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# Selective Reductions. 23. Asymmetric Reduction of Representative Ketones with Diisopinocampheylborane of High Optical Purity

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Diisopinocampheylborane of high optical purity, in tetrahydrofuran, diglyme, ethyl ether, methylene chloride, and *n*-pentane, was used to reduce a representative group of ketones, $RCOCH_3$ (R = Et, *i*-Pr, *t*-Bu, Ph). Asymmetric induction in the alcohol products in the range of 9 to 37% was observed. In contrast to earlier studies in which the reagent evidently contained small amounts of sodium borohydride and other minor constituents, the present results are consistent and reproducible. It was demonstrated that small quantities of sodium borohydride in the reagent can considerably diminish the optical purities of the product alcohols.

The asymmetric reduction of representative ketones, $RCOCH_3$ (R = Et, *i*-Pr, *t*-Bu, Ph), with optically active (−)-diisopinocampheylborane (from (+)-α-pinene) ($IPC_2BH$) was first reported in 1961.[2] The products obtained exhibited significant asymmetric induction (11 to 30%).

In a later study we attempted to carry out a related reduction of these ketones with (+)-$IPC_2BH$ (from (−)-α-pinene).[3] Here also we realized optically active products with optical purities in the range of 9.5 to 12.8%. Unfortunately, there appeared a serious disagreement in the absolute configuration of the product from pinacolone, as well as major differences in the magnitudes of the rotations realized (Table I).

At that time, the $IPC_2BH$ was a relatively crude product synthesized from α-pinene by hydroboration in diglyme with sodium borohydride (used in ~10% excess) and boron trifluoride etherate.[4] We felt that the discrepancy might be the result of minor components present in the crude product but deferred further study until such a time as we could develop an improved synthesis of $IPC_2BH$.

Recently, Varma and Caspi examined the reduction of these and other ketones and aldehydes by $IPC_2BH$.[5] They utilized borane–THF for the synthesis of their reagent.[4] They realized still different results (Table I). These authors also proposed a model to predict the absolute configuration of the major isomer produced.

We have recently developed an improved synthesis of $IPC_2BH$ based on hydroboration of α-pinene with borane–THF, a procedure which makes available $IPC_2BH$ in very high purity.[6] This new reagent achieves the asymmetric hydroboration of *cis*-2-butene to give after oxidation 2-butanol in an optical purity as high as 98.4%.[6] Consequently, we decided to utilize this reagent for the asymmetric reduction of the series of four ketones in the hope of resolving the conflicting results of the three earlier studies.

We have recently established that high-purity $IPC_2BH$ can also be synthesized in THF and other solvents[7] by utilizing the readily available hydroborating agent, borane–methyl sulfide.[8] Accordingly, we extended the study to (−)-$IPC_2BH$ prepared in this manner in several solvents.

## Results and Discussion

(−)-$IPC_2BH$ was prepared in THF at 0 °C (72 h) using a 15% excess of (+)-α-pinene, following the published procedure.[6] In all experiments the ketone was added to the suspension of the reagent in THF at 0 °C.

The reduction of 2-butanone required about 9 h at −30 °C but was complete within 1 h at 0 °C. The reductions of 3-methyl-2-butanone and acetophenone were complete within 2 h at 0 °C. However, the reduction of pinacolone was much more sluggish, the reaction being incomplete after 11 h at 0 °C with a further 12 h at 25 °C necessary to achieve near completion.

