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Enantioselective borane reduction of aromatic ketones using chiral BINOL derivatives as ligands in an aluminum catalyst

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Abstract—Chiral aluminum complex-catalyzed asymmetric borane reduction of aromatic ketones has been successfully carried out in the presence of (*R*)-BINOL derivatives as ligands. Secondary alcohols were obtained in high yields with good enantioselectivities (up to 90% e.e.).

1. Introduction

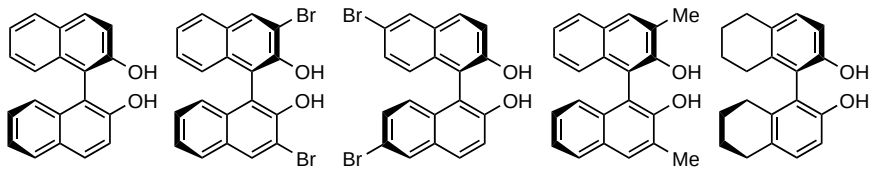
The asymmetric synthesis of enantiomerically enriched secondary alcohols has gained immense importance in view of their utility as versatile synthetic intermediates for various functionalities as well as for many natural products.[1] The enantioselective reduction of prochiral ketones using chiral boron catalysts is one of the most successful approaches to chiral secondary alcohol and the pioneering works of Itsuno[2] and Corey[3] in this area, utilizing homochiral amino alcohols as ligands for a boron catalyst have received considerable attention.[4] Other chiral boron catalysts prepared from chiral sulfoximines,[5] phosphinamides,[6] mercapto alcohols,[7] and β-diamines[8] were also found to be effective for this reaction.

Shibasaki et al. have employed an efficient binaphthol based chiral catalyst ALB in the asymmetric Michael reactions and Horner–Wadsworth–Emmons reactions achieving excellent enantioselectivity.[9] Recently, we made use of a similar catalyst prepared in situ from aluminum tri-*iso*-propoxide and (*R*)-BINOL in the asymmetric borane reduction of aromatic ketones.[10] To explore the scope of our methodology, we have now modified the BINOL system, envisaging enhanced enantioselectivity by using them as ligands in the preparation of a chiral aluminum catalyst. Herein we report our results obtained in the borane reduction of aromatic ketones using (*R*)-BINOL derivatives **2**–**5** as chiral ligands.[11]

2. Results and discussion

2.1. Variation of the chiral ligand

We have chosen chiral BINOL derivatives **1**–**5** as ligands in the asymmetric reduction of aromatic ketones. As a representative example, reduction of acetophenone was carried out with borane–dimethylsulfide complex in the presence of chiral BINOL derivatives **1**–**5** and the results are presented in Table 1. The highest enantioselectivity (71% e.e.) was observed when (*R*)-H_8–BINOL **5** was used as ligand (entry 11). Interestingly, when 3,3′-disubstituted BINOLs **2** and **4** were used, the absolute configuration of the resultant carbinols was found to be opposite to that observed with (*R*)-BINOL **1** (entries 3, 5 and 9). As our catalyst and Shibasaki's ALB have comparable basic components, we presumed



1 **2** **3** **4** **5**

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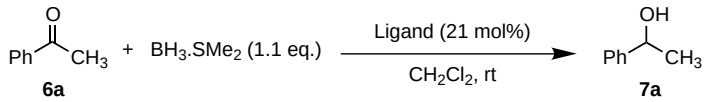
Table 1. Enantioselective reduction of acetophenone with chiral BINOL derivatives as ligands



6a **7a**

Entry	Ligand	$Al(O^iPr)_3$ (mol%)	Time (h)	Yield (%)	% e.e.[a]	Config.[b]
1	–	10	24	99	0	–
2	–	–	24	91	0	–
3	**1**	10	0.3	97	60	*S*
4	**1**	–	24	78	0	–
5	**2**	10	0.5	94	46	*R*
6	**2**	–	24	90	0	–
7	**3**	10	1	98	0	–
8	**3**	–	24	96	0	–
9	**4**	10	2	97	10	*R*
10	**4**	–	24	93	0	–
11	**5**	10	0.5	95	71	*S*
12	**5**	–	24	91	0	–

[a] Determined by HPLC analysis.
[b] Absolute configurations were determined by comparison of specific rotations with literature values.

that they have close structural similarity. However, our attempts to elucidate the structure of our catalyst could not succeed owing to its moisture sensitivity.

