

Asymmetric Reduction of Prochiral Aromatic Ketones by Borane–Amine Complexes in the Presence of a Chiral Amine–BF₃ Catalyst

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The (–)-*N*- α -Methylbenzyl-3,5-dihydrodinaphthazepine–BH₃ complex reduces aromatic ketones to alcohols with 11–57% enantiomeric excess (e.e.) in the presence of BF₃·OEt₂; the (–)-*N*- α -methylbenzyl-3,5-dihydrodinaphthazepine–BF₃ complex catalyses asymmetric reduction of acetophenone by *N,N'*-diethylaniline–BH₃ to give α -phenylethyl alcohol in 51% e.e.

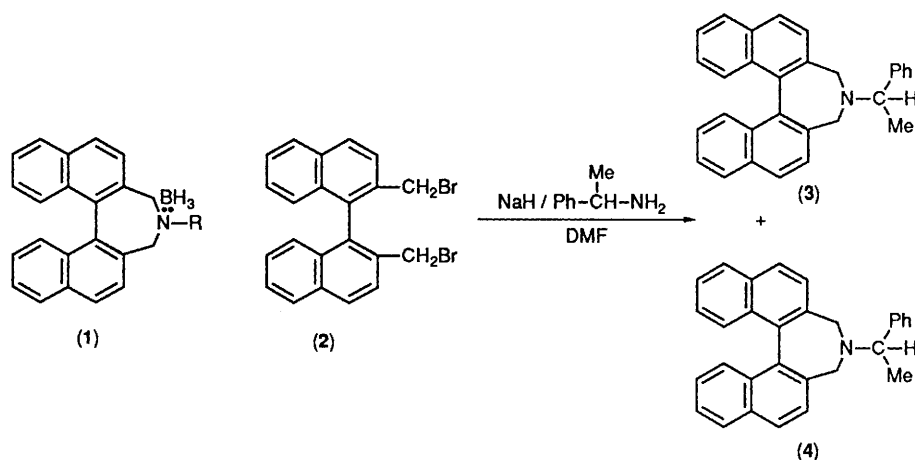
Chiral amine–BH₃ complexes are promising reagents for asymmetric reduction of prochiral carbonyl compounds since the amine can be readily recovered and recycled. It has been reported that the (+)- α -methylbenzylamine–BH₃ complex reduces aromatic ketones in the presence of BF₃·OEt₂ to the corresponding alcohols with 5–13.5% enantiomeric excess (e.e.).¹ More recently, the chiral di- α -methylbenzylamine–BH₃ complex has been reported to reduce acetophenone with 42% e.e. in the presence of BF₃·OEt₂.² We report the asymmetric reduction of acetophenone by the *N,N*-diethylaniline–BH₃ complex using catalytic amounts of chiral (–)-*N*- α -methylbenzyl-3,5-dihydrodinaphthazepine–BF₃ complex (**1**) (R = α -methylbenzyl).

In the course of investigations on the synthetic utilization of amine–boranes,^{3,4} we became interested in the synthesis and utilization of C₂-chiral amine (**1**)–borane systems containing a binaphthyl moiety, since similar systems give high levels of asymmetric induction in several transformations.⁵

The reaction of dibromide (**2**) (20 mmol) with (+)- α -methylbenzylamine in the presence of NaH (30 mmol) in dimethylformamide (DMF, 30 ml) at 70 °C for 2 h gives a mixture of diastereoisomers (**3**) and (**4**) in 85% yield. The isomers are readily separated by column chromatography (silica gel, hexane–ethyl acetate). The (–)-isomer, [α]_D²⁵ –173° (c, 1), CHCl₃, was obtained in 40% yield as a solid and recrystallized from hexane–ethylacetate, m.p. 177 °C.†