**Table I. Asymmetric Reduction of Ketones by Diisopinocampheylborane[a]**

| Ketone, $RCOCH_3$, R = | Registry No. | Bigley[b] % opt purity[f] | Bigley[b] Config | Munekata[c] % opt purity[f] | Munekata[c] Config | Caspi and Varma[d] % opt purity[f] | Caspi and Varma[d] Config | Present study[e] % opt purity[f] | Present study[e] Config |
|---|---|---|---|---|---|---|---|---|---|
| Ethyl | 78-93-3 | 11 | *R* | 9.5 | *R* | 7 | *S* | 16.5 | *S* |
| Isopropyl | 563-80-4 | 17 | *R* | 4 | *R* | 20 | *S* | 37 | *S* |
| *tert*-Butyl | 75-97-8 | 30 | *S* | 8.9 | *R* | 12.4 | *S* | 19.8 | *S* |
| Phenyl | 98-86-2 | 14 | *R* | 12.8 | *R* | | | 9 | *R* |

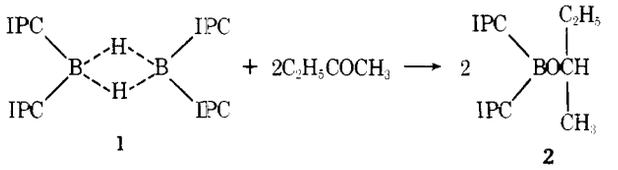
[a] All results translated to (−)-$IPC_2BH$ from (+)-α-pinene to facilitate comparison. [b] (−)-$IPC_2BH$ in diglyme from (+)-α-pinene, $NaBH_4$, and $BF_3$·$OEt_2$ (ref 2). [c] (+)-$IPC_2BH$ in diglyme from (−)-α-pinene, $NaBH_4$, and $BF_3$·$OEt_2$ (ref 3). [d] (−)-$IPC_2BH$ in THF from (+)-α-pinene and borane–THF. [e] (−)-$IPC_2BH$ in THF from (+)-α-pinene and borane–THF, using the latest improved synthesis (ref 6). [f] Based on the following $[\alpha]_D$ values for 100%: 2-butanol, *R* −13.5°, P. J. Leroux and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 41 (1951); 3-methyl-2-butanol, *S* +5.34°, R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **103**, 1957 (1913); 3,3-dimethyl-2-butanol, *S* +8.1°, P. Newman, P. Lutkin, and K. Mislow, *J. Am. Chem. Soc.*, **80**, 465 (1958); 1-phenylethanol, *R* +42.85°, R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911). Absolute configuration from W. Klyne and J. Buckingham, "Atlas of Stereochemistry", Oxford University Press, New York, N.Y., 1974.

**Table II. Reduction of Ketones with High Purity (−)-Diisopinocampheylborane in THF**

| Ketone, $RCOCH_3$, R =, and mmol[a] | Reaction condition | $H_2$ on hydrolysis, mmol | α-Pinene displaced, mmol | After the reaction ROH Yield,[b,c] % | ROH $[\alpha]^{25}_D$ | ROH Opt purity, % | ROH Config | Unreacted ketone, mmol |
|---|---|---|---|---|---|---|---|---|
| Ethyl, 50 | 0 °C, 1 h | | | 95 (72) | +1.80° | 13.4 | *S* | |
| Ethyl, 50 | −30 °C, 9 h | | | 92 (73) | +2.23° | 16.5 | *S* | |
| Isopropyl, 50 | 0 °C, 2 h | 13.5 | 15.8 | 97.5 (72) | +1.98° | 37.0 | *S* | |
| *tert*-Butyl, 50 | 0 °C, 11 h and 25 °C, 12 h | 19.6 | 20.5 | 94 (78) | +1.61° | 19.8 | *S* | 1.87 |
| Phenyl, 50 | 0 °C, 2 h | 13.2 | 13.3 | 89 (65) | +3.96° | 9 | *R* | |

[a] In each case, reactants for the synthesis of $IPC_2BH$ were: 115 mmol of α-pinene, 50 mmol of $BH_3$, and 50 mmol of $IPC_2BH$. [b] Analyzed by GC using *n*-dodecane as an internal standard. [c] Figures in the parentheses indicate isolated yield.

