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# Convenient Procedures for the Asymmetric Reductions Utilizing α,α-Diphenylpyrrolidinemethanol and Borane Complexes Generated Using the $I_2/NaBH_4$ System

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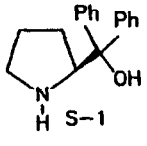
**Abstract:** Syntheses of oxazaborolidine *in situ* in benzene using α,α-diphenylpyrrolidinemethanol and diborane, generated from the iodine-sodium borohydride system are described. The oxazaborolidine (10 mole%), generated by the reaction of α,α-diphenylpyrrolidinemethanol and diborane in benzene followed by heating with N,N-diethylaniline, in combination with borane-tetrahydrofuran complex reduces acetophenone to 1-phenylethanol in 94.7% ee.

Although several oxazaborolidines, prepared using chiral aminoalcohols and a borane reagent, have been found to be useful as catalysts in the asymmetric reduction of prochiral ketones by borane complexes, the catalysts derived from the α,α-diphenylpyrrolidinemethanol have been more widely utilized.[1] Even though the parent catalyst 2 (R=H) has been found to give good results in asymmetric reductions, the corresponding B-methyl derivative is preferred since the unsubstituted catalyst is sensitive to air and moisture.



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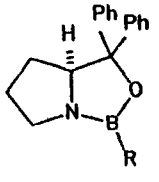


2 a· R=H
b· $R=CH_3$

Recently, it has been reported that erratic results have been obtained in certain reductions using B-methyl derivative prepared using methyl boronic acid and α,α-diphenylpyrrolidinemethanol.[2] It was found that 1mg of water present in 1g of ketone lowers the enantiomeric excess from 95% to 50%.[2] Alternative procedures for the synthesis of the B-methylderivative and the corresponding $BH_3$ complex have been developed.[2]

The preparation of oxazaborolidine (2) using α,α-diphenylpyrrolidinemethanol and borane does not involve water formation. It appeared that this catalyst has not been extensively utilized due to the relatively complicated method of preparation-heating of 3 equivalents of $BH_3$:THF in THF and (S)-α,α- diphenylpyrrolidinemethanol at reflux

under a closed Argon-$B_2H_6$ atmosphere (total pressure 1.7bar). In continuation with our efforts towards the development of convenient procedures for the reductions utilizing the $I_2/NaBH_4$ system,[3-5] we have examined the synthesis of this reagent *in situ* for synthetic applications. The results are described here.

Table I: Reduction of Prochiral ketones with N,N-Diethylaniline-Borane complex in presence of Chiral Oxazaborolidine (1a)[a]

| Achiral amine borane: Chiral Oxazaborolidine molar equiv. | Ketone used | Yield[b] % | $[\alpha]_D^{25}$ | e.e% |
|---|---|---|---|---|
| 1:1 | $PhCOCH_3$ | 90 | +41 (C = 3, $CH_3OH$) | 90.1[c] |
| 1:0.75 | $PhCOCH_3$ | 86 | +41.5 (C = 3, $CH_3OH$) | 91.2[c,e] |
| 1:0.5 | $PhCOCH_3$ | 87 | +41 (C = 3, $CH_3OH$) | 90.1[c] |
| 1:0.25 | $PhCOCH_3$ | 83 | +41 (C = 3, $CH_3OH$) | 90.1[c] |
| 1:0.25 | $PhCOC_2H_5$ | 84 | +43 (C = 1, $CH_3COCH_3$) | 91.4[d,e] |
| 1:0.1 | $PhCOCH_3$ | 85 | +37 (C = 3, $CH_3OH$) | 82.0[c] |

(a) All reactions were carried out using 10 mmol of N,N-diethylaniline-borane, 10 mmol of ketone and oxazaborolidine as mentioned above.

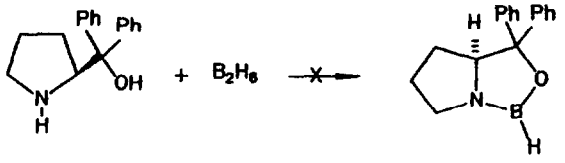
(b) Yields are of isolated, chromatographed and distilled products. Products were identified by spectral data (IR, $^1H$ NMR and $^{13}C$ NMR) and physical constant data.

