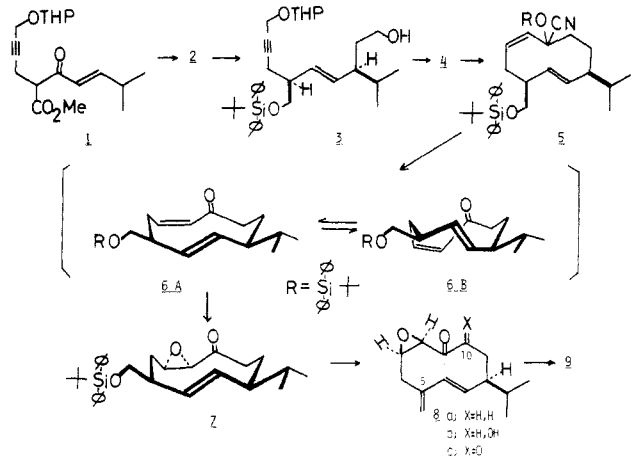
Scheme II



that our intermediate **6** should lead to the α-epoxide with high stereoselectivity.

The enone **6** was prepared in the following way. Stereoselective reduction of the ketone of 1[9] with L-Selectride followed by reduction of the ester group with $LiAlH_4$ gave the syn product **2a** (R = H) in 50% overall yield. The ratio of **2a** to the anti product was approximately 10:1.[10] Selective silylation of the diol **2a** (t-$BuPh_2SiCl/Et_3N$/DMAP; 76% yield), Claisen rearrangement of the silylated product **2b** (R = t-$BuPh_2Si$) with trimethyl orthoacetate, and reduction of the resulting ester with $LiAlH_4$ gave **3** in 50% overall yield. Tosylation of **3** and removal of the THP group (78% yield in two steps) and cis reduction of the triple bond ($Pd-BaSO_4/H_2$) gave **4a** (X = H, Y = OH). Oxidation of **4a** with MnO_2 and protected cyanohydrin formation[7] in three steps gave **4b** (X = CN, Y = OCHMeOEt) in 77% overall yield. Cyclization of **4b** with $LiN(TMS)_2$ in benzene at 80 °C gave **5a** (R = CHMeOEt) in 70% yield. Acid treatment[7] of **5a**, followed by base treatment[7] of the resulting cyanohydrin **5b** (R = H), gave **6** in 85% overall yield.[11]

Stereoselective epoxidation of **6** (t-BuOOH-KH/THF at -20 °C)[2] provided the desired epoxide **7** in 76% yield; none of the stereoisomer was detected in the crude product.[12] Rationalization for this high stereoselectivity was available by MM2 calculations of the model compound **10** as described above. They predict that the peripheral addition of peroxide should proceed through the most likely conformations[13] **6A** and (or) **6B** to give the β-epoxide **7**. Transformation[14] of **7** to periplanone B required three operations; (1) generation of the exocyclic diene at C(5); (2) introduction of the ketone at C(10); (3) epoxidation of the ketone at C(1). Deprotection of the silyl group (Bu_4NF; 81% yield) and selenation of the resulting alcohol (o-$NO_2C_6H_4SeCN$, Bu_3P/THF) and elimination of the o-nitrophenyl selenide (H_2O_2/THF) gave the diene **8a** (mp 83-86 °C) in 82% yield. The regioselective α-oxidation of **8a** ($LiN(TMS)_2$/THF at -70 °C and then $O_2/P(OEt)_3$[15]; 50% yield) and oxidation of the resulting α-hydroxy ketone **8b** (mp 109-111 °C) with PCC afforded the diketone **8c** in 70% yield. Epoxidation at C(1) of **8c** (Me_3SI/Me_2SO/NaH) gave the (±)-periplanone B (**9**) in 54% yield; the C(10)-diepoxide was also formed in 17% yield. None of this triepoxide or any stereoisomer at C(1) were detected. Satisfactory ^1H NMR (300 MHz), IR, and MS spectral properties of the synthetic (±)-periplanone B were obtained.

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Supplementary Material Available: Experimental details and spectral data of compounds in this paper (50 pages). Ordering information is given on any current masthead page.

(10) The stereostructures of syn product **2a** and anti product were determined by ^1H NMR coupling constants after conversion to the corresponding cyclic carbonates.

(11) Cyclization of **4b** (44-g scale), followed by acid and base treatments gave **6** in 58% overall yield (three steps).