The amine (**3**) forms a strong complex with BH₃ in benzene

† Selected spectroscopic data for (–)-isomer: ¹H NMR δ 1.3 (d, 3H), 3.14 (d, 2H), 3.5 (q, 1H), 3.8 (d, 2H), and 7.1–7.95 (m, 12H); ¹³C NMR δ 22.76, 53.23, 62.25, 124.47, 125.8, 127.12, 127.45, 128.12, 128.3, 128.4, 128.8, 131.53, 133.24, 134.24, 135.36, and 146.65; mass, *m/z* 399. The (+)-isomer was obtained as a gum [α]_D²⁵ +253° (c 1, CHCl₃). ¹H NMR δ 1.6 (d, 3H), 3.12 (d, 2H), 3.4 (q, 1H), 3.8 (d, 2H), and 7.1–7.95 (m, 12H). We have used the (–)-isomer for this study as it is more convenient to purify for utilization.



Scheme 1

Table 1. Reduction of prochiral ketones using chiral amine-borane complex.^a

Substrate	Product ^b	Yield/% ^c	$[\alpha]_D^{25}$ (c, solvent) ^d	% E.e. ⁱ
PhCOMe		82	+23° (c 3, MeOH) ^e	51.1
PhCOEt		81	+20° (c 1, Me ₂ CO) ^f	41.1
PhCOPr ⁿ		80	+5° (c 2, benzene) ^g	11.0
α-NapCOMe		78	+45° (c 2, MeOH) ^h	57.0

^a Reactions were carried out at 0 °C with 10 mmol of amine-BH₃ and 10 mmol of ketone in benzene (60 ml). The experiments were run at least twice in each case. α-Nap = α-naphthyl. ^b Products were identified by analysis of spectral data (IR and ¹H NMR) and comparison with the reported data. ^c Yields are of isolated, chromatographed, and distilled products. ^d Optical rotations were measured with an Autopol-II automatic polarimeter (observed rotation accuracy ±0.01°). ^e Based on the maximum $[\alpha]_D^{25}$ -45.5° (c 3, MeOH).¹ ^f Based on the maximum $[\alpha]_D^{25}$ -47.03° (c 1, Me₂CO).⁶ ^g Based on the maximum $[\alpha]_D^{25}$ +45.2° (c 3, benzene).⁶ ^h Based on the maximum $[\alpha]_D^{25}$ -78.9° (c 3, MeOH).⁷ ⁱ Enantiomeric excess.

which does not reduce ketones at 0 °C. However in the presence of one molar equivalent of BF₃·OEt₂, it reduces prochiral aromatic ketones to give the corresponding secondary alcohols with 11 to 57% e.e. (Table 1).[‡] The configurations of products are consistently *R* and the optical induction decreases with increasing chain length of the alkyl moiety.

We have carried out further investigations in order to understand the role of BF₃·OEt₂ in this reaction. It is known that BF₃·OEt₂ liberates diborane from amine-BH₃ complexes. Also, diborane does not displace BF₃ from amine-BF₃ adducts.⁸ Accordingly, the formation of an amine-BF₃

complex as an intermediate cannot be ruled out. In any case, it was of interest to prepare the amine-BF₃ complex and examine whether it could catalyse the asymmetric reduction of acetophenone by an achiral Lewis base borane complex. In order to examine this, we have carried out experiments using various amounts of chiral amine-BF₃ complex and *N,N*-diethylaniline-BH₃ complex (10 mmol) with acetophenone (10 mmol) at 0 °C for 3 h. The results (Table 2) indicate that the asymmetric inductions are decreased only to a small extent by reducing the concentration of the chiral amine-BF₃ complex by 50%. However, further reduction of concentration of the chiral amine-BF₃ leads to a significant decrease in asymmetric inductions. This may be due to competitive uncatalysed reduction of the ketone by the *N,N*-diethylaniline-BH₃ complex.

