Table II. Syntheses of Alkylboron Derivatives by the Hydroboration of Olefins with $H_2BCl{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$

Dialkylboron derivative	Solvent	Yield, %	Bp, °C (mm)
Methyl di-*n*-butylborinate	Pentane	93[a]	
Methyl di-*sec*-butylborinate	Pentane	89[a]	
Methyl diisobutylborinate	Pentane	93[a]	
Methyl dicyclopentylborinate	Ether	89[b]	
Diisobutylchloroborane	Ether	84[c]	78–80 (62)
Dicyclopentylchloroborane	Pentane	79[c]	69–70 (1.2)
Dicyclopentylchloroborane	Ether	81[c]	69–70 (1.2)
Di-*n*-butylchloroborane	Ether	85[c]	68–70 (19)
n-Octyldichloroborane	Pentane	85[c]	92–94 (19)

[a] GLC yield. [b] Yield determined by ^1H NMR using benzene as the internal standard. [c] Yields by isolation of the product.

mixture followed by distillation (eq 4). The results of the syntheses of the representative dialkylboron derivatives are given in Table II.

$$R_2BCl{\cdot}SMe_2 + R'OH \rightarrow R_2BOR' + Me_2S + HCl \quad (4)$$

The reaction of $HBCl_2{\cdot}SMe_2$ with olefins is slow and incomplete in pentane or ether, similar to the slow reaction of the etherate $HBCl_2{\cdot}OEt_2$.[2] Again, as in the case of the etherate,[2] $HBCl_2{\cdot}SMe_2$ reacts with olefins cleanly and quantitatively at 25 °C in pentane in the presence of 1 mol equiv of BCl_3 to give the corresponding alkyldichloroborane, $RBCl_2$. The $Cl_3B{\cdot}SMe_2$ precipitates from the reaction medium during the reaction (eq 5). The $RBCl_2$ is readily isolated from the reaction mixture by distillation following removal of the solid $Cl_3B{\cdot}SMe_2$ by filtration under nitrogen. *n*-Octyldichloroborane was isolated in 85% yield by this method.

$$\text{olefin} + HBCl_2{\cdot}SMe_2 \xrightarrow[BCl_3]{\text{pentane}} RBCl_2 + Cl_3B{\cdot}SMe_2\downarrow \quad (5)$$

The following experimental procedure is typical. The addition compound, $Cl_3B{\cdot}SMe_2$, mp 86–87 °C, was prepared by adding boron trichloride to an equimolar amount of methyl sulfide. The $H_2BCl{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$ were then prepared by mixing the two reagents, $Cl_3B{\cdot}SMe_2$ and $H_3B{\cdot}SMe_2$,[10] in the stoichiometric ratios (eq 1, 2). Cyclopentene (210 mmol) was dissolved in 90 mL of pentane or ether at 0 °C under nitrogen. While stirring at 0 °C, 100 mmol of $H_2BCl{\cdot}SMe_2$ was slowly added and the stirring continued for 2 h at 25 °C. The solvent was then removed using a water aspirator and pure dicyclopentylchloroborane[12] was obtained by distillation at 69–70 °C (1.2 mm) in 79–81% yield. The methyl dicyclopentylborinate was synthesized in 89% yield by methanolyzing the reaction mixture of cyclopentene and $H_2BCl{\cdot}SMe_2$[13] with 100% excess methanol, followed by removal of the solvent, the excess methanol, and the hydrogen chloride with a water aspirator. The regiospecificity in the hydroboration with $H_2BCl{\cdot}SMe_2$ was established as described earlier for $H_2BCl{\cdot}OEt_2$.[1]

For the synthesis of *n*-octyldichloroborane, 50 mmol of 1-octene was dissolved in 61 mL of pentane and cooled to 0 °C; 25 mL of a 2 M solution of BCl_3 in pentane was added. While the mixture stirred at 0 °C, 50 mmol of $HBCl_2{\cdot}SMe_2$ was slowly added. The mixture was stirred for 2 h at 25 °C. The procedure then follows that previously described for the isolation of the $RBCl_2$ using $HBCl_2{\cdot}OEt_2$. *n*-Octyldichloroborane was isolated in 85% yield.