(12) ^1H and ^{13}C NMR spectra and GLC, HPLC analyses of the crude reaction mixture showed the absence of the isomeric epoxide. Moreover, the structure of **7** was confirmed by the conversion of **7** to the Schreiber's intermediate.

(13) ^1H NMR spectrum of **6** at -30 °C indicated the presence of two conformers similar to conformers **10A** and **10B**.

(14) These operations were carried out in a similar manner to that reported by Schreiber[3] with several modifications. Details are available in supplementary material.

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Highly Efficient Asymmetric Reduction of α-Tertiary Alkyl Ketones with Diisopinocampheylchloroborane

Summary: (-)-Diisopinocampheylchloroborane, which reduces many aralkyl and heteroaralkyl ketones with remarkably high stereoselectivity, has now been found to reduce α-tertiary alkyl ketones with similar high enantiomeric excess. Such ketones have resisted asymmetric reduction by Alpine-Borane and many other reagents previously described.

Sir: Practical procedures for the synthesis of optically active secondary alcohols, highly useful chiral building blocks, have been actively explored by organic chemists in recent years. One convenient approach has been the chiral reduction of prochiral ketones.[2] Many new reagents have been described in the recent past to achieve such asymmetric reductions. Modifications of lithium aluminum hydride using resolved 2,2'-dinaphthol[3] and of borane, using amino alcohols,[4] are representative examples. Midland and his co-workers introduced the trialkylborane, B-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (Aldrich, Alpine-Borane)[5] and the modified borohydride reagent,

(1) Postdoctoral research associate on Grant DAAG 29-85-K-0062 from the United States Army Research Office.

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Table I. Asymmetric Reduction of Representative α-Tertiary Alkyl Ketones with Ipc_2BCl (Neat) at 25 °C

ketone	reactn time	isolated yield, %	$[\alpha]^{20}_D$, deg	% ee[a]	confign
3,3-dimethyl-2-butanone	12 days	50	+7.53 (neat)	93[b] (95)[c]	*S*
ethyl 2,2-dimethylacetoacetate	12 days	69	α^{21} +3.43 (neat, 0.5)	(84)[c]	*S*[d]
2,2-dimethylcyclopentanone	12 h	71	+24.2 (*c* 5.64, C_6H_6)	(98)[e]	(*S*)[f]
2,2-dimethylcyclohexanone	12 h	60		(91)[e]	(*S*)[f]
spiro[4.4]nonan-1-one	12 h	65	+40.53 (*c* 0.6, C_6H_6)	>100[g] (95)[e]	*S*
methyl 1-methyl-2-oxocyclopentane-carboxylate[h]	5 h		+31.2 (*c* 2.62, C_6H_6)	(93)[c]	*i*
	60 h (−25 °C)[j]			(96)[c]	
1-methyl-2-norbornanone[h]	15 h			(89)[e]	1*S*,2*S*

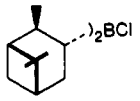
[a] Values in parentheses are by capillary GC analyses. [b] Based on 8.1° (neat).[12] [c] Analysis of the (+)-α-methoxy-α-(trifluoromethyl)phenyl acetate. [d] Reference 13. [e] Analysis of the (−)-menthyl chloroformate derivative. [f] Based on analogy with the reduction of spiro[4.4]nonan-1-one by Ipc_2BCl. [g] Based on +39.8° (*c* 1.5, C_6H_6).[14] [h] Since the tertiary center was optically active, one-half equiv of the reagent was used to reduce the more reactive isomer. [i] Absolute configuration not yet assigned. [j] Reaction carried out in THF, 1 M.

Table II. Comparison of Chiral Induction Obtained by Various Reagents in Reduction of 3,3-Dimethyl-2-butanone

reagent	reactn conditn	% ee
Alpine-Borane	neat, 25 °C, 40 days	0.6[a]
Alpine-Borane	neat, 6 kbar, 9 days	inert[b]
Binal-H	THF, −100 °C	inert[c]
NB-Enantride	−100 °C, THF/Et_2O/pentane	2[d]
TBDAH[e]		
amino alcohol/borane[f]	THF, 0 °C	96
amino alcohol/borane[f]	THF, −78 °C	89
Ipc_2BCl	neat, 25 °C, 12 days	95

[a] Reference 3. [b] Reference 5b. [c] Reference 9. [d] Reference 6. [e] Reference 8. Excellent results are reported for this enzymatic reduction, but pinacolone was not included. [f] Amino alcohol prepared by treating the ester of isoleucine with excess phenylmagnesium bromide. Amino alcohol/borane ratio was 1:2. Reference 4.