(c) Based on the maximum[6] $[\alpha]_D^{25}$ = -45.5 (C = 3, $CH_3OH$)

(d) Based on the maximum[7] $[\alpha]_D^{25}$ = -47.03 (C = 1, $CH_3COCH_3$)

(e) Enantiomeric excess was also confirmed by HPLC analysis using Chiralsel-OD column with 5% isopropanol in hexane as solvent.

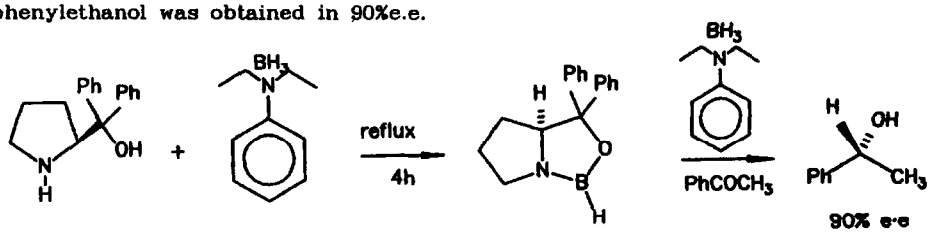
The reagent generated by passing excess of $B_2H_6$ through a benzene solution of (S)-α,α-diphenylpyrrolidinemethanol at 10°C failed to reduce acetophenone at room temperature. Clearly, the $BH_3$ complex of the oxazaborolidine or any other species capable of reducing acetophenone is not formed here.




In another run, diborane gas was passed through a benzene solution of (S)-1 at

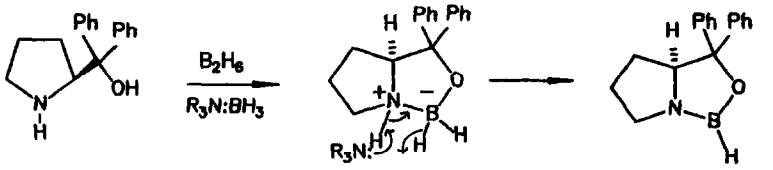
$10^{o}C$ and the resulting mixture was heated under reflux for 3h. It was cooled to $10^{o}C$ and again diborane was passed. It was found that the reagent [10mmol of (S)-1] prepared in this way reduces acetophenone to 1-phenylethanol in 86% yield with 57% e.e.

It was then found that the N,N-diethylaniline-$BH_3$ complex gives better results. N,N-Diethylaniline-$BH_3$(1eq), prepared in dry benzene[3] and (S)-1 (1eq) in THF were mixed at $0^{o}C$ and refluxed for 4h. The contents were cooled to $10^{o}C$ and N,N-diethylaniline-$BH_3$ (1eq) was added followed by acetophenone (1eq) at $0^{o}C$. After workup, 1-phenylethanol was obtained in 90%e.e.




Reduction of acetophenone has been carried out utilizing different amounts of S-(1) and N,N-diethylaniline-borane and the results are summarized in Table I

It appeared that the presence of amine facilitates the 5,5-ring fusion.




In order to examine this, we carried out several experiments. Diborane gas was bubbled through the benzene solution of S-1 (1eq) during 4h at $10^{o}C$. Triethylamine (0.2eq) was added and the mixture was refluxed for 4h. Again, diborane gas was bubbled through the mixture. The reagent prepared in this way reduces acetophenone (1eq) in 90.7% e.e at $0^{o}C$. Similar results were obtained using N,N-diethylaniline in place of triethylamine.

The oxazaborolidine obtained as mentioned above along with various borane reduction systems was used in the catalytic reduction of acetophenone (1eq). The results are summarized in table 2. Recently, a borane reduction system using $I_2/NaBH_4$ in THF has found to be useful for several synthetic applications.[4,5] Unfortunately, this system gives only 70-80% e.e with the catalyst prepared as above (entries no. 1-4, Table 2). However, it has been found that good results are obtained using $H_3B$:THF reagent, prepared by passing $B_2H_6$ generated using $I_2/NaBH_4$, through THF (entries no. 5&6, Table 2)

In conclusion, simple, convenient procedures have been developed for the *in situ* synthesis of oxazaborolidine asymmetric reduction catalysts which should be useful for synthetic applications.

