Note

Asymmetric Reduction of Acetophenone *O*-Methyloxime with Reagents Prepared from *L*-Proline and Borane

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Asymmetric reduction of acetophenone *O*-methyloxime with reagents *in situ* prepared from *L*-proline and borane has been investigated. A series of conditions optimization were made, including an examination of the effect of the temperature of catalyst pretreatment, the temperature of reduction, the amount of borane, the additive, the solvent, the reducing agent and various chiral auxiliaries on the enantioselectivity. Under the optimal condition, (*S*)-α-phenylethylamine was obtained in 53% yield with 83.1% *ee* in the presence of 25 mol% *L*-proline.

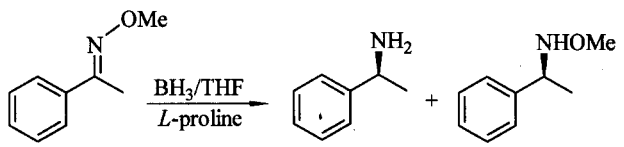
Keywords asymmetric reduction, chiral auxiliary, *L*-proline, borane, acetophenone *O*-methyloxime

Introduction

Asymmetric reduction of C = N double bond is one of the easiest ways to obtain active amines. Whereas asymmetric reduction of ketones has been intensively investigated,[1] only a few references appear in the literature on the corresponding reduction of compounds with C = N double bonds in ketoximes.[2,3] One most important reducing system is the oxazaborolidine-catalyzed borane reduction reported by Itsuno *et al*.[2] in the 1980s. However, catalytic reduction is not rather successful and stoichiometric amount of chiral amino alcohol is necessary.

L-Proline is a bifunctional compound with a carboxyl group and an amino group, in particular, possessing a five-numbered rigid ring. So the application of *L*-proline as an enzyme mimic in asymmetric synthesis appears to be very interesting for many chemists.[4] Buono *et al*.[5] firstly demonstrated asymmetric reduction of ketone using *L*-proline as chiral auxiliary and obtained moderate to good enantioselectivity. This result spurred us to apply this chiral auxiliary to the borane reduction of ketoxime ether, and the experiment was conducted under similar conditions according to Itsuno and Buono's procedure. In the case of the reduction of acetophenone *O*-methyloxime (**1**), α-phenylethylamine (**2**) as well as the incomplete reductive product, hydroxylamine methyl ether (**3**), were obtained (Scheme 1). In this paper, the detailed studies in the reduction of acetophenone *O*-methyloxime are reported.

Scheme 1 Asymmetric reduction of acetophenone *O*-methyloxime with reagents prepared from *L*-proline and borane



1 **2** **3**

Results and discussion

In the first explore, stoichiometric amount of *L*-proline (125 mol%) was used and (*S*)-α-phenylethylamine was achieved in 69% yield with 91.1% *ee* (Table 1, Entry 1), which proved that *L*-proline was an efficient chiral auxiliary in this procedure. However, our greatest interest was focused on catalytic reduction and our attention was directed to catalytic reduction in the presence of 25 mol% of *L*-proline only to get the amine product in 43.5% *ee* with 64% yield under the same condition (Table 1, Entry 2). In order to improve the enantioselectivity, many attempts were made to optimize the reaction condition.

Firstly, the amount of borane was decreased, and the better enantioselectivity (69.4% *ee*) was obtained but resulted in the lower yield (Table 1, Entry 3). The following was attempts to improve the enantioselectivity by addition of various additives in this reaction. Lewis acids $AlCl_3$ or BF_3 were effective to improve the enantioselectivity (Table 1, Entries 4 and 5). On the other hand, Lewis base Et_3N was also efficient additive (Table 1, Entry 6). However, the yield decreased by a different degree respectively. As for other additives such as $TiCl_4$ and Me_2S were not effective (Table 1, Entries 7 and 8). A possible presumption was that it might be favorable to the enantioselectivity by addition of the additives such as $AlCl_3$ and Et_3N in this reaction. The solvent was one important reaction parameters to be considered. By substituting toluene for THF, (*S*)-α-phenylethylamine was obtained with 82.2%

