# Selective Reductions. 34. Asymmetric Reduction of Representative Ketones with Monoisopinocampheylborane of High Optical Purity

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Monoisopinocampheylborane of high optical purity was used for the reduction in tetrahydrofuran of a representative group of ketones, $RCOCH_3$ (R = Et, *i*-Pr, *t*-Bu, and Ph), in both 1:1 (1 ketone/reagent) and 2:1 ratios (2 ketones/reagent). In the former case, the asymmetric induction achieved in the products, consistently enriched in one enantiomer, was in the range of 14.8–46.3% ee, consistently higher than those achieved when the reduction was carried out in the 2:1 ratio, viz, 11.5–25%. The reduction pathway was explored in the case of 3-methyl-2-butanone as a representative ketone with $^{11}B$ NMR as the experimental probe. The reaction mixture for the 1:1 molar ratio involves formation of both 1:1 and 2:1 reduction products.

Diisopinocampheylborane ($Ipc_2BH$), an excellent chiral hydroborating agent for *cis*-olefins,[2] has also been utilized for the asymmetric reduction of a series of representative ketones, $RCOCH_3$ (R = Et, *i*-Pr, *t*-Bu, and Ph), to yield optically active alcohols.[3-5] The reaction pathway, however, is complex and is often associated with the displacement of α-pinene from the reagent. Consequently, the product alcohols are not consistently enriched in one enantiomer. Recently, monoisopinocampheylborane ($IpcBH_2$) of high optical purity has been prepared[6] and its hydroboration characteristics studied.[7-9] It has been observed that the reagent is valuable for the hydroboration of hindered olefins where $Ipc_2BH$ fails to achieve significant optical induction. Thus, the hydroboration of phenyl-substituted tertiary olefins[7,9] and *trans*-olefins[8,9] with the reagent yields product alcohols in the range of 85–100% ee and 72–93% ee, respectively. Therefore, it appeared of interest to explore this reagent for the asymmetric reduction of hindered and unhindered ketones in the hope of achieving high asymmetric induction in the product alcohols.

## Results and Discussion

(+)-$IpcBH_2$ was prepared in THF by the reaction of boron trifluoride etherate with the bis adduct of $IpcBH_2$ and *N,N,N',N'*-tetramethylethylenediamine ($2IpcBH_2$·TMED), itself obtained as a crystalline solid, mp 140.5–141.5 °C, by the reaction of 0.5 equiv of TMED with (−)-$Ipc_2BH$ in THF.[6] As representative ketones, 2-butanone, 3-methyl-2-butanone, 3,3-dimethyl-2-butanone, and acetophenone were selected. In all of the experiments, the ketone was added to the reagent in THF, maintained either at 0 °C or at −25 °C.

**General Method for the Determination of Rate of Reduction.** Four representative ketones were selected for the present study. Each ketone was reduced with (i) an equimolar quantity of $IpcBH_2$ (0.7 M in ketone and $IpcBH_2$) and (ii) a one-half molar quantity of $IpcBH_2$ (1.4 M in ketone and 0.7 M in $IpcBH_2$). Aliquots were removed at intervals and analyzed for (i) active hydride by measuring the volume of hydrogen generated on hydrolysis and (ii) residual ketone and product alcohol by GLC following oxidation of the aliquot with alkaline hydrogen peroxide solution. The rate of reduction was established by combining these two analyses.

**Reduction of Ketones with $IpcBH_2$ in 1:1 Ratio.** The reduction of 2-butanone required 3 h at −25 °C. Similarly, the reduction of 3-methyl-2-butanone required about 6 h at −25 °C but was complete within 1 h at 0 °C. Acetophenone and 3,3-dimethyl-2-butanone are also reduced rapidly at 0 °C, requiring 2 and 2.5 h, respectively, for completion.