In view of these observations, H_8–BINOL **5** was chosen as a ligand for the further investigation of various parameters such as temperature, solvent, catalyst ratio, and nature of substrate which could influence the enantioselectivity in the asymmetric reduction of ketones.[12]

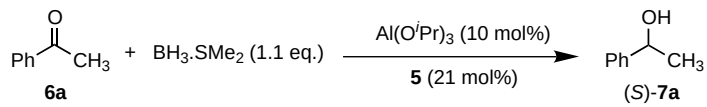
2.2. Effect of solvent and reaction temperature

Since the coordinative solvents appear to be deleterious to the enantioselectivity,[10] the reactions were conducted in chlorinated solvents such as dichloromethane and 1,2-dichloroethane. Similar e.e. was observed in all these solvents indicating that the solvent has no significant effect on enantioselectivity. As shown in Table 2, the optimum temperature appears to be around 40°C (entries 1 and 8).

2.3. Effect of catalyst ratio

Variation of enantioselectivity with the catalyst ratio is shown in Table 3. The best molar ratio of $Al(O^iPr)_3$:ligand seems to be 1:2, and lower e.e. was observed when the quantity of $Al(O^iPr)_3$ or ligand was decreased (entries 1–4 and 9–10). However, there was no apparent change in e.e. when the quantity of $Al(O^iPr)_3$ was increased (entries 5–7). An experiment to increase the S/C ratio was also conducted, but less satisfactory results were obtained (entry 8).

Table 2. Effect of temperature and solvent on the enantioselectivity in the reduction of acetophenone

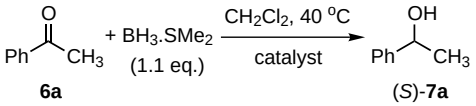


6a (*S*)-**7a**

Entry	Temp (°C)	Solvent	Time (min)	Yield (%)	% e.e.[a]
1	40	CH_2Cl_2	10	99	81
2	30	CH_2Cl_2	10	90	77
3	20	CH_2Cl_2	30	95	73
4	0	CH_2Cl_2	2880	87	40
5	70	CH_2ClCH_2Cl	10	95	64
6	60	CH_2ClCH_2Cl	10	94	72
7	50	CH_2ClCH_2Cl	10	99	78
8	40	CH_2ClCH_2Cl	10	96	80
9	40	$CHCl_3$	10	90	79
10	40	Chlorobenzene	10	84	78
11	40	1,2-Dichlorobenzene	10	80	75

[a] Determined by HPLC analysis.

Table 3. Effect of catalyst ratio on the enantioselectivity in the reduction of acetophenone



6a (S)-**7a**

Entry	**5** (mol%)	Al(O^{i}Pr)$_3$ (mol%)	Yield (%)	% e.e.[a]
1	21	2.5	99	57
2	21	5	96	66
3	21	7.5	94	75
4	21	10	99	81
5	21	20	91	77
6	21	30	95	75
7	21	100	90	76
8	10.5	5	92	26
9	10.5	10	90	68
10	5.5	10	89	38

[a] Determined by HPLC analysis.

2.4. Effect of substrate

To examine the efficacy of our procedure, a variety of aromatic ketones were subjected to the conditions under the reaction conditions optimized for acetophenone (40°C, CH_2Cl_2 as solvent, catalyst prepared in situ from 10 mol% Al(O^{i}Pr)$_3$ and 21 mol% **5**) (Table 4). In the reduction of ketones **6a**–**6e**, the e.e. of the corresponding alcohols decreased with increasing size of alkyl group, except in the case of propiophenone **6b** which has undergone reduction with the highest e.e. (90%) (entries 1–5). However, a dramatic decrease in selectivity was observed with cyclic ketones, which probably results from their relatively rigid conformations (entries 6–7). A halogen substituent appears to have a little influence on the e.e. (entry 8–11), as does the 2-naphthyl group and electron-withdrawing nitro group (entry 13–14), but the presence of an electron-donating group seems to decrease the enantioselectivity (entry 12).

