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Enantioselective borane reduction of aromatic ketones catalyzed by chiral aluminum alkoxides

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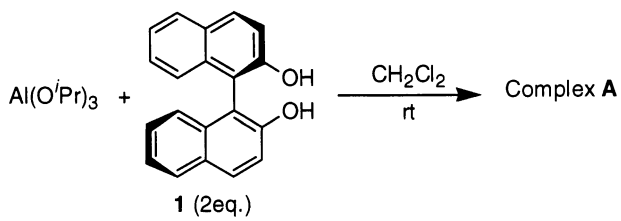
Abstract—The asymmetric borane reduction of prochiral ketones with an alkoxide catalyst prepared in situ from aluminum tri-*iso*-propoxide and (*R*)-binaphthol was examined. Using these conditions, alcohols were obtained in high yield and e.e.'s of up to 83%.

The synthesis of enantiomerically enriched alcohols is an interesting challenge since they are often valuable intermediates for the synthesis of natural products. Among the variety of asymmetric reactions that may lead to optically active alcohols, the enantioselective reduction of prochiral ketones with borane and a chiral ligand, following the pioneering works of Itsuno[1] and Corey,[2] has received considerable attention.[3] In a recent study, organo-aluminum compounds have been reported to accelerate the catalytic asymmetric borane reduction of ketones.[4] On the other hand, so far as we know, there are no reports of using aluminum based catalysts reported herein, which are easily obtainable and inexpensive. Thus, we tried the asymmetric borane reductions of acetophenone **2** using the complex **A** readily generated in situ from aluminum *iso*-propoxide and (*R*)-binaphthol **1** as catalyst (Scheme 1). A selection of results is presented in Table 1.

Optimum results were obtained when the reaction was carried out at 40°C in dichloromethane using the complex prepared from 21 mol% of **1** and 10 mol% of aluminum *iso*-propoxide (entry 9). Under these conditions, the reaction was complete in 10 minutes and the desired phenylethanol was isolated in 96% yield with an e.e. of 74%. At the same time chiral ligand **1** was recovered in 95% yield. It should be pointed out that (*R*)-binaphthol alone is not a catalyst. In the absence of aluminum *iso*-propoxide, the combination of (*R*)-binaphthol and borane–dimethylsulfide complex for the reduction of acetophenone under the same conditions as in entry 9 gave only 50% yield with no enantioselectivity after 24 hours (entry 10). This observation is in agreement with those reported previously by Chan's group.[5] It is also noteworthy that the presence of a coordinative solvent appears to be deleterious to the enantioselectivity of the reaction (entry 1). The selectivity was also found to be temperature dependent; when the reaction was carried out at 0°C, phenylethanol was obtained in only 50% yield with an e.e. of 39% after 48 hours (entry 13). Enantioselectivity also remained unchanged when the ratio of aluminum tri-*iso*-propoxide and binaphthol was increased to 1:3 or 1:4, but lower e.e. of 40% was obtained when the ratio was decreased to 1:1.

To examine the efficacy of this catalytic process with regards to substrate structure, a variety of aromatic ketones were subject to the conditions optimized in the case of acetophenone, and the results are summarized in Table 2. When ketones **2**–**5** were subjected to reaction (entries 1–4), the e.e. of the resulting alcohols decreased as the size of the alkyl group increased, except for propiophenone **3**, which was reduced with the highest enantioselectivity. A halogen substituent



Scheme 1. Synthesis of complex **A**.

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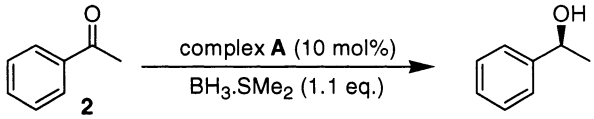
Table 1. Enantioselective borane reduction of acetophenone in the presence of complex **A**



