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Chemoselective Reduction of Phenyl Ketones with Amino Alcohol-Borane Complexes

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A new reducing agent was prepared from borane and amino alcohols. The reagent is very effective for chemoselective reduction of ketones in the presence of esters, oxime ethers, tertiary amides, nitriles, halides, and acyl chlorides. The polymeric reagent prepared from borane and polymer-supported amino alcohol was also prepared easily. Aldehydes are highly selectively reduced to primary alcohols in the presence of ketone with the polymeric reagent. Simple filtration separated cleanly the unchanged ketone from the polymeric reagent which gave, after hydrolysis, only primary alcohol as the product. The polymeric reagent was regenerated by treatment with borane and could be reused.

Borane reagents such as diborane, borane–tetrahydrofuran (THF), borane–dimethyl sulfide, alkylboranes, and amine–boranes are known to be effective reducing agents for a number of organic compounds.[1] Many attempts for the chemoselective reductions have been made using borane and its derivatives to get significant selectivities.[2–6] In previous papers,[7–9] we have shown that the borane complexes with chiral amino alcohols reduced prochiral ketones highly enantioselectively to give optically active alcohols with quantitative yields. In order to apply these novel borane–amino alcohol complexes to chemoselective reductions their reducing properties were investigated. Indeed a high chemoselectivity was realized in the reduction of ketones in the presence of many other functional groups by use of the reducing agents, easily prepared from commercially available amino alcohols and borane in THF. Polymer-supported amino alcohol–borane complexes were also examined to show an excellent selectivity in the reduction of aldehyde in the presence of ketone. Easy separation of the polymer-supported species from unreacted species present in the reaction mixture was performed by simple filtration. Easy recovery of the polymer-supported amino alcohol makes it possible to regenerate and reuse the reagent.

Results and Discussion

In the first place, the reducing agent prepared from 2-aminoethanol and borane was used to investigate its reducing properties. The molar ratio of borane to the amino alcohol affected the reactivity of the complex in the reduction of ketones. Acetophenone was reduced rapidly by the reagent prepared from 2:1 ratio of borane and 2-aminoethanol, whereas the reagent from 1:1 reacted slowly under the experimental conditions. Isopropylamine–borane and ethoxyborane did not also show so high reactivity. Surprisingly, the rate of ketone reduction by the reagent from 2:1 of borane and the amino alcohol was faster than borane itself as shown in Fig. 1. After treatment of 2-aminoethanol with two equimolar borane in THF, the excess of borane and solvent was evaporated off to give a white pasty solid which could also reduce acetophenone as