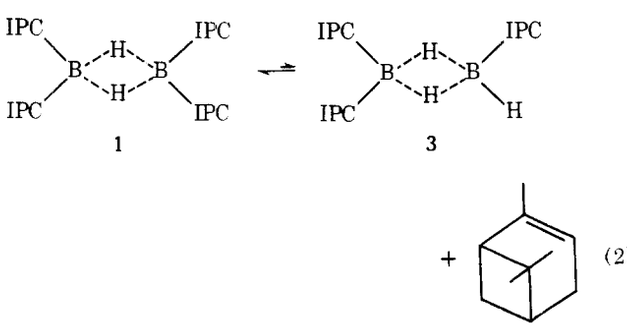
In the case of 2-butanone, the reaction appears to be a simple reduction, involving addition of the B–H bond to the carbonyl group to give the borinic ester **2** (eq 1). (Diisopinocampheylborane actually exists as the dimer **1**, *sym*-tetraisopinocampheyldiborane,[9] as shown in eq 1.)



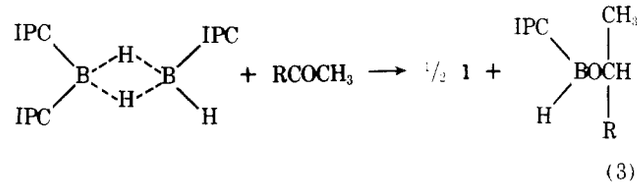

1 2 (1)

However, in the case of the other three ketones, a significant amount of α-pinene appeared in the reaction mixture during the reduction. Following completion of the reduction, hydrolysis of the reaction mixture produced hydrogen in amounts equivalent to the α-pinene formed.

We attribute the formation of α-pinene to a small equilibrium dissociation of the reagent, *sym*-tetraisopinocampheyldiborane, **1**, into α-pinene and triisopinocampheyldiborane[10,11] (**3**) (eq 2). Thus, in cases where the reaction of the ketone with the simple dimer (eq 1) is relatively slow, a significant amount of the reaction can proceed through **3** (eq 3).




1 3 (2)




(3)

This proposed mechanism is consistent with the displacement of α-pinene previously observed in the hydroboration of trans and hindered olefins[11] and nicely accounts for the appearance of α-pinene in the reduction of the more hindered ketones and the formation of an equivalent amount of hydrolyzable hydride in the reaction product.

Two procedures were utilized for the isolation of the products. For ketones other than acetophenone, the reaction mixtures, following the reduction, were oxidized with alkaline hydrogen peroxide (converting the borinic acid moiety into boric acid and isopinocampheol). The alcohol products from the ketones were then isolated by distillation. In the case of acetophenone, the similarity in the bp of isopinocampheol and 1-phenylethanol led to a modified procedure. In this case, the alcohol was distilled from the diisopinocampheylborinic intermediate following hydrolysis, without oxidation of the intermediate. Finally, the alcohol products from both procedures were subjected to preparative GC. The optical rotations and optical purities are summarized in Table II.

The results reveal that 2-butanone, 3-methyl-2-butanone, and 3,3-dimethyl-2-butanone with (−)-$IPC_2BH$ yield the corresponding *S* alcohols in 16.5, 37, and 19.7% optical purity, respectively. The values are significantly higher than those reported by Caspi and Varma, presumably a consequence of

the higher optical purity of the present reagent. The configurations realized agree with those achieved by Caspi and Varma but disagree with our earlier results.

For these three ketones the observed configuration agrees with the model they proposed. However, acetophenone, reduced by (−)-$IPC_2BH$, provided *R*-1-phenylethanol. The formation of this isomer is contrary to that predicted from their model.

Their model assumes a mechanistically simple reduction by $IPC_2BH$ or its dimer **1**. However, of the ketones studied, this is true only for methyl ethyl ketone. Reduction of the more hindered ketones apparently proceeds in part through **1** (eq 1) and in part through **3** (eq 3). Evidently it is too much to hope that a single model can handle such different processes.

We have recently developed a simple synthesis of monoisopinocampheylborane. Its use in the reduction of ketones appears to be mechanistically simple and its application may provide a definitive test of the utility of the Caspi–Varma model.