We have observed that in the absence of amine-BF₃, acetophenone reacts with the *N,N*-diethylaniline-BH₃ complex at 0 °C in 3 h to give the corresponding alcohol in 30% yield. The catalysis by amine-BF₃ is interesting as there is no free co-ordination site available on the borane for further

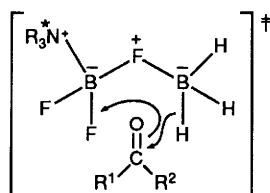
[‡] The borane complex of (3) was prepared by passing B₂H₆ into a solution of (3) in benzene.³ Ketone and BF₃·OEt₂ were added to this complex; the mixture was stirred at 0 °C for 3 h. The reaction was quenched with water-tetrahydrofuran (THF), the amine was separated as the BF₃ complex, and the alcohol was purified by chromatography on a silica gel column using hexane-ethyl acetate as eluant followed by distillation under reduced pressure.

Table 2. Catalytic reduction of acetophenone in the presence of chiral amine-BF₃ complex.^a

Ketone: Amine-BF ₃ / mol. equiv.	Reaction time/h	External reducing agent	Yield/ % ^b	[α] _D ²⁵ (c 3, MeOH) ^c	E.e./ % ^c
1:1	3	Ph(Et ₂)N·BH ₃	81	+23°	51.1
	15	Et ₃ N·BH ₃	80	+22°	48.9
1:0.75	3	Ph(Et ₂)N·BH ₃	82	+23°	51.1
	3	Ph(Et ₂)N·BH ₃	80	+22°	48.9
1:0.5	15	Et ₃ N·BH ₃	80	+22°	48.9
	3	Ph(Et ₂)N·BH ₃	80	+19°	42.2
1:0.4	3	Ph(Et ₂)N·BH ₃	80	+19°	42.2
1:0.25	3	Ph(Et ₂)N·BH ₃	75	+9°	20

^a Reactions were carried out with ketone (10 mmol) and amine-BH₃ (10 mmol) at 0°C. The experiments were run at least twice in each case.

^b Yields are of isolated and purified products. ^c Enantiomeric excess based on the maximum [α]_D²⁵ -45.5° (c 3, MeOH).¹

**Figure 1**

complexation with the ketone. The nature of the actual reactive species may be deduced from the results summarised in Tables 1 and 2. § The reaction of R₃N·BH₃ with BF₃·OEt₂ is expected to give R₃N·BF₃ and borane.⁸ Since diborane is not liberated, the >B-H unit must be present in an associated form along with the R₃N·BF₃ to provide the reactive intermediate. Also the same reactive intermediate would have been formed by the reaction of chiral R₃N·BF₃ with Ph(Et)₂N·BH₃ or Et₃N·BH₃. The results can be best explained by considering the transition state outlined in Figure 1.

In order to get further information about the reactive species, we have prepared R₃*N·BF₃ from R₃*N in ether by treating the amine (3) with BF₃·OEt₂. The precipitated R₃*N·BF₃ (10 mmol) was dissolved in benzene (60 ml) and B₂H₆ (20 mmol) was bubbled through the solution. The IR spectrum of the solution exhibits strong >B-H absorption at

2450 cm⁻¹. Since B₂H₆ cannot displace BF₃ from the R₃*N·BF₃ complex,⁸ the >B-H must be present in an associated form with R₃*N·BF₃. Further, it was observed that the reagent prepared in this way using B₂H₆ reduces acetophenone (10 mmol) at 0°C in 2 h to give the corresponding alcohol (80% yield) in 48.9% (e.e.), [α]_D²⁵ +22° (c 3, MeOH).

In conclusion, the reactive species involved in chiral reductions using R₃*N·BF₃-BH₃ are identified from the results described here. This development should facilitate further work towards improving the chiral recognition abilities of this reducing system.

Support of this research work by DST and CSIR (New Delhi) is gratefully acknowledged. We also thank UGC (New Delhi) for Special Assistance and COSIST support.

Received, 1st March 1990; Com. 0/00952K

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§ We thank one of the referees for suggesting this interpretation.