**Table II: Reduction of Acetophenone using Oxazaborolidine along with various Borane systems.**[a]

| S No. | Catalyst | Catalyst quantity (in molar equiv.) | Reducing agent | Yield [%] | e.e(%) |
|---|---|---|---|---|---|
| 1 | 1 + $(NaBH_4/I_2)$[b] | 0.2 | $NaBH_4/I_2$ | 85 | 65 |
| 2 | 1 + $(NaBH_4/I_2)$[c] | 0.2 | $NaBH_4/I_2$ | 80 | 69 |
| 3 | 1 + $B_2H_6$[d] | 0.2 | $NaBH_4/I_2$ | 82 | 72 |
| 4 | 1 + $B_2H_6$ | 0.2 | $NaBH_4/I_2$[e] | 80 | 82 |
| 5 | 1 + $B_2H_6$ | 0.2 | $BH_3$:THF[f] | 91 | 95.5[g] |
| 6 | 1 + $B_2H_6$ | 0.1 | $BH_3$:THF | 90 | 94.7[g] |

(a) To the catalyst prepared, reducing agent (10 mmol) was added followed by acetophenone (10 mmol) and the contents were stirred for 10 min at 30°C.

(b) To the $BH_3$:THF prepared in situ using $NaBH_4$(12 mmol) and $I_2$(6 mmol) aminol was added and the contents were heated for 3h.

(c) To the $BH_3$:THF prepared in situ, aminol, N,N-diethylaniline (1:1) were added and refluxed for 4h.

(d) To benzene solution (15ml) of aminol excess diborane was bubbled, 1 eq. of N,N-diethylaniline was added and heated for 4h.

(e) To the $BH_3$:THF prepared using $NaBH_4$(10 mmol) and $I_2$(5 mmol), dry benzene (10ml) was added and the supernatent solution was transferred in to reaction flask under nitrogen atmosphere.

(f) Diborane prepared using $NaBH_4$(10 mmol) and $I_2$(5 mmol) was bubbled into THF (15ml) at 0°C for 3h.

(g) Enantiomeric excess was determined using Shimadzu HPLC on chiralsel OD column using 95:5 / hexane:isopropanol solvent.

## Experimental Section

**General:** α,α-Diphenylpyrrolidinemethanol was prepared following the literature procedure.[8] Acetophenone and propiophenone (98%) supplied by Fluka were utilized. N,N-Diethylaniline was distilled over KOH prior to use. Benzene and THF freshly distilled over benzophenone-sodium were used. Infrared spectra were recorded on a Perkin-Elmer IR spectrometer 1310 with polystyrene as reference. NMR spectra were recorded on a JEOL-FX-100 and BRUKER-AC-200 spectrometers in deuterated chloroform

using tetramethyl silane as internal standard. The chemical shifts (δ) are expressed in (δ) ppm down field from the signal for internal $Me_4Si$. Optical rotations were measured with an Autopol II automatic polarimeter at 20°C. For TLC analysis, plates coated with silicagel were run in hexane/ethyl acetate mixture and spots were developed in an iodine chamber. For column chromatographic separations under gravity, column grade silicagel (100–200 mesh) was employed.

Reduction of acetophenone using α,α–diphenylpyrrolidinemethanol and $B_2H_6$: Diborane gas, generated utilizing $NaBH_4$(20 mmol) and $I_2$(10 mmol) was bubbled through a benzene (30 ml) solution of S-1 (2.52g, 10 mmol) during 4h at 10°C. The bubbler was replaced by a glass stopper and the mixture was refluxed for 3h. The contents were brought to 10°C and again diborane gas (20 mmol) was bubbled through the reaction mixture during 4h at 10°C. Acetophenone (1.2g, 10mmol) was added and the contents were further stirred for 1h at 10°C. The reaction was quenched with water and the organic layer was washed with 3N HCl (3x10ml) to remove the amino alcohol as hydrochloride salt. The organic layer was further washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was subjected to column chhromatography using hexane:ethyl acetate /85:15 as eluent. The alcohol thus obtained was further purified by distillation under reduced pressure. Yield : 1.05g, (86%) I.R (neat) $\nu_{max}$: 3350, 3050, 1600 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): 1.4(d, 3H), 2.9 (bs, H), 4.8(q, 1H), 7.3(m, 5H). $[\alpha]_D^{25}$= +26 (C = 3, $CH_3OH$) Lit.[6] $[\alpha]_D^{25}$= -45.5 (C = 3, $CH_3OH$).