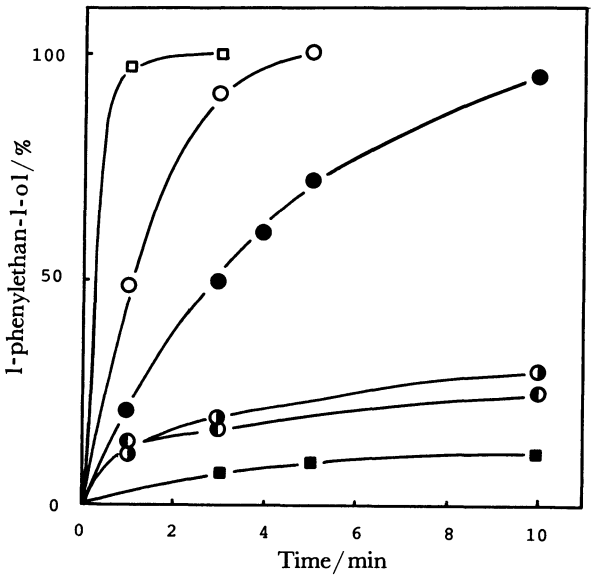


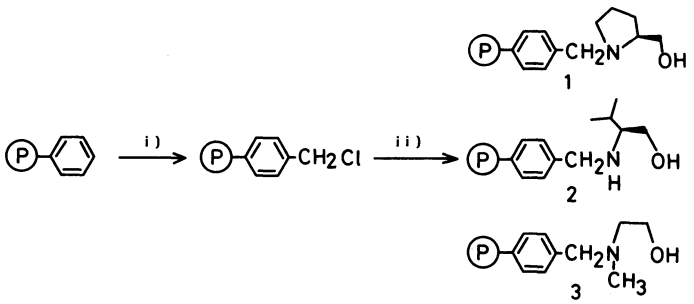
Fig. 1. Time-Conversion Curves for the Reduction of Acetophenone with Amino Alcohol–Borane Complexes.
□: 2-Aminoethanol–borane (1:2) complex; [2-aminoethanol]:[borane]:[acetophenone]=1:2:1, ○: [borane]:[acetophenone]=2:1, ●: [borane]:[acetophenone]=1:1, ■: 2-Aminoethanol–borane (1:1) complex; [2-aminoethanol]:[borane]:[acetophenone]=1:1:1, ◑: ethoxyborane; [ethanol]:[borane]:[acetophenone]=1:1:1, ◐: isopropylamine–borane; [isopropylamine]:[borane]:[acetophenone]=1:1:1.

rapidly as the non-evaporated reagent. In order to avoid the reduction by free borane, this highly-reactive, evaporated 2:1 complex was used for the selected organic compounds containing various functional groups. Results are summarized in Table 1. Carbonyl groups of aldehydes and ketones are rapidly and quantitatively reduced at room temperature in THF to give the primary and secondary alcohols, respectively. Epoxide ring of styrene oxide was cleaved with the complex at the more substituted position (anti-Markovnikov opening as a consequence of electrophilic attack). This high regioselectivity is the same as found for the conventional borane reduction. Unlike the ketone reductions, hydroboration of styrene with this complex was not so fast as with borane itself. The

Table 1. Reactivity of the reagent prepared from 2-aminoethanol and borane in THF at 30 °C

Substrate	Product	Reaction time[a)]/h
$C_6H_5-\overset{O}{\overset{\|\|}{C}}-H$	$C_6H_5-CH_2OH$	1 min
$C_6H_5-\overset{O}{\overset{\|\|}{C}}-CH_3$	$C_6H_5-\overset{OH}{\overset{\|}{C}}H-CH_3$	5 min
$C_6H_5\overset{O}{\overset{/\backslash}{C}}H-CH_2$	$C_6H_5CH_2CH_2OH$	2
$C_6H_5-CH=CH_2$	$C_6H_5CH_2CH_2OH + C_6H_5-\overset{OH}{\overset{\|}{C}}H-CH_3$	3
$C_6H_5-\overset{N-OCH_2C_6H_5}{\overset{\|\|}{C}}-CH_3$	$C_6H_5-\overset{NH_2}{\overset{\|}{C}}H-CH_3$	20
$C_6H_5-\overset{O}{\overset{\|\|}{C}}N(CH_3)_2$	$C_6H_5CH_2N(CH_3)_2$	48
$C_6H_5-\overset{O}{\overset{\|\|}{C}}OH$	Unreactive	—
C_6H_5-CN	Unreactive	—
$C_6H_5CH_2Cl$	Unreactive	—
$C_6H_5-\overset{O}{\overset{\|\|}{C}}Cl$	Unreactive	—

a) Reaction time required for quantitative reduction.



Scheme. Reagents: i) CH_3OCH_2Cl, $SnCl_4$; ii) amino alcohol, K_2CO_3, toluene.

regioselectivity was the same as borane, producing mainly 2-phenylethanol after oxidative treatment with alkaline hydrogen peroxide. The reduction of oxime ethers and tertiary amides proceeded slowly and smoothly to give the corresponding primary and tertiary amine respectively. Although this complex reacts with carboxylic acid to generate hydrogen, reduction did not occur under the experimental conditions. The use of more than two fold excess of the reagent allowed to reduce carboxylic acid to primary alcohol in good yield. It was observed that ester, nitrile, chloride, and acyl chloride are all inert toward the reagent. H. C. Brown *et al.*[10] already reported that the reactivity of borane with various functional groups decreases in the order; carboxylic acids>olefins>ketones>nitriles>epoxides>esters>acyl chlorides. Therefore, the amino alcohol-borane complex is quite different in the order of reactivity.