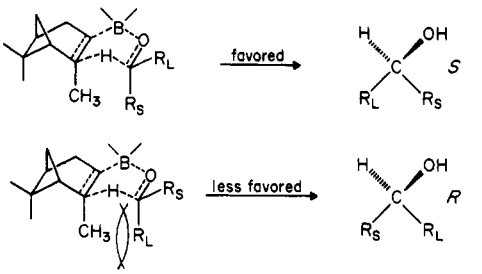
NB-Enantride,[6] for such chiral reductions. Another modified borohydride reagent, K 9-*O*-DIPGF-9-BBNH, is highly promising.[7] An enzymatic chiral reduction of ketones was recently reported by E. Keinan.[8] We have recently reported[9] an unusually highly effective procedure to achieve asymmetric reductions of prochiral aromatic ketones with the new reagent, diisopinocampheylchloroborane, Ipc_2BCl.



Although most of the nonenzymatic reagents reduce prochiral arylalkyl ketones in high optical purity, not much success has been achieved in the realm of aliphatic ketones, especially for relatively hindered derivatives. NB-Enantride, while reducing straight-chain alkyl ketones with relatively high efficiency, is surprisingly inefficient if one side of the carbonyl moiety is bulky. Alpine-Borane and Binal-H proved inert for the reduction of pinacolone. Alpine-Borane left the ketone unaffected even at 6000 atm![10]

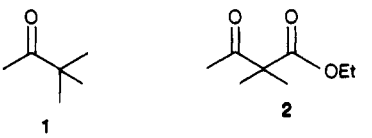
In pursuit of an efficient reagent for all classes of ketones, we continued to explore the characteristics of Ipc_2BCl. Although it did not give promising results for straight-chain prochiral alkyl ketones, it did reveal exceptionally high efficiency for ketones containing a bulky group attached to the carbonyl center. Thus, while 2-butanone and 3-methyl-2-butanone are reduced rapidly at −25 °C (THF, 1 M) with only 4% and 31% ee, respectively,

Scheme I



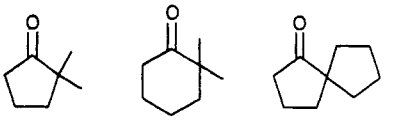
the reduction of 3,3-dimethyl-2-butanone is accomplished with an induction as high as 95%, even though the reaction is relatively slow (12 days). The alcohol is isolated readily, utilizing a nonoxidative removal of the boron byproducts by complexation with diethanolamine.[9]

We then examined the reduction of a series of representative α-tertiary alkyl ketones with Ipc_2BCl. The reduction of ethyl 2,2-dimethylacetoacetate (**2**) resembles pinacolone (**1**) in its slow rate of reduction, but the optical yield, 84% ee, is very good.



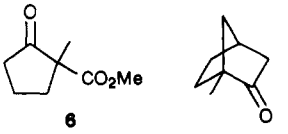
1 **2**

The reduction of the alicyclic derivatives is considerably faster, but the optical yields are excellent. For example, 2,2-dimethylcyclopentanone (**3**) gives product in 98% ee. 2,2-Dimethylcyclohexanone (**4**) yields the corresponding alcohol in 91% ee, and spiro[4.4]nonan-1-one (**5**) gives alcohol in 95% ee.



3 **4** **5**

We also examined the reduction of methyl 1-methyl-2-oxocyclopentanecarboxylate (**6**) and 1-methyl-2-norbornanone (**7**). Since these ketones consist of a racemic



6 **7**

pair of isomers, we treated them with one-half an equivalent of the reagent, Ipc_2BCl. Isolation of the alcohol revealed that **6** had been reduced in 93% ee (96% ee at −25 °C) and **7** had been reduced in 89% ee. All reductions are at 25 °C, unless otherwise indicated.

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All of the reductions with (-)-Ipc_2BCl (from (+)-α-pinene) gave predominantly *S* configurations in the product alcohols. As noted previously, the reaction is considerably faster with the cyclic and bicyclic ketones than with the acyclic derivatives. Although we did not explore which functional groups can be accommodated, it is clear from the reduction of **2** and **6** that ester groups do not interfere. Possibly, many other groups will prove to be inert to the reagent.

