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ASYMMETRIC SYNTHESIS XXI. ENANTIOSELECTIVE REDUCTION OF KETONES CATALYZED BY NEW (4S,5R)-4,5-DIPHENYL-1,3,2-OXAZABOROLIDINE

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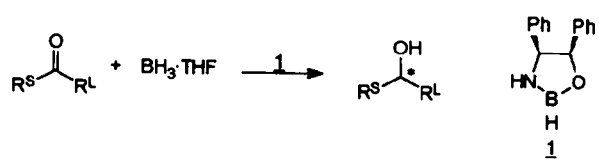
Abstract: Oxazaborolidine prepared from (1R,2S)-1,2-diphenyl-2-aminoethanol with borane was used as catalyst in the enantioselective reduction of ketones; Excellent enantioselectivities with e.e. >99% for acetophenone and e.e. >96% for ω-bromo acetophenone have been achieved.

Enantioselective reduction of prochiral ketones leading to chiral secondary alcohols is a topic of current interest[1]. One of the more successful methods has been based on the use of chiral 1,3,2-oxazaborolidines as catalysts, a method which was developed by Itsuno et al[2], and then improved by Corey et al[3]. Numerous examples describing the application of this method have been reported by several groups[4].

During the course of our asymmetric synthetic studies, previous work indicated that (1R,2S)-1,2-diphenyl-2-aminoethanol was an efficient ligand for the stereocontrolled addition of benzaldehyde with diethylzinc[5]. This paper reports the performance of oxazaborolidine 1 formed in situ as a catalyst for the enantioselective reduction of various ketones.



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It was easy to convert (1R, 2S)-1, 2-diphenyl-2-aminoethanol to oxazaborolidine 1. 1 could be prepared by the reaction of (1R, 2S)-1, 2-diphenyl-2-aminoethanol with 3 equiv of borane at room temperature for 10 hrs. Removal of excess borane and solvent in vacuo gived crude 1. Pure 1 was obtained by sublimation at 220～240℃ and 1 Torr. $[\alpha]_D^{20} = -53.7$ (c = 1, THF). IR (paraffin oil), 2480cm^{-1} (B—H). ^{1}H-NMR (TMS, $CDCl_3$), 1. 20ppm (1H, B-H, broadened), 2. 60ppm (1H, N—H, broadened), 5. 05ppm (1H, di, PhCHN), 5. 60ppm (1H, di, PhCHO), 6. 40～7. 15ppm (10H, m, PhH). MS (m/e, EI), 223 ($M^+ - 1$).

Although oxazaborolidine 1 could be isolated, it was not stable enough for storage. Oxazaborolidine 1 used as a catalyst was formed in situ , where it was shown to be an efficient catalyst, the reduction proceeding quickly[6]. The effect of reaction temperature and addition rate of acetophenone on the enantioselectivity was investigated, since other authors have found that higher temperature[7] and slow addition of ketone were beneficial for enhancing enantioselectivity. The optimal conditions were obtained at 45～50℃ and $\leqslant 3.5 \times 10^{-2}$mmol/minute addition rate, and these were then used in the reduction of aromatic ketones. As shown in Table 1, the reduction of acetophenone in the presence of 20mol% 1 afforded R-1-phenylethanol in >99% e. e. ; the reduction of ω-bromo acetophenone in the presence of 5mol% 1 gived S-2-bromo-1-phenylethanol in >96%e. e.. The configuration of 2-bromo- 1- phenylethanol was formally contrary to that of phenylethanol, consistant with the transition state of ω-bromo acetophenone being the same as for other aromatic ketones (visualized in Fig. 1). The reduction of other aromatic ketones also afforded R-configuration alcohols in good enantioselectivities.

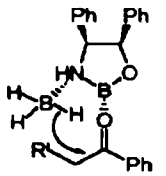

Fig. 1. R'=H, Me, Br

However, low optical yields appeared in the asymmetric reduction of aliphatic ketones. The reason why low enantioselectivities were induced for aliphatic ketones was not fully understood, but two factors seemed to contribute to the results. First, there was no bulky substituent adjacent to the carbonyl group; second, the addition rate of aliphatic ketones (about 30×10^{-2}mmol/minute) was faster than that of aromatic ketones (3.5×10^{-2}mmol/minute).