Entry	Solvent	Temp. (°C)	Time	Yield (%)	% E.e.[a]
1	THF	Rt	15 min	91	7
2	CH_2Cl_2	Rt	15 min	97	60
3	$(CH_2Cl)_2$	Rt	15 min	96	45
4	$CHCl_3$	Rt	15 min	94	53
5	PhH	Rt	15 min	94	39
6	Toluene	Rt	15 min	95	52
7	$CHCl_3$	40	10 min	95	70
8	Toluene	40	10 min	96	73
9	CH_2Cl_2	40	10 min	96	74
10[b]	CH_2Cl_2	40	24 h	50	0
11	$CHCl_3$	60	10 min	95	58
12	Toluene	110	10 min	95	39
13	CH_2Cl_2	0	48 h	50	39

[a] Determined by HPLC with Chiralcel OD-H column.
[b] Catalyzed by 20 mol% (*R*)-BINOL without $Al(O^iPr)_3$.

seems to have a slight influence on the observed enantioselectivity (entries 5–6), as does the naphthyl group (entry 9). However, a dramatic decrease in selectivity was observed with cyclic ketones, which probably results from their relatively rigid conformations (entries 7–8).

Due to the moisture sensitivity and instability, characterizing the structure of complex **A** is not trivial and is still under investigation. We speculate that the structure of complex **A** should be similar to Al-Li–BINOL complex (ALB) **11**[6] and La-linked–BINOL complex **12**[7] (Fig. 1). The postulated working model is depicted in Scheme 2. The reaction of BH_3 with complex **A**, followed by coordination of ketone gives the conformers **II** and **III**. Due to the steric hindrance of aromatic ring and naphthyl group, the reaction via **III** would be more favorable than via **II**. The hypothetical transition structure **III** could explain why the product had (*S*)- absolute configuration. To verify this hypothesis, we examined the catalytic ability of ALB **11** and complex **B** prepared in situ from (*R*)-2′-methoxy-1,1′-binaphthyl-2-ol **13**[8] and **1** (Scheme 3). Results of the borane reduction of acetophenone are summarized in Table 3. Obviously, the enantiomeric excess decreased when the hydroxy group was removed from the catalyst (entries 2–3). This is consistent with the results of Shibasaki's recent works, in which the highest e.e. was obtained in the asymmetric Michael addition catalyzed by **12** with M = H.[7]

In conclusion, we have developed a highly active catalytic system based on the use of chiral aluminum alkoxides for the borane reduction of prochiral ketones to the corresponding alcohols with e.e.'s of up to 83%. Further modification of this catalytic system is currently in progress.

Table 2. Enantioselective borane reduction of various ketones using complex **A**[a]

Entry	Ketone	Time	Yield (%)	% E.e.[b] (config.)[c]
1	Acetophenone **2**	10 min	96	74 (*S*)
2	Propiophenone **3**	10 min	94	83 (*S*)
3	Isobutyrophenone **4**	3 h	92	55 (*S*)
4	2,2-Dimethylpropiophenone **5**	12 h	91	30 (*S*)
5	2-Bromoacetophenone **6**	10 min	96	71 (*R*)
6	4′-Chloroacetophenone **7**	10 min	96	62 (*S*)
7	α-Tetralone **8**	12 h	91	43 (*S*)
8	1-Indanone **9**	12 h	92	34 (*S*)
9	2′-Acetonaphthone **10**	10 min	97	70[d] (*S*)

[a] Representative procedure: To a mixture of $Al(O^iPr)_3$ (41 mg, 0.2 mmol) and (*R*)-BINOL (121 mg, 0.42 mmol) in dichloromethane (5 mL) previously stirred for 1 h was added acetophenone **2** (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. After 10 min stirring, the reaction mixture was treated with 1N HCl (2.0 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine, dried ($NaSO_4$) and concentrated. The residue was distilled under reduced pressure (100°C/0.3 mmHg) to give the corresponding product (235 mg, 96% yield) in 74% e.e.
[b] Determined by HPLC with Chiralcel OD-H column.
[c] Absolute configurations were determined by comparison of specific rotations with literature values.
[d] Determined by HPLC with Chiralcel OB-H column.