The mechanism of reduction of Ipc_2BCl is believed to be similar to that proposed by Midland[10] for the Alpine-Borane reductions via a six-membered, cyclic, "boat-like" transition state. The eliminating boron moiety and the β-hydrogen are cis, probably resulting in a syn elimination. In the preferred transition state, only the smaller alkyl group (R_S) has to face the syn axial methyl interaction, while the bulky alkyl group (R_L) assumes an equatorial-like orientation. This explains the formation of predominantly *S* alcohols. The *R* alcohol produced in the reduction of pivalophenone[9] arises from the fact that the bulky *tert*-butyl group occupies the equatorial position in the transition state (Scheme I).

A comparison of various other reagents tested for the asymmetric reduction of 3,3-dimethyl-2-butanone, **1** (Table II), shows that Ipc_2BCl is superior to most of them for the reduction of prochiral α-tetriary ketones. Only Itsuno's isoleucine-derived borane reagent appears to be comparable. Unfortunately, the generality of Itsuno's reagent for such reductions has not yet been demonstrated. In addition, the abundant availability of both forms of α-pinene, the simple preparative procedure for Ipc_2BCl, the simple experimental conditions (room temperature, neat), and the easy workup add to the attractiveness of the Ipc_2BCl reagent. A further advantage at the present time is the fact that Ipc_2BCl is a well-defined chemical, whereas the precise nature of the Itsuno reagent remains to be defined.

The following procedure is representative. An oven-dried, 100-mL, round-bottomed flask equipped with a septum-capped side arm, magnetic stirring bar, and stopcock adaptor connected to a mercury bubbler was assembled while hot and flushed with a stream of nitrogen.[11] Ipc_2BCl (8.8 g, 27.5 mmol) was transferred into the flask under a nitrogen atmosphere in a glovebag. While stirring, 3,3-dimethyl-2-butanone (3.13 mL, 25 mmol) was added via a syringe. Ipc_2BCl goes into solution within a few hours. Aliquots (0.1 mL) of the reaction mixture was quenched with methanol and followed by ^{11}B NMR spectroscopy for the completion of the reaction. When the reaction was complete (12 days), the α-pinene formed during the reaction was removed under reduced pressure (0.1 mmHg, 8 h). The residue was dissolved in Et_2O (50 mL) and diethanolamine (2.2 eq) was added. The separated solid was filtered off after 2 h and washed with pentane, and the combined filtrate was concentrated by distilling off the volatiles. The residual liquid distilled at 117–119 °C, giving 1.28 g (50% yield) of 3,3-dimethyl-2-butanol, $[\alpha]^{20}_D$ +7.53° (neat), after purification by preparative gas–liquid chromatography on Carbowax 20M; 93% ee based on $[\alpha]_D$ 8.1° (neat) for the maximum reported rotation.[12] GC analysis of its menthyl chloroformate derivative (made from (-)-menthyl chloroformate, Aldrich) on Supelcowax glass capillary column (15 M) showed a composition of 97.5% *S* + 2.5% *R* (i.e., 95% ee).

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Asymmetric Reduction of α-Keto Esters with Potassium 9-*O*-(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane. Chiral Synthesis of α-Hydroxy Esters with Optical Purity Approaching 100% ee

Summary: The asymmetric reduction of α-keto esters with potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane (K 9-*O*-DIPGF-9-BBNH) to the corresponding α-hydroxy esters in optical purities approaching 100% ee has been achieved.

Sir: Optically active α-hydroxy esters are important intermediates for chiral syntheses of biologically active substances such as steroids,[2] pheromones,[3] antibiotics,[4] and peptides.[5] One of the most convenient methods for the preparation of optically active α-hydroxy esters is the asymmetric reduction of the corresponding α-keto esters with chiral reducing agents.[6] Among such reducing agents, Alpine-Borane[7] (neat) has proven to be the most promising reducing agent now available for the reduction of α-keto esters, especially *tert*-butyl α-keto esters, achieving optical purities approaching 100% ee.[6b,c] However, its reaction with relatively hindered α-keto esters is very slow, accompanied by poor optical yields. For example, methyl 3-methyl-2-oxobutanoate can be reduced to the corresponding α-hydroxy ester in only 11% ee.[6b,c] We now

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