$^{11}B$ NMR proved to be very helpful[11] for examining the reduction. The reduction of 3-methyl-2-butanone at 0 °C was chosen as representative. After completion of the reduction (1 h, 0 °C), an aliquot (0.5 mL) was removed and the $^{11}B$ NMR spectrum taken. The spectrum showed absorption at δ 53.9 (relative to $BF_3$·$OEt_2$) attributed to the intermediate **1**. The two peaks at δ 30.9 and 22.8, attributed to the boronic ester **2** and dimeric $IpcBH_2$ **3** were not well resolved. We made use of the fact that addition of an amine (A) to the reaction mixture should form a complex with **3** to yield $IpcBH_2$·A, which would then absorb downfield (relative to $BF_3$·$OEt_2$) in the $^{11}B$ NMR. The boron atom in **1** and **2** should be less electrophilic, so that **3** should coordinate preferentially with the amine, facilitating the analysis. The above assumption was confirmed by the addition of 0.1 mL of pyridine to the above aliquot. The $^{11}B$ NMR spectrum now showed three distinct, well-resolved absorptions, viz, δ 53.9 due to **1**, 31.2 due to **2**, and −0.45 due to $IpcBH_2$·py. Integration of the peaks then provided the relative amounts of **1**, **2**, and **3** in the reduction product to be 15%, 43%, and 41%, respectively, indicating a reasonable material balance (eq 1).

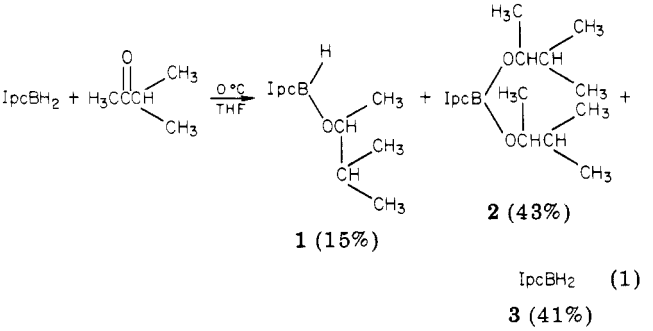


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**Table I. Asymmetric Reduction of Ketones with Monoisopinocampheylborane ($IpcBH_2$) of High Optical Purity in THF[a]**

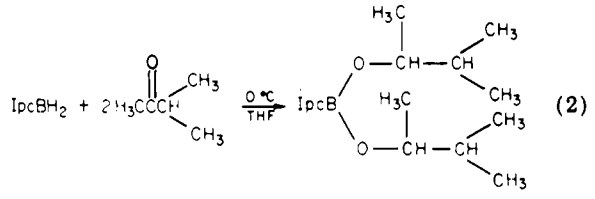
| ketone $RCOCH_3$, R = | ratio of ketone to reagent | reaction, conditions | | alcohol product | | | |
|---|---|---|---|---|---|---|---|
| | | temp, °C | time, h | yield,[b,c] % | $[\alpha]^{25}D$ | % ee | config |
| ethyl | 1:1 | −25 | 3 | 95 (66) | +2.99 | 22.2 | *S* |
| ethyl | 2:1 | −25 | 6 | 91 (65) | +3.01 | 22.3 | *S* |
| isopropyl | 1:1 | 0 | 1 | 95.4 (70) | +1.97 | 37.0 | *S* |
| isopropyl | 2:1 | 0 | 6 | 94 (69) | +1.36 | 25.0 | *S* |
| isopropyl | 1:1 | −25 | 6 | 92 (70) | +2.47 | 46.3 | *S* |
| *tert*-butyl | 1:1 | 0 | 2.5 | 96 (85) | +1.72 | 21.2 | *S* |
| *tert*-butyl | 2:1 | 0 | 24 | 90 (80) | +0.68 | 15.8 | *S* |
| phenyl | 1:1 | 0 | 2 | 88 (55) | −6.38 | 14.9 | *S* |
| phenyl | 2:1 | 0 | 4.5 | 90 (58) | −4.89 | 11.4 | *S* |