In view of the considerable attention focused in recent years on the use of polymer-supports to modify the reactivity and selectivity of various reagents,[11] we prepared polymer-supported amino alcohols (Scheme) which were treated with borane to give polymeric reducing agents. Polymer-supported amino alcohol-borane complex could also reduce ketones. Heterogeneous reactions by the use of cross-linked poly(styrene-divinylbenzene) copolymer as a polymer-support took place more slowly than those with the corresponding monomeric reagents. Complete reduction of acetophenone with a 2% cross-linked polymer-supported reagent required 50 h. The higher the degree of cross-linking, the slower is the reaction rate.

Chemoselective Reduction. By taking advantage of a high reactivity of this complex toward ketones, chemoselective reduction of ketones in the presence of ester was examined in THF at room temperature. 2-Aminoethanol-borane complex reduced acetophenone exclusively to give 1-phenylethanol within 30 min. No reduction of ethyl benzoate occured under these conditions. After usual work-up GLPC analysis showed only

Table 2. Chemoselective reduction of 1:1 molar mixture of acetophenone and ethyl benzoate with amino alcohol–borane complex in THF

Run	Amino alcohol	Reaction time/h	Product distribution[a]/%			
			$PhCCH_3$ (O)	$PhCHCH_3$ (OH)	$PhCOEt$ (O)	$PhCH_2OH$
1	$H_2NCH_2CH_2OH$	0.5	0	100	100	0
2[b]	**2**	2.4	0	100	100	0
3[c]	**1**	55	0	100	100	0

a) Determined by GLPC. b)Ⓟ: 2% cross-linked polystyrene resin. Degree of ring substitution is 61%. c) P: 1% cross-linked polystyrene resin. Degree of ring substitution is 60%.

Table 3. Chemoselective reduction of 1:1 molar mixture of acetophenone and oxime ether with amino alcohol–borane complex

Amino alcohol	Reaction time/h	Product distribution/%			
		$PhCCH_3$ (O)	$PhCHCH_3$ (OH)	$PhCCH_3$ (N-OBz)	$PhCHCH_3$ (NH_2)
$H_2NCH_2CH_2OH$	0.5	0	100	100	0
1[a]	50	0	100	100	0

a)Ⓟ: 2% Cross-linked polystyrene resin. Degree of ring substitution is 67%.

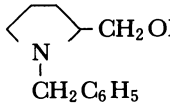
Table 4. Chemoselective reduction of 1:1 molar mixture of acetophenone and N,N-dimethylbenzamide with amino alcohol–borane complex

Amino alcohol	Reaction time/h	Product distribution/%			
		$PhCCH_3$ (O)	$PhCHCH_3$ (OH)	$PhCNMe_2$ (O)	$PhCH_2NMe_2$
$H_2NCH_2CH_2OH$	0.5	20	80	83	17
1[a]	50	0	100	100	0

a)Ⓟ: 2% Cross-linked polystyrene resin. Degree of ring substitution is 67%.

