic samples derived from known chiral amino alcohols.[16]

Table 2 Asymmetric Borane Reduction of α-Ketoxime Trityl Ethers

Starting material	Products *anti* (*cis*)	Products *syn* (*trans*)	Amino alcohol	Time[a] (h)	Yield (%)	*anti* : *syn*[b] (*cis* : *trans*)	% ee[b] (Config.) *anti* (*cis*)	% ee[b] (Config.) *syn* (*trans*)
 **10**	 (1*S*, 2*R*) - **11**	 (1*R*, 2*R*) - **11**	**1**	1 40	82	68 : 32	90 (1*S*, 2*R*)	94 (1*R*, 2*R*)
			2	1 40	90	66 : 34	98 (1*R*, 2*S*)	93 (1*S*, 2*S*)
 **12**	 (1*R*, 2*S*) - **13**	 (1*R*, 2*R*) - **13**	**1**	3 18	94	88 : 12	46 (1*R*, 2*S*)	7 (1*R*, 2*R*)
			2	2 18	93	95 : 5	91 (1*S*, 2*R*)	54 (1*S*, 2*S*)
 **14**	 (1*S*, 2*R*) - **15**	 (1*S*, 2*S*) - **15**	**1**	3 65	35[d]	79 : 21	90 (1*S*, 2*R*)	75 (1S, 2S)
			2	6[c] 65	31[e]	70 : 30	31 (1*R*, 2*S*)	35 (1*R*, 2*R*)
 **16**	 (1*S*, 2*R*) - **17**	 (1*S*, 2*S*) - **17**	**1**	2 18	92	90 : 10	90 (1*S*, 2*R*)	92 (1*S*, 2*S*)
			2	1 20	91	89 : 11	69 (1*S*, 2*R*)	58 (1*S*, 2*S*)
			3	1 20	94	89 : 11	69 (1*R*, 2*S*)	64 (1*R*, 2*R*)
 **18**	 (1*S*, 2*R*) - **19**	 (1*S*, 2*S*) - **19**	**1**	3 40	84	74 : 26	85 (1*S*, 2*R*)	75 (1*S*, 2*S*)
			2	1 40	79	75 : 25	85 (1*S*, 2*R*)	81 (1*S*, 2*S*)
			3	1 40	82	80 : 20	85 (1*R*, 2*S*)	83 (1*R*, 2*R*)

a) Reaction time at 0~5°C, upper value; reaction time for heating under reflux, lower value. b) Initial reaction was conducted at room temperature. c) Determined by HPLC analysis using a Chiralcel OJ-R chiral column except for the analysis of compound **17**, where a Chiralcel OJ chiral column was used. d) Compound (*R*)-**20** was obtained in 60 % yield with 85 % ee. e) Compound (*S*)-**20** was obtained in 61 % yield with 34 % ee.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Highly enantioselective reductions were achieved for every α-oxoketoxime ether by adopting the optimal chiral amino alcohol of **1-3**. For the reduction of compounds **10** and **12**, amino alcohol **2** gave a higher enantiomeric excess than **1**. The opposite tendency was observed for the reduction of **14** and **16**. Substrates **12** and **16** were reduced with high diastereoselectivities by means of chelating intermediates such as **6**. On the other hand, the reduction of **10** and **14** required much longer reaction times to reduce the oxime group and gave moderate diastereoselectivities. These results may be due to the (*Z*)-geometry of the oxime group in **10** and **14** which prevents the formation of chelating intermediate.

For the reduction of cyclic substrates **16** and **18** with amino alcohols **1** and **2**, the same enantiomers were predominantly formed. The reason for these unexpected results, which conflicted with those observed in the reduction of acyclic substrates and prochiral ketones, is not yet fully understood.

In summary, we have developed an efficient method for the preparation of chiral 1,2-amino alcohols. Even with catalytic amounts of chiral sources, both cyclic and acyclic α-oxoketoxime trityl ethers were reduced by our asymmetric borane reduction in high enantioselectivity. This practical method should be applicable to the stereoselective synthesis of biologically active compounds.