Although the reactivity and usefulness of $H_2BCl{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$ are comparable with those of the corresponding chloroborane etherates reported previously, these new reagents are far more advantageous and convenient to use, as a consequence of their indefinite stability at room temperature and their availability as neat reagents.

Because of the thermal stability of $H_2BCl{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$, these reagents will surely find their major place in the laboratory along with other valuable hydride reagents. This would greatly facilitate application of the recently discovered many synthetically useful reactions of R_2BCl and $RBCl_2$ and their derivatives.[3-8]

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(12) In the case of unhindered R_2BCl, like *n*-Bu_2BCl, the methyl sulfide addition compound breaks up completely upon vacuum distillation only, whereas in hindered cases like *sec*-Bu_2BCl, the Me_2S addition compounds breaks up completely at 25 °C under aspirator vacuum (10–20 mm).
(13) NMR examination of $H_2BCl{\cdot}SMe_2$ reveals the presence of small amounts of $H_3B{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$. Consequently, the maximum yields of ~93% for R_2BCl (Table II) probably correspond to the actual amount of $H_2BCl{\cdot}SMe_2$ present in the reagent. Distillation readily removes the minor components, R_3B and $RBCl_2$.
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Lithium *B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonyl Hydride. A New Reagent for the Asymmetric Reduction of Ketones with Remarkable Consistency

Summary: Lithium *B*-isopinocampheyl-9-borabicyclo-[3.3.1]nonyl hydride [Li(HB-IPC-9-BBN)], a highly hindered trialkylborohydride containing an asymmetric alkyl group, reduces rapidly and quantitatively a variety of ketones to the corresponding optically active alcohols, consistently enriched in the *R* enantiomer.

Sir: The asymmetric reduction of ketones has been examined with a number of chiral metal hydride complexes.[1] In particular, lithium aluminum hydride complexes with chiral alkaloids (ephedrine, quinine, cinchonine, etc.), chiral amino alcohols [(2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol], and monosaccharides (3-*O*-benzyl-1,2-cyclohexylidene-α-D-glucofuranose) have been recently explored in detail. Unfortunately, such reagents appear not reliable for stereochemical correlations. In the majority of cases, the precise structures of the reducing species are not well defined. Further, both enantiomeric forms of the complexing agent may not be available, thereby limiting the choice of the enantiomer to be synthesized.

Table I. Asymmetric Reduction of Representative Ketones with Lithium *B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonyl Hydride in Tetrahydrofuran at −78 °C[a,b]

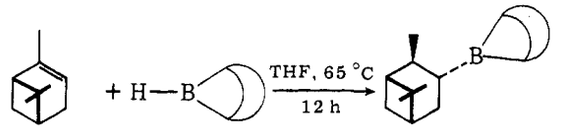
Ketone	Workup procedure[c]	Alcohol[d] (lit.[e] 100% e.e.)	$[\alpha]^{25}_D$, deg, measd	Optical purity, %	Confign
2-Butanone	A	2-Butanol (13.5)	−3.85	29	*R*
2-Hexanone	A	2-Hexanol (11.6)	−3.46	30	*R*
3-Methyl-2-butanone	A	3-Methyl-2-butanol (5.3)	−1.91	36	*R*
3,3-Dimethyl-2-butanone	A	3,3-Dimethyl-2-butanol (8.1)	−0.23	3	*R*
4-Methyl-2-pentanone	A	4-Methyl-2-pentanol (20.5)	−3.38	16	*R*
Acetophenone	B	1-Phenylethanol (42.9)	+6.95	17	*R*
2-Methyl-3-pentanone	A	2-Methyl-3-pentanol (9.8)	+3.61	37	*R*
Propiophenone	B	1-Phenylpropanol (27.7)	+3.6	13	*R*
2-Methylcyclohexanone[f]	B	*cis*-2-Methylcyclohexanol (21.2)	−3.05	14	1*R*,2*S*

[a] Reactions were carried out essentially in stoichiometric ratio of reagent and ketone (10% excess hydride); concentrations were 0.3 M. [b] Precooled hydride solution (−78 °C) was added to the ketone solution of THF maintained at −78 °C; reductions were essentially over in 1 h. [c] A, oxidative workup; B, hydrolysis and direct distillation. [d] Alcohols were isolated in 70–80% range and purified by preparative GLC. [e] W. Klyne and J. Buckingham, "Atlas of Stereochemistry", Oxford University Press, New York, N.Y., 1974. The values listed are the maximum values for $[\alpha]_D$, degree, reported, presumably 100% e.e. or close to that quality. [f] One mole equivalent of hydride was added to 2 mol equiv of the ketone.

