Asymmetric Reduction of Prochiral Aromatic Ketones by Borane–Amine Complexes in the Presence of a Chiral Amine–BF_3 Catalyst

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The (−)-*N*-α-Methylbenzyl-3,5-dihydrodinaphthazepine–BH_3 complex reduces aromatic ketones to alcohols with 11—57% enantiomeric excess (e.e.) in the presence of $BF_3{\cdot}OEt_2$; the (−)-*N*-α-methylbenzyl-3,5 dihydrodinaphthazepine–BF_3 complex catalyses asymmetric reduction of acetophenone by *N,N'*-diethylaniline–BH_3 to give α-phenylethyl alcohol in 51% e.e.

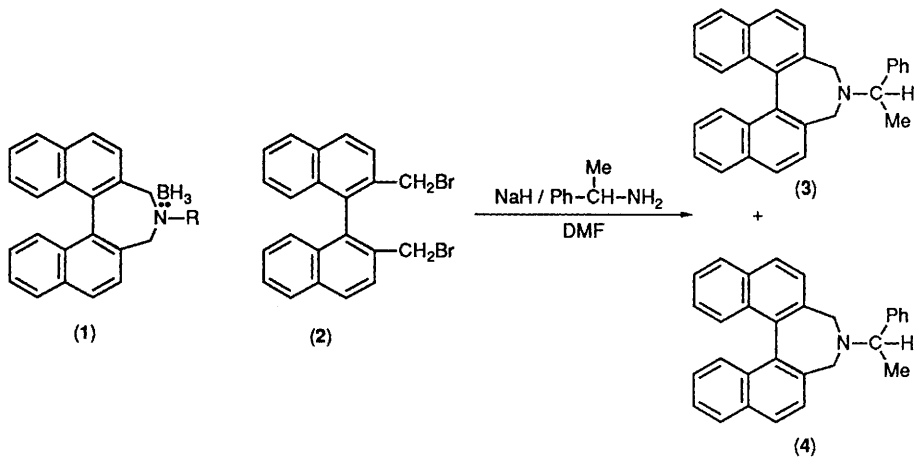
Chiral amine–BH_3 complexes are promising reagents for asymmetric reduction of prochiral carbonyl compounds since the amine can be readily recovered and recycled. It has been reported that the (+)-α-methylbenzylamine–BH_3 complex reduces aromatic ketones in the presence of $BF_3{\cdot}OEt_2$ to the corresponding alcohols with 5—13.5% enantiomeric excess (e.e.).[1] More recently, the chiral di-α-methylbenzylamine–BH_3 complex has been reported to reduce acetophenone with 42% e.e. in the presence of $BF_3{\cdot}OEt_2$.[2] We report the asymmetric reduction of acetophenone by the *N,N*-diethylaniline–BH_3 complex using catalytic amounts of chiral (−)-*N*-α-methylbenzyl-3,5-dihydrodinaphthazepine–BF_3 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 C_2-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, $[\alpha]_D^{25}$ −173° (*c*, 1), $CHCl_3$, 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 BH_3 in benzene

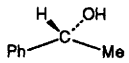
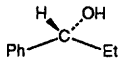
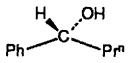
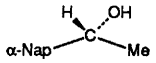
† *Selected spectroscopic data* for (−)-isomer: ^{1}H NMR δ 1.3 (d, 3H), 3.14 (d, 2H), 3.5 (q, 1H), 3.8 (d, 2H), and 7.1—7.95 (m, 12H); ^{13}C NMR δ 22.76, 53.23, 62.25, 124.47, 125.8, 127.12, 127.45, 128.12, 128.3, 128.4, 128.8, 131.53, 133.24, 134.24, 135.36, and 146.65; mass, *m/z* 399. The (+)-isomer was obtained as a gum $[\alpha]_D^{25}$ +253° (*c* 1, $CHCl_3$). ^{1}H 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.