two peaks of unreacted ethyl benzoate and 1-phenylethanol (Table 2). Polymer-supported amino alcohol–borane complexes (run 2,3) also gave the same result. As we expected from our previous results[12] the polymer-supported complex containing tertiary amine such as **1** required a longer reaction time to attain a quantitative reduction of ketone than the complex of secondary amine **2**. In addition to the successful chemoselective reduction, polymer-supported complex could be advantageously used to separate the reacted ketones from the unreactive esters by simple filtration. In other words, the ketone was selectively taken out of the mixture containing esters. This useful separation was realized only when the polymer-supported complex was used. We also examined the selective reduction of keto esters. Methyl acetoacetate and methyl benzoylformate were reduced chemoselectively to give only hydroxy esters. No diols were detected by ^{1}H-NMR or GLPC. Similarly, the inertness of organic halides toward the reagent allows the selective reduction of ketones in the presence of halo groups. Thus, chloroacetophenone and bromoacetophenone were selectively reduced to halohydrins which could be transformed to the synthetically useful epoxides. In the mixture of acetophenone and its oxime ether 2-aminoethanol–borane or polymer-supported complex reduced the ketone selectively (Table 3). Although a clear discrimination between acetophenone and *N,N*-dimethylbenzamide was difficult by 2-aminoethanol–borane complex because of its powerful reducing ability, polymer-supported complex from **1** and borane could reduce only acetophenone in the presence of *N,N*-dimethylbenzamide in 50 h (Table 4). The chemoselective reduction of aldehydes to primary alcohols in the presence of ketones was then examined with the complex. The chemoselectivity in the competitive reductions of benzaldehyde and acetophenone with several amino alcohol–borane complexes is illustrated in Table 5. In the case of the soluble amino alcohol–borane complexes (run 1, 2), its powerful reducing ability to the ketone carbonyl groups could not discriminate between aldehyde and ketone. On the other hand, the polymer-supported reagents could clearly discriminate between them. Degree of cross-linking of the polymer-support affects not only chemoselectivity but also reaction rate. Both reactivity and selectivity increased with decreasing degree of cross-linking (run 3—5). Separation of the aldehyde, reacted with polymer-supported complex, from the unreacted ketone was performed easily also in this case by simple filtration. Benzyl alcohol was obtained quantitatively after hydrolysis. The recovered polymer-supported amino alcohol could be reused for the reduction after the treatment with borane. In conclusion, the present study confirms the versatility of

Table 5. Chemoselective reduction of 1:1 molar mixture of benzaldehyde and acetophenone with amino alcohol–borane complex

Run	Amino alcohol	Degree of cross-linking/%	Degree of ring substitution/%	Reaction time/h	Product distribution/%			
					PhCH(=O)	: $PhCH_2OH$	: $PhCCH_3$(=O)	: $PhCHCH_3$(OH)
1	$H_2NCH_2CH_2OH$	—	—	0.5	0	100	0	100
2		—	—	0.5	0	100	0	100
3	**1**	1	61	1	0	100	100	0
4	**1**	2	43	3	2	98	98	2
5	**1**	5	48	20	20	80	80	20
6	**2**	1	60	1	0	100	100	0
7	**3**	2	54	3.5	0	100	100	0
8	**3**	2	54	5	0	100	80	20

the reagent has the unique reducing properties different from borane itself and the other hydrides. The complex showed an exceptionally powerful reducing ability toward the ketone carbonyl groups. This enabled the chemoselective reduction of ketone in the presence of other functional compounds such as esters, oximes, amides, nitriles; and halides. Its relatively easy availability should make this complex valuable for a variety of selective reductions. Furthermore, water-soluble amino alcohol made separation and isolation of organic products easy. Polymer-supported amino alcohol–borane complex also reduced ketones selectively. Aldehydes were distinguishable from ketones only when the polymer-supported complex was used as reducing agent. In addition to this highly chemoselective property, there are several advantages that polymer-supported complex makes the separation of the reacted substrate from the unreacted one easy by simple filtration and that it was easily recovered and reused.

Experimental

General. GLPC analyses were performed on a Yanaco G180 instrument with a stainless steel analytical column (3 m×3 mm) packed with PEG 20 M on Diasolid L. The products distributions were determined by their peak areas. ^{1}H-NMR spectra were measured on a JEOL JNM-PMX60 (60 MHz) spectrometer. IR spectra were measured on a JASCO A-3 instrument for nujol mulls. TLC was run on silica gel 60 F-254 pre-coated plates with chloroform as the mobile phase.