[a] All reactions were carried out in 50-mmol scale. The reagent is prepared from (+)-α-pinene, 94% ee. [b] GC yield after oxidation with alkaline $H_2O$. [c] Figures in parentheses indicate isolated yield from separate reaction mixture. [d] Based on the following $[\alpha]_D$ value for 100%: 2-butanol, *R* −13.5° (Leroux, P. J.; Lucas, H. J. *J. Am. Chem. Soc.* **1981**, *73*, 41); 3-methyl-2-butanol, *S* +5.34° (Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1913**, *103*, 1957); 3,3-dimethyl-2-butanol, *S* +8.1° (Newman, P.; Lutkin, P.; Mislow, K. *J. Am. Chem. Soc.* **1950**, *80*, 465); 1-phenylethanol, *R* +42.85° (Pickard, R. H:; Kenyon, J. *J. Chem. Soc.* **1911**, *99*, 45). Absolute configuration from Klyne, W.; Buckingham, J. "Atlas of Stereochemistry"; Oxford University Press: New York, 1974.

(It should be recognized that such integration of $^{11}B$ peaks is not precise.) The results, therefore, indicate that in the reduction of 3-methyl-2-butanone in the 1:1 ratio, the reaction is not a simple one, involving addition of one B–H of $IpcBH_2$ bond to the carbonyl group to give the intermediate 1. A considerable amount of the reduction proceeds through the reagent 1 to yield 2.

**Reduction of Ketones with $IpcBH_2$ in 2:1 Ratio.** As expected, the reduction of ketones with $IpcBH_2$ in the 2:1 ratio proceeds more sluggishly. Thus, the reduction of 2-butanone requires 6 h at −25 °C for completion. Similarly, the reduction of 3-methyl-2-butanone, 3,3-dimethyl-2-butanone, and acetophenone required about 6, 24, and 5 h for approximate completion (Table I).

As before, the reduction pathway was followed by $^{11}B$ NMR, using 3-methyl-2-butanone as the ketone. After completion of the reduction, the $^{11}B$ NMR spectrum of an aliquot revealed only one absorption at δ 31.5 (relative to $BF_3{\cdot}OEt_2$), attributed to the boronic ester 2 (eq 2). The



(2)

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more sluggish reduction in this 2:1 case is understandable because 50% of the reduction proceeds through the intermediate 1 as the reducing agent. The boron atom in 1 should be less electrophilic than that in 3 due to the overlap of its vacant p orbital with the lone pair of the oxygen atom.

Two procedures were utilized for isolation of the products. For ketones other than acetophenone, the reaction mixtures, following the reduction, were oxidized with alkaline hydrogen peroxide. The alcohol products from the ketones were then isolated by distillation from the isopinocampheol formed from the reagent. In the case of acetophenone, the alcohol was distilled directly from the isopinocampheyl–boron intermediates 1 and 2. Finally, the alcohol products from both procedures were purified by preparative GC. The optical rotations and optical purities are summarized in Table I.

The results reveal that the reduction of ketone with $IpcBH_2$ in both 1:1 and 2:1 ratios yields alcohols consistently enriched in *S* enantiomer when the reagent $IpcBH_2$ is prepared from (+)-α-pinene. In the case of reduction in the 1:1 ratio, the optical yields of the product alcohols from 2-butanone, 3-methyl-2-butanone, 3,3-dimethyl-2-butanone, and acetophenone are 22.2%, 46.3%, 21.2%, and 14.9%, respectively, which are significantly higher than those obtained when the reduction was carried out in the 2:1 ratio, viz, 22.3%, 25%, 15.8%, and 11.4%, respectively. We believe that the lower optical yield in the latter case must arise from the fact that 50% of the reaction in this case proceeds through a new chiral reagent 1, which must induce lower optical induction in the product alcohol, thereby lowering the overall optical yield. It is probable that the much higher enantiomeric excess realized in the reduction of 3-methyl-2-butanone at −25 °C (46.3%), as compared to 0 °C (37%), is due to the fact that at the lower temperature a larger fraction of the reduction product is 1.