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Table 1 Asymmetric reduction of acetophenone *O*-methyloxime with reagents prepared from *L*-proline and borane[a]

Entry	Ratio[b]	Additive	Solvent	Reducing agent	α-Phenylethylamine		
					Yield[c] (%)	ee[d] (%)	Config.[e]
1	0.8:1.0:3.0	None	THF	BH_3-THF	69	91.1	*S*
2	0.8:0.2:2.2	None	THF	BH_3-THF	64	43.5	*S*
3	0.8:0.2:1.2	None	THF	BH_3-THF	38	69.4	*S*
4	0.8:0.2:2.2	$AlCl_3$	THF	BH_3-THF	43	65.5	*S*
5	0.8:0.2:2.2	BF_3	THF	BH_3-THF	49	56.8	*S*
6	0.8:0.2:2.2	Et_3N	THF	BH_3-THF	32	63.8	*S*
7	0.8:0.2:2.2	$TiCl_4$	THF	BH_3-THF	54	43.6	*S*
8	0.8:0.2:2.2	Me_2S	THF	BH_3-THF	65	44.1	*S*
9	0.8:0.2:2.2	None	Toluene	BH_3-THF	47	82.2	*S*
10	0.8:0.2:2.2	None	THF	BH_3-Me_2S	64	74.0	*S*
11	0.8:0.2:2.2	$AlCl_3$	Toluene	BH_3-Me_2S	55	58.5	*S*
12[f]	0.8:0.2:2.2	None	Toluene	BH_3-Me_2S	53	83.1	*S*

[a] The catalyst was pretreated at 80 ℃ for 6 h, and the reduction was carried out at 30 ℃ for 24 h. [b] The ratio indicated the molar proportion of [acetophenone *O*-methyloxime]:[*L*-proline]:[reducing reagent]. [c] Isolated yield by column chromatographic separation. [d] Determined by GC analysis of the composition of the product. [e] Determined by the comparison of elution order of the TFA amides of optically authentic amines in GC analysis. [f] The temperature of catalyst pretreatment is 110 ℃.

ee, but the yield decreased somewhat (Table 1, Entry 9). By chance it was found that the enantioselectivity! could be substantially improved when the reducing agent was BH_3-Me_2S (Table 1, Entry 10). It is strange to us that the enantioselectivity had no obvious improvement using Me_2S as the additive when BH_3-THF was used as the reducing reagent (Table 1, Entry 8).

Based on the results above, the reaction condition was modified as follows: choosing $AlCl_3$ as the additive, toluene as the solvent, BH_3-Me_2S as the reducing reagent. Under this condition, the amine product was only obtained in 58.5% *ee* with 55% yield (Table 1, Entry 11). The reason why the enantioselectivity decreased might be attributed to the counteractivity of various reaction parameters. Furthermore, in the absence of the additive $AlCl_3$, the temperature of catalyst pretreatment being raised to 110 ℃, (*S*)-α- phenylethylamine was achieved in 53% yield with 83.1% *ee* (Table 1, Entry 12).

In the presence of the additive $AlCl_3$, the effects of the derivatives of *L*-proline and other amino acids on the enantioselectivity were studied (Table 2). It is interesting to note that there was little change in the enantioselectivity when using *L*-proline and its hydrochloride or ammonium as chiral auxiliary (Table 2, Entries 1, 2 and 3). As for other amino acids such as *L*-hydroxyproline and *L*-phenylalanine, the *ee* was rather bad (Table 2, Entries 4 and 5). The conclusion was made that *L*-proline with a five-numbered rigid ring is the best choice of amino acids.