Very recently conditions were developed for the synthesis from (+)-α-pinene of (−)-diisopinocampheylborane (IPC_2BH) in high optical purity.[2] The hydroboration of *cis*-2-butene with this high purity reagent followed by oxidation provided (*R*)-(−)-2-butanol in 98.4% e.e. (enantiomeric excess), indicating essentially complete asymmetric induction. It has also been examined in considerable depth for the asymmetric reduction of ketones.[3] Unfortunately, the rate of reduction with hindered ketones is quite sluggish and side reactions, such as the displacement of α-pinene, occurs with possible changes in the stereochemical results.

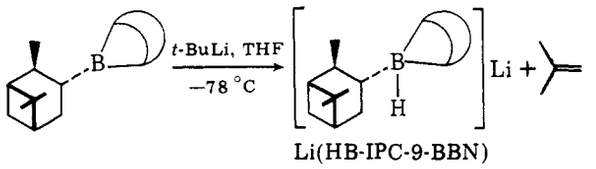
Moreover, lithium trialkylborohydrides have recently emerged as highly attractive reducing agents.[4] One of the major applications of hindered trialkylborohydrides is their ability to introduce steric control in the reduction of cyclic ketones. Thus, the discovery of lithium tri-*sec*-butylborohydride and lithium trisiamylborohydride have revolutionized procedures for the stereoselective reduction of cyclic ketones.[5,6]

In the course of our extensive study of highly hindered trialkylborohydrides, we examined a number of borohydride anions derived from *B*-alkyl-9-borabicyclo[3.3.1]nonane (B-alkyl-9-BBN) derivatives. Hydroboration of (+)-α-pinene ($[\alpha]^{23}_D$ +49.3°, 96% optically pure) with 9-BBN gives *B*-isopinocampheyl-9-BBN (B-IPC-9-BBN) in quantitative yield[7] (eq 1). This can be readily converted into the corresponding



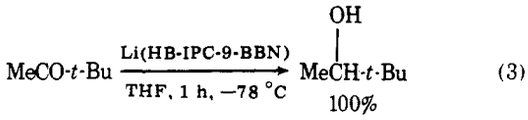
(1*R*,5*R*)-(+)-α-pinene — 100% (1)

trialkylborohydride in quantitative yield[8] (eq 2). ^{11}B NMR

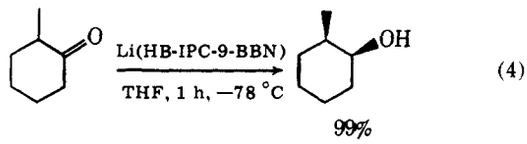


Li(HB-IPC-9-BBN) (2)

of the reagent in tetrahydrofuran (THF) solution exhibits a clean doublet at δ +6.45 (relative to $Et_2O{\cdot}BF_3$), J = 78 Hz. It is an active reducing agent and reduces completely even relatively hindered ketones such as 3,3-dimethyl-2-butanone in <1 h at −78 °C; it is also quite effective in introducing steric control in the reduction of cyclic ketones (eq 3 and 4).

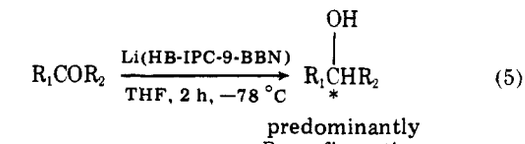


(3)



(4)

Consequently, it appeared desirable to explore the applicability of this reagent for the asymmetric reduction of ketones. Accordingly, we undertook to reduce a series of ketones of representative structural features and to examine the resulting alcohols for the magnitude of the optical induction. The general procedure adopted was to add slowly an essentially stoichiometric quantity of the reagent (precooled to −78 °C) to a THF solution of the ketone (cooled to −78 °C). The resulting mixture was stirred for 2 h at −78 °C (eq 5).