DMF = dimethylformamide

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_2CO)[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–BH_3 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 ^{1}H 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,Me_2CO).[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 BF_3·OEt_2, 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 BF_3·OEt_2 in this reaction. It is known that BF_3·OEt_2 liberates diborane from amine–BH_3 complexes. Also, diborane does not displace BF_3 from amine–BF_3 adducts.[8] Accordingly, the formation of an amine–BF_3 complex as an intermediate cannot be ruled out. In any case, it was of interest to prepare the amine–BF_3 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–BF_3 complex and *N,N*-diethylaniline–BH_3 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–BF_3 complex by 50%. However, further reduction of concentration of the chiral amine–BF_3 leads to a significant decrease in asymmetric inductions. This may be due to competitive uncatalysed reduction of the ketone by the *N,N*-diethylaniline–BH_3 complex.

We have observed that in the absence of amine–BF_3, acetophenone reacts with the *N,N*-diethylaniline–BH_3 complex at 0 °C in 3 h to give the corresponding alcohol in 30% yield. The catalysis by amine–BF_3 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 B_2H_6 into a solution of (**3**) in benzene.[3] Ketone and BF_3·OEt_2 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 BF_3 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–BF_3 complex.[a]

Ketone: Amine–BF_3/ mol. equiv.	Reaction time/h	External reducing agent	Yield/ %[b]	$[\alpha]_D^{25}$ (c 3, MeOH)[c]	E.e./ %[c]
1:1	3	$Ph(Et_2)N{\cdot}BH_3$	81	+23°	51.1
	15	$Et_3N{\cdot}BH_3$	80	+22°	48.9
1:0.75	3	$Ph(Et_2)N{\cdot}BH_3$	82	+23°	51.1
1:0.5	3	$Ph(Et_2)N{\cdot}BH_3$	80	+22°	48.9
	15	$Et_3N{\cdot}BH_3$	80	+22°	48.9
1:0.4	3	$Ph(Et_2)N{\cdot}BH_3$	80	+19°	42.2
1:0.25	3	$Ph(Et_2)N{\cdot}BH_3$	75	+9°	20

[a] Reactions were carried out with ketone (10 mmol) and amine–BH_3 (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 $[\alpha]_D^{25}$ −45.5° (c 3, MeOH).[1]

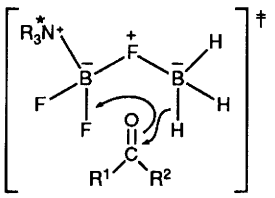


Figure 1

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 $R_3N{\cdot}BH_3$ with $BF_3{\cdot}OEt_2$ is expected to give $R_3N{\cdot}BF_3$ and borane.[8] Since diborane is not liberated, the >B–H unit must be present in an associated form along with the $R_3N{\cdot}BF_3$ to provide the reactive intermediate. Also the same reactive intermediate would have been formed by the reaction of chiral $R_3N{\cdot}BF_3$ with $Ph(Et)_2N{\cdot}BH_3$ or $Et_3N{\cdot}BH_3$. 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 $R_3{*}N{\cdot}BF_3$ from $R_3{*}N$ in ether by treating the amine (**3**) with $BF_3{\cdot}OEt_2$. The precipitated $R{*}_3N{\cdot}BF_3$ (10 mmol) was dissolved in benzene (60 ml) and B_2H_6 (20 mmol) was bubbled through the solution. The IR spectrum of the solution exhibits strong >B–H absorption at 2450 cm^{-1}. Since B_2H_6 cannot displace BF_3 from the $R_3{*}N{\cdot}BF_3$ complex,[8] the >B–H must be present in an associated form with $R_3{*}N{\cdot}BF_3$. Further, it was observed that the reagent prepared in this way using B_2H_6 reduces acetophenone (10 mmol) at 0 °C in 2 h to give the corresponding alcohol (80% yield) in 48.9% (e.e.), $[\alpha]_D^{25}$ +22° (c 3, MeOH).

In conclusion, the reactive species involved in chiral reductions using $R_3{*}N{\cdot}BF_3$–BH_3 are identified from the results described here. This development should facilitate further work towards improving the chiral recognition abilities of this reducing system.

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