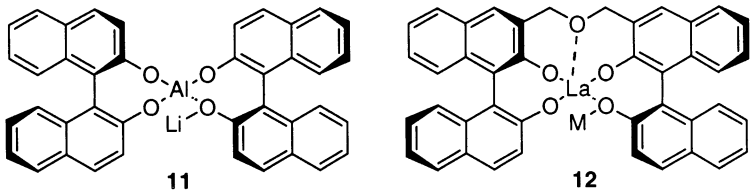
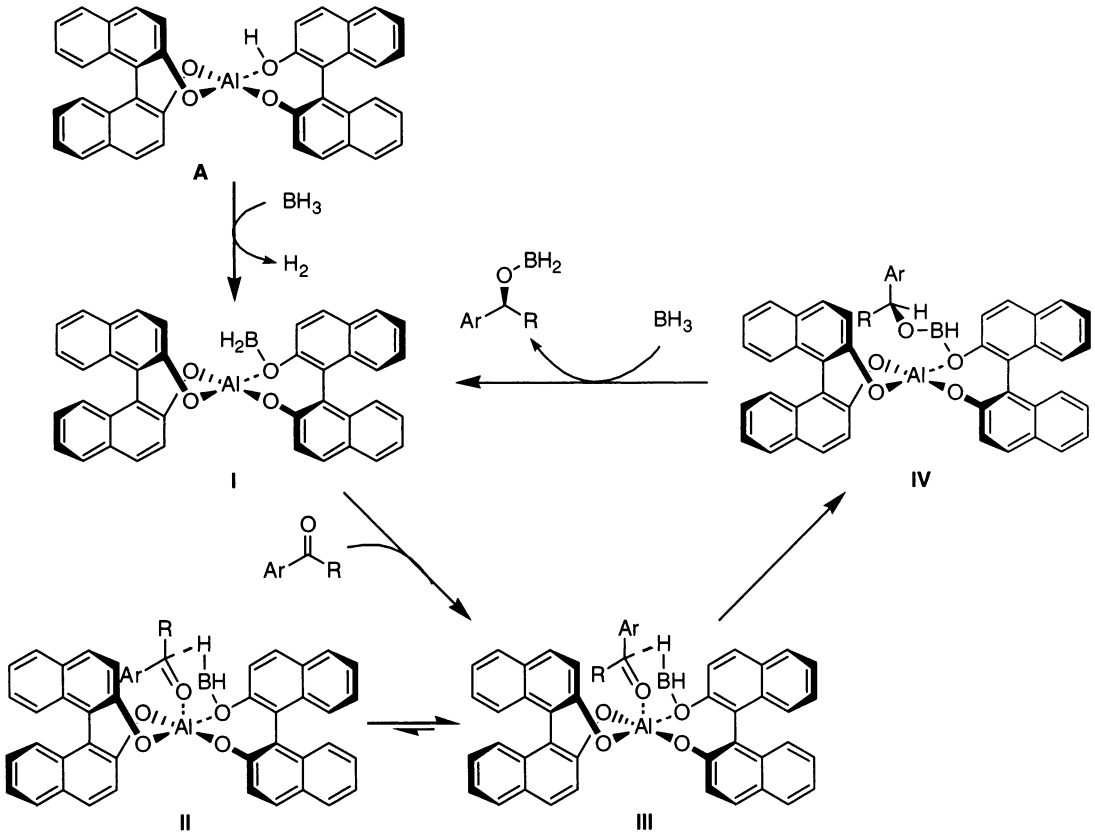
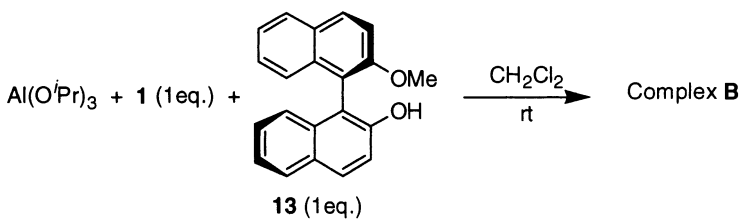


Figure 1.



Scheme 2. Postulated working model for catalytic cycle.



Scheme 3. Synthesis of complex **B**.

Table 3. Enantioselective borane reduction of acetophenone in the presence of various aluminum alkoxides

Entry	Catalyst	Yield (%)	% E.e.[a] (config.)[b]
1	Complex **A**	96	74 (*S*)
2	Complex **B**	93	42 (*S*)
3	ALB **11**	94	26 (*S*)

[a] Determined by HPLC with Chiralcel OD-H column.

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

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