## Experimental Section

**Materials.** Tetrahydrofuran and boron trifluoride etherate were purified following standard procedures.[11] Borane–methyl sulfide (BMS) (Aldrich) was analyzed for hydride concentration by the standard hydrolyzing technique.[11] The commercial ketones were purified by distillation and kept under nitrogen. (+)-α-Pinene (Dragoco & Co.) was used after distillation from LAH, which showed an optical rotation of $[\alpha]^{26}_D$ 48.03°, corresponding to 94.0% ee. The optical rotations were measured in a Rudolph 222 automatic polarimeter.

**Preparation of $IpcBH_2$.** $2IpcBH_2{\cdot}TMED$ of high optical purity was prepared by following literature procedures.[6,12] A stock solution of 0.85 M $2IpcBH_2{\cdot}TMED$ in THF was made in THF. To 46.1 mL (30 mmol) of the solution was added 7.4 mL (60 mmol) of $BF_3{\cdot}OEt_2$ at 25 °C. The reaction mixture was stirred at 25 °C for 1.5 h. The solution containing free $IpcBH_2$ was then removed from the slurry of $TMED{\cdot}2BF_3$ through a filtration chamber.[13] The solid $2BF_3{\cdot}TMED$ was washed with three 8-mL portions of THF. Thus a 0.86 M solution of $IpcBH_2$ in THF (confirmed by hydrolysis) was obtained.

**General Method of Analysis.** The following procedure for the reduction of 2-butanone with $IpcBH_2$ in 1:1 molar ratio is representative. In a 50-mL flask equipped with a septum inlet and a condenser connected to a mercury bubbler was added 11.6 mL (10 mmol) of a 0.86 M solution of $IpcBH_2$ in THF. To this was added at −25 °C 0.4 mL (2 mmol) of *n*-decane (an internal standard for GC) and 1.4 mL of THF (to make the solution 0.7 M in $IpcBH_2$), followed by 0.9 mL (10 mmol) of 2-butanone. After

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(13) For a description of the filtration chamber, see ref 11, page 224.

regular intervals of time, 1-mL aliquots were hydrolyzed and the volume of hydrogen corresponding to unreacted hydride was measured. At the same time, another 1-mL aliquot was oxidized with alkaline hydrogen peroxide and then analyzed for unreacted 2-butanone and 2-butanol produced by GC by using a 6 ft × $^1/_4$ in. 10% SE-30 on Chromosorb W (60/80) column. Combining these two analyses, the rate of reduction was established. The reaction of 2-butanone with $IpcBH_2$ in a 1:1 molar ratio at −25 °C required 3 h for completion.

**Reduction of Ketone with $IpcBH_2$ in THF (a) in 1:1 Ratio and (b) 2:1 Ratio.** **(a)** The reduction of 3-methyl-2-butanone is representative. An oven-dried, 250-mL flask with the usual experimental setup was cooled in an ice-bath under a slow stream of nitrogen. The flask was charged with $IpcBH_2$ in THF (58.1 mL, 50 mmol) and THF (8 mL). To it was added with stirring 3-methyl-2-butanone (5.35 mL, 50 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. Water (5 mL) was added and the volume of hydrogen was noted. Oxidation was effected by adding 20 mL of 3 M NaOH and 13.5 mL of 30% aqueous $H_2O_2$ (1 h, 50 °C). The aqueous phase was saturated with anhydrous $K_2CO_3$ and the THF layer separated. The aqueous phase was extracted with 3 × 30 mL portions of ether. The combined extract was washed once with saturated brine solution and then dried over anhydrous magnesium sulfate. Distillation using a 30-cm Widmer column provided 3.1 g of 3-methyl-2-butanol, a yield of 70%. It was further purified with a preparative gas chromatograph by using a 5 ft 20% SE-30 column (75 °C): $n^{20}D$ 1.4120; $[\alpha]^{26}D$ +1.98° (*c* 100, benzene); 37% ee.