3. Conclusion

In conclusion, (*R*)-H_8–BINOL **5** is demonstrated to be an ideal chiral ligand for aluminum-catalyzed borane reduction of aromatic ketones providing 1-phenylpropanol **7b** in 99% yield with 90% e.e. There is significant enhancement of enantioselectivities with ligand **5** when compared to that of our earlier reported ligand **1** making the present finding more useful. Efforts to establish the structure of the catalyst are under active exploration.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR were recorded on a Varian Mercury-400 or a Varian Unity-400 spectrometer. HPLC analyses were performed on a HITACHI L-6200 chromatography with L-4200 UV detector. Chiral columns were purchased from Daicel Chemical Industries, Ltd. Optical rotations were measured on a Jasco DIP-1000 polarimeter. Anhydrous solvents were freshly distilled under argon. All reactions were performed under an argon atmosphere.

4.2. Typical procedure of catalytic asymmetric borane reduction

To a mixture of Al(O^{i}Pr)$_3$ (40 mg, 0.2 mmol) and (*R*)-H_8–BINOL (123 mg, 0.42 mmol) in dichloromethane (10 mL) previously stirred for 1 h was added acetophenone **6a** (0.24 mL, 2 mmol) under Ar at room temperature. After 0.5 h stirring, the reaction mixture was heated to 40°C and borane dimethylsulfide complex (2.2 mL, 1 M in CH_2Cl_2) was added. Once all the acetophenone had been exhausted (monitored by TLC) the reaction was quenched with 1N HCl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2×10 mL), the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was distilled under reduced pressure (100°C/0.3 mmHg) to give the 1-phenylethanol **7a** (239 mg, 99% yield) in 90% e.e.

Table 4. Enantioselective reduction of aromatic ketones

Entry	Ketone	Time (min)	Yield (%)	% e.e.[a] (config.)[b]
1	Acetophenone **6a**	10	99	81 (*S*)
2	Propiophenone **6b**	10	99	90 (*S*)
3	2-Methylpropiophenone **6c**	120	94	50 (*S*)
4	2,2-Dimethylpropiophenone **6d**	720	93	32 (*S*)
5	Heptanophenone **6e**	10	96	78 (*S*)
6	α-Tetralone **6f**	20	90	62 (*S*)
7	1-Indanone **6g**	30	89	31 (*S*)
8	2-Chloroacetophenone **6h**	10	92	72 (*R*)
9	2-Bromoacetophenone **6i**	10	93	85 (*R*)
10	4′-Chloroacetophenone **6j**	10	90	76 (*S*)
11	3′-Chloroacetophenone **6k**	10	92	70 (*S*)
12	4′-Methoxyacetophenone **6l**	10	89	52 (*S*)
13	4′-Nitroacetophenone **6m**	20	94	78 (*S*)
14	2′-Acetonaphthone **6n**	10	87	83 (*S*)

[a] Determined by HPLC analysis.
[b] Absolute configurations were determined by comparison of specific rotations with literature values.

4.3. Determination of the enantiomeric excess for the secondary alcohols by HPLC

4.3.1. 1-Phenylethanol 7a. $[\alpha]_D^{24}$ −43.7 (*c* 1.64, $CHCl_3$).[13] Chiralcel OD-H, 2-propanol:hexane 2.5:97.5, 1.0 mL/min, UV 254 nm; $t_R = 10.84$ min, $t_S = 13.87$ min.

4.3.2. 1-Phenylpropanol 7b. $[\alpha]_D^{24}$ −43.7 (*c* 0.65, $CHCl_3$).[13] Chiralcel OD-H, 2-propanol:hexane 2.5:97.5, 0.5 mL/min, UV 254 nm. $t_R = 19.86$ min, $t_S = 24.50$ min.