Table 1. Borane reductions of ketones in the presence of 1 formed in situ, the crude yields of corresponding alcohols were 100% in each case[a]

Ketones	Equiv 1	Chiral alcohols		
		$[\alpha]_D^{25}$(c,solvent)	E. e. (%)	Configuation
PhCOMe[b]	0. 05	+39. 2(3. 02,CH_2Cl_2)	77. 1[d]	R
	0. 10	+46. 7(2. 70,CH_2Cl_2)	88. 9	R
	0. 20	+52. 5(3. 60,CH_2Cl_2)	>99	R
PhCOEt[b]	0. 05	+29. 9(5. 10,$CHCl_3$)	65. 8[e]	R
	0. 20	+36. 0(4. 26,$CHCl_3$)	79. 3	R
$PhCOCH_2Br$[b]	0. 05	+40. 2(9. 10,$CHCl_3$)	>96[f]	S
p-ClPhCOMe[b]	0. 05	+34. 3(4. 82,Et_2O)	68. 8[g]	R
	0. 20	+44. 2(4. 20,Et_2O)	88. 7	R
$CH_3COCH_2CH_3$[c]	0. 05	−3. 07(neat)	22. 7[h]	R
$CH_3COCH_2CH_2CH_3$[c]	0. 05	−3. 56(neat)	26. 0[i]	R
$CH_3COCH_2CH(CH_3)_2$[c]	0. 05	−3. 97(neat)	19. 3[j]	R

[a]Crude yields monitored by GLC, isolated yields >90% for aromatic ketones, about 60% for aliphatic ketones. [b]Optimal condition: 40～45℃, 3. 5×10^{-2}mmol/minute. [c]45～50℃, 30×10^{-2}mmol/minute. [d]Based on the maximum $[\alpha]_D^{25}$ = −52. 5(2. 27,CH_2Cl_2,S)[3a]. [e]Based on the maximum $[\alpha]_D^{25}$ = −45. 45(5. 15,$CHCl_3$,S)[3a]. [f]Based on the maximum $[\alpha]_D^{25}$ = −39(8. 00,$CHCl_3$,R) for 93% e. e.[3a]. [g]Based on the maximum $[\alpha]_D^{25}$ = +49. 9(2,Et_2O,R)[3a]. [h]Based on the maximum $[\alpha]_D^{25}$ = +13. 52(neat,S)[3a]. [i]Based on the maximum $[\alpha]_D^{25}$ = +13. 7(neat,S)[3a]. [j]Based on the maximum $[\alpha]_D^{25}$ = +20. 54 (neat,S)[3a].

In summary, oxazaborolidine 1 is an efficient catalyst for enantioselective borane reductions to provide good to excellent enantioselectivities for aromatic ketones. Further investigation such as developing N- and B-substituent oxazaborolidine and their application will be forthcoming.

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6. In a typical procedure, to (1R, 2S)1, 2-diphenyl-2-aminoethanol (0. 128g, 0. 6mmol) was added 3. 6mmol BH_3 (1. 2M in THF) at 0℃ under N_2, then warmed to room temperature (10℃) and maintained overnight. A solution of acetophenone (3mmol) in THF (15mL) was dropped slowly to prepared oxazaborolidine 1 over 90～100 minutes at 45～50℃. Three minutes late of the last dropping, acetophenone was clean reduced monitored by GLC. The mixture was quenched with 10mL MeOH and 1mL of 3M $Et_2O \cdot HCl$, the chiral ligand was easily recovered (83%) by driving solvent, adding Et_2O(20mL), and filtration. The filtrate was washed with saturated $NaHCO_3$(5mL), brine (2×5mL), dried over anhydrous $MgSO_4$. Removal of ether, the residue was distilled by bulb to bulb to give R configuration phenylethanol (0. 338g, 92. 3% yield), $[\alpha]_D^{20} = +52.5$ (c = 3. 06, CH_2Cl_2), the optical yield (>99%) was based on the reported maximum rotation[8a].

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