predominantly *R* configuration (5)

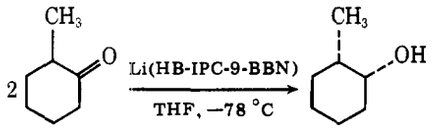
Two procedures can be used to isolate the product. The reaction mixture can be treated with alkaline hydrogen peroxide to oxidize the trialkylborane and the alcohol separated by distillation from 1,5-cyclooctanediol and isopinocampheol. Alternatively, the reaction mixture is hydrolyzed with aqueous potassium carbonate and dried and the alcohol distilled from the trialkylborane. Finally, in both procedures, the alcohol is purified by preparative GLC to remove any optically active components. The results are summarized in Table I.

Thus, 2-butanone is reduced to (*R*)-(−)-2-butanol in 29% e.e. Increasing the chain length has little effect [(*R*)-(−)-2-hexanol obtained in 30% e.e.].

The introduction of a single alkyl substituent in the α position increases the optical induction [(*R*)-(−)-3-methyl-2-butanol, 36% e.e.]. However, introduction of two alkyl substituents decreases the asymmetric induction [(*R*)-(−)-3,3-dimethyl-2-butanol, 3% e.e.]. Going from a particular alkyl

methyl ketone to the corresponding alkyl ethyl ketone does not influence the selectivity significantly [(*R*)-(+)-2-methyl-3-pentanol, 37% e.e.]. Phenyl alkyl ketones also yield alcohols enriched in the *R* enantiomer.

Reduction of 2-methylcyclohexanone represents an interesting case. The ketone already has an asymmetric center. Fortunately, the product is *cis*-2-methylcyclohexanol in 99% isomeric purity. Consequently, the product will contain only two of the four possible diastereomers.[9] Indeed, the product is enriched in (1*R*,2*S*)-(−)-*cis*-2-methylcyclohexanol (eq 6).



(6)

racemic (1*R*,2*S*)-(−)

It is clearly evident from the above discussion that all of the alcohols obtained from the reduction of nine different ketones with this new reagent [from (+)-α-pinene] are consistently enriched in the enantiomer with the *R* configuration.

The following procedure for the asymmetric reduction of 2-hexanone to (*R*)-(−)-2-hexanol is representative. An oven-dried 500-mL flask with a side arm, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler was flame dried and cooled under a dry stream of nitrogen. Tetrahydrofuran, 45 mL, was introduced into the reaction flask followed by 8 mL (65 mmol) of 2-hexanone and the contents of the flask were cooled to −78 °C (dry ice–acetone). Then 164 mL (72 mmol) of a 0.44 M solution of Li(HB-IPC-9-BBN) in THF (cooled to −78 °C) was introduced slowly (~15–20 min). The resulting mixture was stirred at −78 °C for 2 h. Then it was brought to 0 °C, excess hydride was destroyed, and the organoborane was oxidized (NaOH, H_2O_2, 60 °C, 2 h). The aqueous phase was saturated with anhydrous K_2CO_3. The THF layer was separated. The aqueous phase was extracted with four 25-mL portions of ether. The combined organic extracts were dried ($MgSO_4$). The volatile solvents were largely removed by distillation through a Widmer column. The pot residue was then transferred to a smaller flask and distilled under reduced pressure, the main fraction being collected at 68–72 °C (40 mm) in a yield of 75–80%.

The 2-hexanol product was purified by preparative GLC, 10% Carbowax 20M, 6 ft × 0.5 in., and appeared to be devoid of any impurities: n^{20}_D 1.4160, $[\alpha]^{23}_D$ −3.46° (neat), 30% e.e. in *R*.

In conclusion, it should be pointed out that the new asymmetric reducing agent reduces even relatively hindered ketones rapidly and quantitatively in <2 h at −78 °C; THF solutions of this reagent appear to be quite stable. The reagent is consistent and highly promising for configurational assignments and stereochemical correlations (no exceptions observed to date). Further, the ready availability of both (+)- and (−)-α-pinene in high optical purities provides a convenient route to both enantiomers. We are actively exploring other applications of this reagent in asymmetric organic synthesis.

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