We briefly explored the question as to whether the presence of excess sodium borohydride, present in the product from the earlier synthetic procedure for $IPC_2BH$ in diglyme, could have influenced the earlier results.[2,3] The reaction of sodium borohydride with ketones in diglyme is very slow, if not negligible, at these temperatures.[12] However, we observed that the presence of 10% sodium borohydride in a reaction mixture of 3-methyl-2-butanone and (−)-$IPC_2BH$ speeded up the reaction of the latter two components and lowered drastically the optical purity of the *S*-3-methyl-2-butanol produced to 2%. This could account for the lower optical rotations observed in the earlier studies but not for the variations in the sign. The presence of variable amounts of **3** in the crude reagents then used could affect the sign of rotation, although we cannot at this time say that this was indeed the responsible factor.

In any event, it is gratifying that our present results agree so well with those realized by Caspi and Varma.

Borane–methyl sulfide (BMS) is finding increasing application as a hydroborating agent because of a number of advantages over $BH_3$·THF.[7] Recently we demonstrated the versatility of this readily available reagent for the convenient preparation of a number of valuable borane reagents.[7] Thus we prepared very pure (−)-$IPC_2BH$ in a wide variety of solvents using BMS as the hydroborating agent. Hence it seemed desirable to explore the utilization of this reagent for the asymmetric reduction of this ketone in representative solvents and to compare the optical purities of the alcohol produced with those realized with the high optical purity reagent in THF.

The solvents utilized were THF, ethyl ether (EE), $CH_2Cl_2$, pentane, and diglyme (DG). 3-Methyl-2-butanone was taken as a representative ketone. (−)-$IPC_2BH$ in THF, EE, $CH_2Cl_2$, pentane, and DG were prepared from BMS following the procedure reported earlier.[7] The reductions were carried out as before and the optical purities of the *S*-3-methyl-2-butanol obtained were in the range of 29–30.5%, irrespective of the particular solvent utilized. The reductions by this reagent of 2-butanone, 3,3-dimethyl-2-butanone, and acetophenone in THF were also carried out. The products, *S*-2-butanol, *S*-3,3-dimethyl-2-butanol, and *R*-1-phenylethanol, were obtained in 12, 17, and 9.8% optical purity, respectively. As before, α-pinene was displaced in all of the cases, except for 2-butanone.

These results are comparable to those realized with the high optical purity reagent in THF reported in the present study. The BMS procedure thus offers an advantage over the $BH_3$·THF procedure in that the preparation of $IPC_2BH$ and its utilization for reduction is more convenient, utilizing a commercially available reagent, and is complete in less time (48 h, compared to 96 h in the case of the $BH_3$·THF procedure) with comparable optical purities of the product alcohols produced.

## Experimental Section

**Materials.** THF, diglyme, EE, $CH_2Cl_2$, pentane, and $BF_3$·$OEt_2$ were purified by standard procedures.[13] Borane in THF was prepared from $NaBH_4$ and $BF_3$·$OEt_2$.[13] The borane·THF solution was standardized by hydrolyzing an aliquot of the solution with glycerine–water–THF mixture and measuring the hydrogen evolved.[13] BMS (Aldrich) was analyzed for hydride concentration as in the case of borane·THF and used directly. 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 $[\alpha]^{26.5}_D$ +48.7° and an optical purity of 95.2%.[14] The optical rotations were measured in a Zeiss polarimeter.