References and Notes

1. For a recent review, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
2. For recent reviews of asymmetric borane reductions, see: (a) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497. (b) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763. (c) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475. (d) Singh, V. K. *Synthesis* **1992**, 605.
3. For a recent review of metal-mediated reactions, see: Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935.
4. Masui, M.; Shioiri, T. *Synlett* **1997**, 273.
5. Tillyer, R. D.; Boudreau, C.; Tschaen, D.; Dolling, U.-H.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 4337.
6. Shimizu, M.; Tsukamoto, K.; Fujisawa, T. *Tetrahedron Lett.* **1997**, *38*, 5193.
7. The starting materials were prepared from 2,3-butadione monoxime by the reaction with the following reagents: (a) methyl iodide and K_2CO_3 in acetone, (b) benzyl chloride and K_2CO_3 in acetone, (c) *tert*-butyldimethylchlorosilane and imidazole in DMF, (d) *tert*-butyldiphenylchlorosilane and imidazole in DMF, or (e) trityl chloride and triethylamine in dichloromethane.
8. **Procedure for reduction of α-oxoketoxime ethers:** A solution of a chiral amino alcohol (0.5 mmol) and trimethyl borate (0.6 mmol) in dry THF (5 ml) was stirred for 1 h at room temperature under N_2 atmosphere and then borane-dimethyl sulfide complex (20 mmol) was added. To the mixture was added dropwise a solution of an α-oxoketoxime ether (5 mmol) in dry THF (5-20 ml) via a syringe pump over 1 h at 0~5°C. After being stirred at the same temperature until the starting material disappeared on TLC, the solution was allowed to warm to room temperature and heated under reflux for 18-65 h. The mixture was cooled to room temperature and cautiously poured into 2N HCl (30 mmol). After being stirred for 5 h at room temperature, the solution was made basic with NaOH (60 mmol). The resulting mixture was used for the next isolation step.[9,14]
9. The solution obtained in the procedure described in note 8 using butadione monoxime ether **4** as a starting material was evaporated under reduced pressure. The aqueous residue was washed with diethyl ether and then benzyloxycarbonyl chloride (20 mmol) was added. The mixture was stirred for 20 h at room temperature and then extracted with dichloromethane. The extract was dried over $MgSO_4$ and evaporated. The crude material was purified by column chromatography to gave the desired product as a mixture of diastereomers.
10. Takahashi, Y.; Nakayama, M.; Watanabe, I.; Deushi, T.; Ishiwata, H.; Shiratsuchi, M.; Otani, G. *J. Antibiotics* **1989**, *42*, 1541.
11. The borane reduction of acetophenone using the catalyst generated *in situ* from 0.1 eq of (2*R*, 3*R*)-3-amino-2-butanol (**9**) and borane-dimethyl sulfide complex afforded (*R*)-2-phenylethanol in only 64 % ee.
12. Masui, M.; Shioiri, T. *Tetrahedron* **1995**, *51*, 8363.
13. Cherry, P. C.; Cottrell, W. R. T.; Meakins, G. D.; Richards, E. E. *J. Chem. Soc. (C)* **1968**, 459.
14. Touster, O. *Organic Reactions* **1966**, *7*, 327.
15. To the resulting mixture obtained in the procedure described in note 8 was added benzoyl chloride (10 mmol), and the mixture was stirred for 0.5 h at room temperature. After the addition of methanol (15 ml), the mixture was stirred for 5~15 h at room temperature. Evaporation of the solvent gave a crude product, which was isolated by filtration and/or extraction. Purification by column chromatography afforded *N*-benzoyl-1,2-amino alcohol as a mixture of diastereomers.
16. (1*R*,2*S*)-Norephedrine and (1*R*,2*S*)-2-amino-1,2-diphenylethanol were commercially available from Aldrich Chemical Company, Inc. Optically active 2-amino-1-tetralol was synthesized as described in reference 5. Optically active 1-amino-1-phenyl-2-propanol and 2-amino-1-indanol were prepared as described, respectively, in: (a) Zietlow, A.; Steckhan, E. *J. Org. Chem.* **1994**, *59*, 5658. (b) Dornhege, E. *Liebigs Ann. Chem.* **1971**, *743*, 42.