Reduction of acetophenone using the reagent prepared from S-(1) and N,N–diethyl-aniline–borane complex: N,N–Diethylaniline–borane (10mmol) was prepared by bubbling $B_2H_6$, generated using $I_2/NaBH_4$, through a solution of N,N–diethylaniline in benzene (20 ml) folowing the reported procedure.[3] To this α,α–diphenylpyrrolidinemethanol (2.52g, 10mmol) in dry THF (20ml) was added through a cannula under nitrogen atmosphere at 0°C. The contents were slowly brought to room temperature and then refluxed for 4h. The reaction mixture was cooled to 0°C under nitrogen atmosphere and N,N–diethylaniline–borane (10 mmol) in benzene (30ml) was added under nitrogen atmosphere. Acetophenone (1.2g, 10 mmol) was added at 10°C and the contents were stirred for another 30 min. The reaction was quenched with water (5 ml), N,N–diethylaniline and S-1 were removed as hydrochloride salts by stirring with 3N HCl (3x15ml). The organic layer was separated and washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded crude alcohol which was purified by column chromatography on silica gel using hexane:ethyl acetate/90:10 as eluent, followed by distillation under reduced pressure. Yield : 1.1g(90%). $[\alpha]_D^{25}$= +41 (C = 3, $CH_3OH$).

To examine whether the presence of amine facilitates the formation of oxazabrolidine: Diborane gas, generated using $NaBH_4$(20 mmol) and $I_2$(10mmol), was bubbled through benzene (30ml) solution of S-1 (2.52g, 10mmol) during 4h at 10°C. The bubbler was replaced with a glass stopper and triethyl amine (0.2g, 2mmol) was added. The reaction mixture was refluxed for 4h and then cooled to 10°C under nitrogen

atmosphere. Again diborane gas, generated using $NaBH_4$(20 mmol) and $I_2$(10 mmol) was bubbled through the soluton during 4h at 10°C and the bubbler was replaced with a glass stopper. Acetophenone (1.2, 10mmol) was added and the contents were further stirred for 1h at 10°C. The reaction was quenched with water and the organic layer was washed with 3N HCl (3x10ml) to remove the amino alcohol as hydrochloride salt. The organic layer was further washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was subjected to column chhromatography using hexane:ethyl acetate /85:15 as eluent. The alcohol thus obtained was further purified by distillation under reduced pressure. Yield : 1.05g, (86%) $[\alpha]_D^{25}$= +41.3 (C = 3, $CH_3OH$).

Reduction of acetophenone using S-(1) and $H_3B$:THF: To α,α-diphenylpyrrolidinemethanol (2mmol, 0.51g) in dry benzene (15ml) diborane, generated using $NaBH_4$(6 mmol) and $I_2$(3 mmol) was bubbled. The reaction flask was flushed with nitrogen and N,N-diethyl aniline(2mmol, 0.28g) was added and the contents were refluxed for 4h. In another flask, diborane generated using $NaBH_4$(10mmol) and $I_2$(5 mmol), was bubbled in to dry THF (15ml). This was transferred into the flask containing the oxazaborolidine and acetophenone (10 mmol, 1.2g) was added. After stirring for 10min., water (2ml) was added The contents were washed with 3N HCl (3x10ml), water (5ml), brine, dried oved $MgSO_4$ and concentrated. The product 1-phenylethanol was isolated by distillation. Yield: 2.2g, (90%). Enantiomeric excess was determined to be 94.7% (R) (Shimadzu HPLC on Chiralsel OD column, using 95:5/hexane:isopropanol solvent).

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