**(b).** The reduction was carried out in a similar manner by using $IpcBH_2$ in THF (58.1 mL, 50 mmol), THF (3.3 mL), and 3-methyl-2-butanone (10.7 mL, 100 mmol). The usual workup and distillation afforded 3-methyl-2-butanol in 69% yield. Purification as before yielded pure 3-methyl-2-butanol; $n^{20}D$ 1.4119; $[\alpha]^{26}D$ +1.33° (*c* 8.9, benzene); 25% ee.

**Reduction of Acetophenone with $IpcBH_2$ in THF in 1:1 Ratio.** With the usual experimental setup, the reaction flask containing $IpcBH_2$ in THF (59.4 mL, 50 mmol) and THF (6.2 mL) was cooled to 0 °C. To it was added dropwise with stirring acetophenone (5.83 mL, 50 mmol), and the reaction mixture was stirred at 0 °C for 2 h. Methanol (5.0 mL) was added and the volume of hydrogen corresponded to 51 mmol of unreacted hydride. The reaction mixture was then stirred at 50 °C with saturated aqueous potassium carbonate for 6 h. The organic layer was separated and the aqueous layer extracted with 50 mL of ether. The combined organic layer was dried over anhydrous $K_2CO_3$ overnight. Volatile components were removed under aspirator vacuum (20 mm, 3 h, 25 °C), and the 1-phenylethanol was distilled from the boronic/borinic intermediate under high vacuum (0.08 mm). The distillate 50–51 °C (0.08 mm) (3.42 g, 55%) was collected and then purified through preparative GC by using a 5 ft Carbowax 20M column (150 °C): $n^{20}D$ 1.5265; $[\alpha]^{25}_D$ −6.34° (*c* 3.5, benzene); 14.8% ee.

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**Registry No.** 1, 90387-32-9; 2, 90367-72-9; IpcBH, 64234-27-1; $EtCOCH_3$, 78-93-3; *i*-$PrCOCH_3$, 563-80-4; *t*-$BuCOCH_3$, 75-97-8; $PhCOCH_3$, 98-86-2; (*S*)-2-butanol, 4221-99-2; (*S*)-3-methyl-2-butanol, 1517-66-4; (*S*)-3,3-dimethyl-2-butanol, 1517-67-5; (*S*)-1-phenylethanol, 1445-91-6.

# Synthesis and Reactions of *N*-(2,4-Dichloro-6-oxo-2,4-cyclohexadien-1-ylidene)-4-nitrobenzamide with Alkenes

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The cycloaddition reactions of *N*-(2,4-dichloro-6-oxo-2,4-cyclohexadien-1-ylidene)-4-nitrobenzamide (**3**) and other *o*-quinone monoimides with electron-rich alkenes to give derivatives of 2,3-dihydro-4*H*-1,4-benzoxazine are described. Reaction of **3** with 2,3-dimethyl-1,3-butadiene leads to the formation of the spiro adduct **23**.

1,4-Cycloaddition reactions of alkenes with *o*-quinones,[1-3] *o*-quinone dibenzimides,[4,5] and *o*-quinone methides[6,7] are well-known. Similar cycloadditions of alkenes with *o*-quinone monoimides have not been recorded. A few of the latter compounds have been prepared by the lead tetraacetate oxidation of *o*-amidophenols[8] and by the thermolysis of monoazidohydroquinones.[9] We describe here a novel synthesis of the *o*-quinone monoimide **3** and the reactions of **3** with electron-rich alkenes.

The brightly orange colored **3** was obtained by the routes depicted in Scheme I. Reduction of 2,4,6-trichloronitrobenzene by zinc dust formed the hydroxylamine **1** which by *O*-aroylation with *p*-nitrobenzoyl chloride gave **2**. Treatment of **2** in refluxing chloroform containing sodium carbonate afforded **3**. Compound **3** was also synthesized by *O*-aroylation of the known 2-amino-3,5-dichlorophenol[10] to give **4** followed by thermolysis of **4** to **5** and oxidation of **5** to **3** by oxidation with lead tetraacetate. Compound **3** easily oxidizes 1,4-cyclohexadiene and benzhydrol to benzene and benzophenone, respectively, while at the same time it is reduced to **5**.

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