4.3.3. 2-Methyl-1-phenylpropanol 7c. $[\alpha]_D^{24}$ −24.3 (*c* 0.83, ether).[13] Chiralcel OD-H, 2-propanol:hexane 2.5:97.5, 0.5 mL/min, UV 254 nm. $t_R = 21.26$ min, $t_S = 18.68$ min.

4.3.4. 2,2-Dimethyl-1-phenylpropanol 7d. $[\alpha]_D^{24}$ −5.5 (*c* 0.99, benzene).[14] Chiralcel OD-H, 2-propanol:hexane 2.5:97.5, 1.0 mL/min, UV 254 nm. $t_R = 10.24$ min, $t_S = 8.36$ min.

4.3.5. 1-Phenylheptanol 7e. $[\alpha]_D^{24}$ −25.0 (*c* 1.71, benzene).[15] Chiralcel OD-H, 2-propanol:hexane 2.5:97.5, 0.5 mL/min, UV 254 nm. $t_R = 17.26$ min, $t_S = 18.99$ min.

4.3.6. 1,2,3,4-Tetrahydro-1-naphthol 7f. $[\alpha]_D^{24}$ +16.1 (*c* 1.04, $CHCl_3$).[16] Chiralcel OD-H, 2-propanol:hexane 2.5:97.5, 0.5 mL/min, UV 254 nm. $t_R = 23.24$ min, $t_S = 20.88$ min.

4.3.7. 1-Indanol 7g. $[\alpha]_D^{24}$ +2.4 (*c* 1.40, $CHCl_3$).[16] Chiralcel OD-H, 2-propanol:hexane 2.5:97.5, 0.5 mL/min, UV 254 nm. $t_R = 28.24$ min, $t_S = 24.36$ min.

4.3.8. 2-Chloro-1-phenylethanol 7h. $[\alpha]_D^{24}$ −44.8 (*c* 1.25, $CHCl_3$).[13] Chiralcel OD-H, 2-propanol:hexane 2.5:97.5, 1.0 mL/min, UV 254 nm. $t_R = 14.82$ min, $t_S = 13.38$ min.

4.3.9. 2-Bromo-1-phenylethanol 7i. $[\alpha]_D^{24}$ −43.5 (*c* 1.06, $CHCl_3$).[17] Chiralcel OD-H, 2-propanol:hexane 0.8:100, 1.0 mL/min, UV 254 nm. $t_R = 16.07$ min, $t_S = 14.40$ min.

4.3.10. 1-(4′-Chlorophenyl)ethanol 7j. $[\alpha]_D^{24}$ −36.7 (*c* 1.45, ether).[13] Chiralcel OD-H, 2-propanol:hexane 2.5:97.5, 1.0 mL/min, UV 254 nm. $t_R = 20.92$ min, $t_S = 16.35$ min.

4.3.11. 1-(3′-Chlorophenyl)ethanol 7k. $[\alpha]_D^{22}$ −24.8 (*c* 1.08, $CHCl_3$).[13] Chiralcel OJ, 2-propanol:hexane 5:95, 0.5 mL/min, UV 254 nm. $t_R = 15.86$ min, $t_S = 14.38$ min.

4.3.12. 1-(4′-Methoxyphenyl)ethanol 7l. $[\alpha]_D^{22}$ −17.6 (*c* 0.73, $CHCl_3$).[13] Chiralcel OD-H, 2-propanol:hexane 2:98, 1.0 mL/min, UV 254 nm. $t_R = 16.76$ min, $t_S = 18.24$ min.

4.3.13. 1-(4′-Nitrophenyl)ethanol 7m. $[\alpha]_D^{22}$ −16.1 (*c* 0.21, MeOH).[16] Chiralcel OJ, 2-propanol:hexane 5:95, 0.8 mL/min, UV 254 nm. $t_R = 26.38$ min, $t_S = 24.67$ min.

4.3.14. 1-(2′-Naphthyl)ethanol 7n. $[\alpha]_D^{24}$ −34.7 (*c* 1.15, $CHCl_3$).[16] Chiralcel OB-H, 2-propanol:hexane 5:95, 0.8 mL/min, UV 254 nm. $t_R = 18.75$ min, $t_S = 16.16$ min.

Acknowledgements

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