Materials. All reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran (THF) was heated under reflux over sodium metal and distilled from lithium aluminium hydride in a nitrogen atmosphere. Benzaldehyde, acetophenone, styrene oxide, ethyl benzoate, benzonitrile, benzyl chloride, methyl acetoacetate, methyl benzoylformate, and *N,N*-dimethylbenzamide were dried and distilled over calcium hydride. Benzoyl chloride, 2-aminoethanol, and 2-(methylamino)ethanol were purified by fractional distillation. α-Chloroacetophenone and α-bromoacetophenone were recrystallized from carbon tetrachloride and methanol, respectively. Acetophenone oxime O-benzyl ether was prepared by the methods of French and Harrison[13] and Karabatsos and Hsi[14] and purified by fractional distillation. Bp 145 °C/667 Pa. ^{1}H-NMR($CDCl_3$) δ=2.16 (3H, s), 5.16 (2H, s), 7.00—7.80 (10H, m). Borane–THF was prepared by the reaction of sodium borohydride with boron trifluoride–diethyl ether complex according to the procedure of Brown.[15] Ethoxyborane was prepared by the reaction of borane–THF with 1 equiv of ethanol. Isopropylamine–borane was prepared by the reaction of borane–THF with 1 equiv of isopropylamine. The purities of all reagents were checked by GLPC and ^{1}H-NMR spectroscopy. All materials described were stored under a nitrogen atmosphere prior to use. (*S*)-*N*-Benzylprolinol was prepared by the reaction of (*S*)-prolinol, which was obtained by the reaction of (*S*)-proline with $LiAlH_4$ in refluxing THF, with benzyl chloride in the presence of K_2CO_3 in refluxing toluene according to the method developed by Govindachari *et al.*[16] Bp 90—92 °C/27 Pa. $[\alpha]_D^{25}$ −59.9 °(*c* 1.0, $CHCl_3$). Polymer-supported (*S*)-prolinol (**1**) was prepared from 1,2, or 5% cross-linked chloromethylated polystyrene resin and (*S*)-prolinol according to the method previously reported.[12,17] Polymer-supported (*S*)-valinol (**2**) and polymer-supported 2-(methylamino)ethanol (**3**) were similarly prepared from chloromethylated polystyrene resin and (*S*)-valinol or 2-(aminomethyl)ethanol, respectively. The degree of ring substitution of polymer-supported amino alcohols is 40—70%.

Reduction of Acetophenone with the Reagent Prepared from 2-Aminoethanol and Borane in THF. To a solution of 2-aminoethanol (3 ml, 5 mmol) in dry THF was added borane–THF (5 ml, 10 mmol), initially at −78 °C and the mixture was warmed and kept at 30 °C overnight, followed by evaporation of the unchanged borane under reduced pressure (13 Pa) for 5 h. The reagent thus formed was allowed to desolve in THF (10 ml) under nitrogen. To this solution was added acetophenone (0.6 g, 5 mmol) with stirring, and the resulting mixture was stirred for 30 min at room temperature. After hydrolysis with 1 M† HCl, ether extract was washed with water, and then analyzed by GLPC (100% conversion). The crude product was distilled by bulb-to-bulb distillation to give 1-phenylethanol (0.56 g, 92% of isolated materials); it was characterized by IR and ^{1}H-NMR spectroscopies. Other

† 1 M=1 mol dm^{-3}.

substrates were reduced and analyzed by a similar procedure.

Chemoselective Reduction of Acetophenone in the Presence of Ethyl Benzoate. To a solution of the reagent prepared from aminoalcohol (5 mmol) and borane (10 mmol) in THF was added a mixture of acetophenone (0.6 g, 5 mmol) and ethyl benzoate (0.72 ml, 5 mmol) at 30 °C. After 30 min the reaction mixture was quenched with 1 M HCl. The ether extract of the organic layer was washed with water, and then analyzed by GLPC and ^{1}H-NMR which indicated the mixture to contain only 1-phenylethanol and unreacted ethyl benzoate.