**Reduction of 3-Methyl-2-butanone with (−)-$IPC_2BH$ in THF.** An oven-dried, 250-mL flask, equipped with a septum inlet, a magnetic stirring bar, and a stopcock, connected to a mercury bubbler was cooled in an ice bath under a slow stream of nitrogen. The flask was charged with 17 mL of 2.94 M borane in THF (50 mmol), 5.67 mL of *n*-dodecane (25 mmol), an internal standard for GC, and 4 mL of THF. (+)-α-Pinene (18 mL) (115 mmol) was then added in 10 min. The reaction mixture was stirred at 0 °C for 2 h and then kept in the cold room (−2 °C) for 70 h. An aliquot of the supernatant liquid was then oxidized and analyzed for α-pinene by GC using a 12 ft × 0.25 in. column packed with 10% Carbowax 20M on Chromosorb W containing 0.5% Armac. 3-Methyl-2-butanone (5.35 mL) (50 mmol) was then added at 0 °C, and the reaction mixture was stirred for 2 h at 0 °C, at which time the heavy white precipitate lightened considerably. 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, 40 °C). The aqueous phase was saturated with anhydrous $K_2CO_3$ and the THF layer separated. The aqueous phase was extracted with three 30-mL portions of ether. The combined extract was washed once with saturated brine solution and then dried over anhydrous magnesium sulfate for 4 h. An aliquot of this solution was then analyzed for α-pinene and 3-methyl-2-butanol. The results are summarized in Table II. 3-Methyl-2-butanol was then isolated in 72% yield by distillation using a 30-cm Widmer column. It was further purified through preparative GC using a 5 ft 20% SE-30 column (75 °C): $n^{20}_D$ 1.4118, $[\alpha]^{25}_D$ +1.98°, and an optical purity of 37%.

**Reduction of Acetophenone with (−)-$IPC_2BH$ in THF.** With the usual experimental setup, (−)-$IPC_2BH$ in THF (50 mmol) was prepared as described earlier. To this reagent at 0 °C was added 5.83 mL of acetophenone (50 mmol). The reaction mixture assumes a pale yellow color. The heavy white precipitate of $IPC_2BH$ lightens considerably within 15–30 min. The reaction mixture was stirred at 0 °C for 2 h, in which time the yellow color faded completely. It was methanolyzed (volume of $H_2$ noted) and then stirred with 10 mL of saturated aqueous potassium carbonate solution for 1 h. The organic layer was dried over anhydrous potassium carbonate overnight. THF and most of the α-pinene were removed under aspirator vacuum (15 mm, 3 h) and 1-phenylethanol was distilled from the diisopinocampheylborinic intermediate under high vacuum (0.5 mm). The distillate, bp 55–6 °C (0.5 mm) (4.035 g, 65%), was collected. This still contained a little amount of α-pinene. 1-Phenylethanol was purified from the α-pinene by preparative GC, using a 5 ft Carbowax 20M column (150 °C): $n^{20}_D$ 1.5265, $[\alpha]^{22}_D$ +3.96°, and an optical purity of 9%.

**Reduction of 3-Methyl-2-butanone with (−)-$IPC_2BH$ (Made from (+)-α-Pinene and BMS) in THF.** (−)-$IPC_2BH$ in THF (50 mmol) was prepared following the procedure described earlier.[7] To this reagent at 0 °C was added 5.35 mL of 3-methyl-2-butanone (50 mmol) and the reaction mixture was stirred at 0 °C for 2 h as before. Oxidation and workup procedure were similar to that described in the earlier section. Distillation using a 30 cm Widmer column afforded 3.53 g (70%) of 3-methyl-2-butanol. It was further purified through preparative GC using a 20% SE-30 column: $n^{20}_D$ 1.4117, $[\alpha]^{25}_D$ +1.63°, and an optical purity of 30.5%.

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**Registry No.**—Diisopinocampheylborane, 62929-17-3; borane, 13283-31-3; (+)-α-pinene, 7785-70-8; 3-methyl-2-butanol, 598-75-4; 1-phenylethanol, 60-12-8.