Conclusion

In summary, asymmetric reductions of acetophenone *O*-methyloxime with reagents *in situ* prepared from *L*-proline and borane have been developed innovatively. Under the optimal condition, acetophenone *O*-methyloxime reduced to give (*S*)-α-phenylethylamine in 53% yield with 83.1% *ee* in the presence of 25 mol% *L*-proline. In contrast to the oxazaborolidine-catalyzed asymmetric reduction Itsuno[2] developed, our method is attractive and promising, which shows the following merits: (a) Proline is inexpensive and easily available; (b) the amine is easy to separate from *L*-proline; and (c) the reduction could give satisfactory results in the presence of catalytic amount of *L*-proline. Further studies are in progress, including applying to various substrates and studying the mechanistic rationale.

Table 2 Asymmetric reduction of acetophenone *O*-methyloxime with reagents prepared from various chiral auxiliaries and borane[a]

Entry	Chiral auxiliary	α-Phenylethylamine		
		Yield[b] (%)	ee[c] (%)	Config.[d]
1	*L*-proline	55	58.5	*S*
2	*L*-proline-HCl	58	61.2	*S*
3	*L*-proline-NH_3	64	62.7	*S*
4	*L*-hydroxyproline	48	6.8	*S*
5	*L*-phenylalanine	46	3.1	*S*

[a] The molar ratio of [acetophenone *O*-methyloxime]:[chiral auxiliary]:[$AlCl_3$]:[BH_3-Me_2S] was 0.8:0.2:0.2:2.2, the catalyst was pretreated at 80 ℃ for 6 h, and the reduction was at 30 ℃ for 24 h. [b] Isolated yield by column chromatographic separation. [c] Determined by GC analysis of the composition of the product. [d] Determined by the comparison of elution order of the TFA amides of optically authentic amines in GC analysis.

Experimental

Materials

L-Proline, BH_3-THF, BH_3-Me_2S, Me_2S and trifluoroacetic anhydride were purchased from Acros. Acetophenone *O*-methyloxime, *L*-proline-HCl and *L*-proline-NH_3 were prepared in our laboratory. THF, toluene and Et_2O were freshly distilled from sodium/benzophenone and

CH_2Cl_2 from CaH_2. All other chemicals were of A. R. grade.

Instruments

^1H NMR spectra were recorded in $CDCl_3$ on a Brucker-300 spectrometer at 25 ℃. IR spectra were obtained on a Nicolet MX-1 spectrometer. EI mass spectra were determined on a VG-7070E spectrometer. Gas chromatographic analyses were conducted on a Varian 3380 system.

General procedure

Under an argon atmosphere, *L*-proline (23.0 mg, 0.2 mmol) was dissolved in THF (4.8 mL), then a solution of 2.2 mL of 1 mol/L BH_3-THF (2.2 mmol) was added dropsied at 0 ℃ and the resulting mixture was stirred at 80 ℃ for 6 h. A solution of 119.4 mg of acetophenone *O*-methyloxime (0.8 mmol) in THF (5.0 mL) was added dropwise at 0 ℃ and the mixture was stirred at 30 ℃ for 24 h, then decomposed by addition of 2 mol/L HCl. After hydrolysis and evaporation of THF, the aqueous acid solution was washed with ether, basified with ammonium hydroxide and extracted with ether thrice. The ethereal extract was washed with brine thrice, dried with $MgSO_4$, and then evaporated to give colourless oil. The oil was purified by flash column chromatography to afford α-phenylethylamine; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.64 (d, J = 6.9 Hz, 3H, Me), 4.32 (q, J = 6.6 Hz, 1H, CH), 7.27—7.50 (m, 5 H, Ph); IR (film) ν: 3351, 3278, 3060, 3027, 2964, 2924, 2868, 1602, 1494, 1451, 1370, 1332, 1025, 914, 888, 765, 701 cm^{-1}; MS (70 eV) *m/z* (%): 44 (18), 51 (12), 63 (2), 79 (22), 106 (100), 121(M^+, 6). The enantioselectivity was determined for its trifluoroaceylated derivative by GC analysis using a chiral stationary phase column (CP-Chirasil-*L*-Val) at 90 ℃, t_R = 5.273 min (*R*), t_S = 5.623 min (*S*).

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