Chemoselective Reduction of Acetophenone in the Presence of Benzonitrile. To a solution of the reagent prepared from 2-aminoethanol (5 mmol) and borane (10 mmol) in THF was added a mixture of acetophenone (0.6 g, 5 mmol) and benzonitrile (0.51 ml, 5 mmol) at 30 °C. After 30 min the reaction mixture was quenched with 1M HCl. The ether extract of the organic layer was washed with water, and then analyzed by GLPC and ^{1}H-NMR which indicated the mixture to contain only 1-phenylethanol and unreacted benzonitrile.

Chemoselective Reduction of Acetophenone in the Presence of Benzyl Chloride. To a solution of the reagent prepared from 2-aminoethanol (5 mmol) and borane (10 mmol) in THF was added a mixture of acetophenone (0.6 g, 5 mmol) and benzyl chloride (0.58 ml, 5 mmol) at 30 °C. After 30 min the reaction mixture was quenched with 1 M HCl. The ether extract of the organic layer was washed with water, and then analyzed by GLPC and ^{1}H-NMR which indicated the mixture to contain only 1-phenylethanol and unreacted benzyl chloride.

Chemoselective Reduction of Acetophenone in the Presence of Benzoyl Chloride. To a solution of the reagent prepared from 2-aminoethanol (5 mmol) and borane (10 mmol) in THF was added a mixture of acetophenone (0.6 g, 5 mmol) and benzoyl chloride (0.58 ml, 5 mmol) at 30 °C. After 30 min no acetophenone was detected by TLC (R_f=0.46) and benzoyl chloride was confirmed to remain by TLC (R_f=0.80). The reaction mixture was then hydrolyzed with 1 M HCl. The ether extract of organic layer was shaken with 1 M NaOH, washed with water, and then analyzed by GLPC which indicated 1-phenylethanol.

Chemoselective Reduction of α-Chloroacetophenone to Styrenechlorohydrin. To a solution of the reagent prepared from 2-aminoethanol (5 mmol) and borane (10 mmol) in THF was added α-chloroacetophenone (0.77 g, 5 mmol) in THF (5 ml) at 30 °C. After 30 min the reaction mixture was quenched with 1 M HCl. The ether extract of the organic layer was washed with water, dried ($MgSO_4$), and distilled (bulb-to-bulb) to give 2-chloro-1-phenylethan-1-ol (0.7 g, 90% of isolated material), it was characterized by ^{1}H-NMR spectroscopy. ^{1}H-NMR($CDCl_3$) δ=3.53 (2H, d), 4.40 (1H, s), 4.75 (1H, t), 7.18 (5H, m).

α-Bromoacetophenone was reduced to styrenebromohydrin in 88% yield by a similar procedure mentioned above.

Chemoselective Reduction of Methyl Acetoacetate to Methyl 3-Hydroxybutyrate. Methyl acetoacetate was converted to methyl 3-hydroxybutyrate (92% yield) by a similar procedure as mentioned above. It was characterized by ^{1}H-NMR spectroscopy. ^{1}H-NMR ($CDCl_3$) δ=1.24 (3H, d), 2.46 (2H, d), 3.70 (3H, s), 4.20 (1H, s).

Methyl benzoylformate was also converted to methyl mandelate in 85% yield, which was characterized by ^{1}H-NMR spectroscopy.

Chemoselective Reduction of Benzaldehyde in the Presence of Acetophenone with Polymer-supported Reagent. Polymer-supported reagent was prepared from polymer-bound (*S*)-prolinol (1% cross-linking, 60.8% ring substitution, 3.67 mmol/g, 2.72 g, 10 mmol) and borane (20 mmol) by the same method as monomeric one. To a THF suspension of the reagent was added a mixture of benzaldehyde (5 mmol) and acetophenone (5 mmol) at 30 °C. Reaction was checked by TLC. After 1 h the suspension was filtered carefully under a nitrogen atmosphere. Obtained polymer was hydrolyzed with 1 M HCl to give benzylalcohol alone, determined by GLPC and ^{1}H-NMR analyses. From the filtrate unreduced acetophenone was completely recovered.

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