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# Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. Natural-Abundance Nitrogen-15 Chemical Shifts of Ring-Methylated *N,N*-Dimethylanilines. Effect of Inhibition of Conjugation


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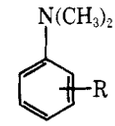
The $^{15}$N chemical shifts of *N*-methylaniline, *N,N*-dimethylaniline, several ring-alkylated *N,N*-dimethylanilines, and their conjugate acids have been measured at the natural abundance level. Relative to aniline, N-methylation induces upfield shifts, in contrast to the downfield shifts expected on $\alpha$-substitution. The influence of ring methyl substitution on the resonance position of dimethylaniline is the same as that reported for aniline, except for ortho substitution. Under these conditions, considerably larger upfield shifts are exhibited. In contrast, the chemical shifts of the conjugate acids of the dimethylanilines all lie within a 2-ppm range. The large diamagnetic shifts induced by ortho methyl substitution are attributed to the torsional distortion of the dimethylamino group from the optimum conformation for nitrogen lone-pair localization. The results correlate with appropriate aniline $^{13}$C chemical shifts and, especially, with the ionization potentials of the corresponding aniline $\pi$ orbitals, which are a measure of nitrogen lone-pair $\pi$ delocalization. The diamagnetic $\alpha$ effects also may be rationalized by this means. The nitrogen shifts of 2,6-diethyl- and 2,6-diisopropyl-*N,N*-dimethylaniline have been used to estimate torsional angles of 77 and 80°, respectively.

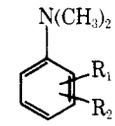

Correlations between the behavior of substituted anilines and extent of nitrogen lone-pair delocalization have been explored by investigation of myriad physical and chemical properties. The several relationships between nuclear magnetic resonance (NMR) properties and various functions of electron distribution make NMR spectroscopy eminently suitable for this type of study. Particularly when the NMR behavior of the nitrogen nucleus itself is affected, nitrogen NMR spectroscopy has been a useful probe of these phenomena. The first studies exploiting this possibility using substituted $^{15}$N-enriched anilines,[1] as well as prior work with $^{14}$N NMR,[2] demonstrated the direct relationship between nitrogen resonance positions and substituent conjugative electronic properties. Subsequently, the nonconjugative methyl group was shown also to influence aniline nitrogen chemical shifts[3] in a systematic, additive manner which could be related to polarization in the $\sigma$ framework.[4] Because nitrogen lone-pair delocalization is possible with both types of substituents, it is of interest to determine the behavior of the nitrogen resonances when delocalization is in fact inhibited. Several lines of evidence[5-9] indicate that this is the case with ortho-methyl-substituted *N,N*-dimethylanilines. Consequently, we have determined the natural-abundance $^{15}$N chemical shifts of a selected group of these compounds, represented in **1a–5**, in order to assess the influence of sterically inhibited conjugation on the resonance positions.

## Experimental Section

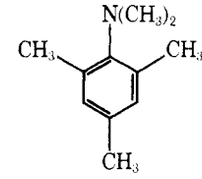
Compounds **1–5** were either commercially available or were prepared by methylation of the primary amine with trimethyl phosphate.[10] Infrared and $^1$H NMR spectra were consistent with the structures, and boiling points agreed with reported values.[11]



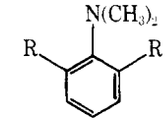
**1a**, R = H
**b**, R = 2-$CH_3$
**c**, R = 3-$CH_3$
**d**, R = 4-$CH_3$



**2a**, $R_1$ = 2-$CH_3$; $R_2$ = 3-$CH_3$
**b**, $R_1$ = 2-$CH_3$; $R_2$ = 6-$CH_3$



**3**



**4**, R = $C_2H_5$
**5**, R = *i*-$C_3H_7$

Spectra were determined on a JEOL PS/PFT-100 spectrometer as described elsewhere.[12] Initially, the free bases were run using 10–15% deuteriobenzene as internal lock in solution, and were referenced to an external capillary of 2.9 M enriched ammonium chloride in 1 M HCl. Subsequently, we noted that the resonance positions were somewhat solvent sensitive. For example, the resonance position of **1a** as a pure liquid (see below) differs by 1.5 ppm from that arising from a 25 vol % solution in cyclohexane. On the other hand, **3** remains unaffected upon dilution of the pure liquid to 25% in cyclohexane, yet moves 4 ppm downfield when 15% deuteriobenzene is used as internal