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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Herbert C. Brown,* J. Chandrasekharan
P. V. Ramachandran[1]
Richard B. Wetherill Laboratory
Purdue University
West Lafayette, Indiana 47907
Received June 10, 1986

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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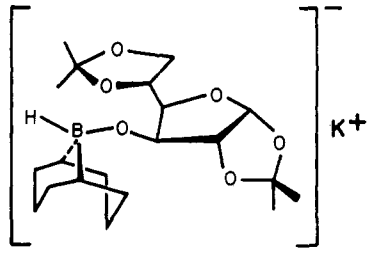
Table I. Asymmetric Reduction of Representative α-Keto Esters with K 9-*O*-DIPGF-9-BBNH in THF at −78 °C[a]

			optically active α-hydroxy ester					
			K 9-*O*-DIPGF-9-BBNH			Alpine-Borane (neat)[c]		
α-keto esters	time, h	yield,[b] %	opt rotatn, deg	% ee	abs config	% ee[d] obsd	% ee corr	abs config
ethyl pyruvate	6	75	$[\alpha]^{22}_D$ −9.74 (neat, 1)	85[e] (86)[f]	*S*	82	89	*S*
ethyl 2-oxobutanoate	6	80	$[\alpha]^{24}_D$ −7.21 (neat, 1)	90[g] (92)	*S*			
ethyl 2-oxopentanoate	6	81	α^{22}_D −5.6 (neat, 1)	111[h] (94)	*S*	88	96	*S*
methyl 3-methyl-2-oxobutanoate	8	83	$[\alpha]^{22}_D$ +20.09 (*c* 1.12, CCl_4)	113[i] (98)	*S*	10	11	*R*
ethyl 3-methyl-2-oxobutanoate	8	85	α^{22}_D +1.85 (neat, 1)	99[j] (97)	*S*			
methyl 3,3-dimethyl-2-oxobutanoate	10	85	$[\alpha]^{22}_D$ +40.37 (3.22, $CHCl_3$)	113[k] (97)	*S*			
ethyl 3,3-dimethyl-2-oxobutanoate	10	87	$[\alpha]^{22}_D$ +27.7 (*c* 3.4, $CHCl_3$)	*l* (98)	*S*[m]			
ethyl 4-methyl-2-oxopentanoate	6	83	$[\alpha]^{22}_D$ −10.06 (neat, 1)	93[n] (93)	*S*	75 (49)[o]	82 (53)[o]	*S*
methyl benzoylformate	10	85[p]	$[\alpha]^{22}_D$ +155.1 (*c* 0.58, $CHCl_3$)	89[q] (92)	*S*	83	90	*R*
ethyl benzoylformate	10	80[p]	$[\alpha]^{22}_D$ +97.33 (*c* 1.01, EtOH)	93[r] (94)	*S*			
isopropyl benzoylformate	10	83[p]	$[\alpha]^{22}_D$ +103.55 (*c* 0.62, $CHCl_3$)	92[s] (93)	*S*	88[t]	96	*R*
ethyl α-oxo-1-naphthaleneacetate	10	78[p]	$[\alpha]^{24}_D$ +153.51 (*c* 2.68, $CHCl_3$)	*l* (96)	*S*[m]			

[a] $[H^-/cpd]$ = 1.1, [cpd] = 0.3 M. [b] GC yield, unless otherwise indicated. [c] From 92% (+)-α-pinene, ref 7, 6b, and 6c. [d] By rotation, unless otherwise indicated. [e] Based in $[\alpha]^{28}_D$ +11.29° (neat, 1): Kenyon, J.; Phillips, H.; Turley, H. G. *J. Chem. Soc.* **1925**, *127*, 411. [f] The figures in parentheses indicated optical purities obtained by capillary GC analysis of MTPA esters, ref 11. [g] Based on $[\alpha]^{24.2}_D$ −8.0° (neat, 1): Horn, D. H. S.; Nearn, R. H.; Siddall, J. B.; Staal, G. B.; Cerf, D. C. *Aust. J. Chem.* **1983**, *36*, 1409. [h] Based on α^{20}_D −5.05° (neat, 1): Levene, P. A.; Haller, H. L. *J. Biol. Chem.* **1928**, *77*, 555. [i] Based on $[\alpha]^{25}_D$ +17.8° (*c* 1.0, CCl_4), ref 4. [j] Based on α^{20}_D +1.87° (neat, 1): Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1977**, *33*, 507. [k] Based on $[\alpha]^{20}_D$ −35.8° (*c* 3.16, $CHCl_3$), ref 10. [l] Specific rotation is not known. [m] Absolute configuration is not known, but probably *S*, based on the order of elution of MTPA derivatives in capillary GC analysis and (+) sign of rotation. [n] Based on $[\alpha]^{23}_D$ −10.8° (neat), ref 3b. [o] Based on new value, $[\alpha]^{23}_D$ −10.8° (neat), ref 3b. [p] Isolated yield. [q] Based on $[\alpha]^{25}_D$ +174.2° (*c* 0.58, $CHCl_3$): Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126. [r] Based on calculated $[\alpha]^{25}_D$(max) −104.4° (*c* 1.75, EtOH): Seki, M.; Baba, N.; Oda, J.; Inouye, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4613. [s] Based on calculated $[\alpha]^{27}_D$(max) +112.4° (*c* 1, $CHCl_3$), ref 6b and 6c. [t] By ^{19}F NMR of MTPA esters.

report a new reagent which achieves the reduction of α-keto esters in optical purities approaching 100% ee, even relatively hindered derivatives.

Recently, we reported the preparation of a well-defined new, chiral borohydride reducing agent, 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, 1).[8] This reducing agent achieved high optical yields in the asymmetric reduction of alkyl aryl ketones and relatively hindered aliphatic ketones.[8]



K 9-*O*-DIPGF-9-BBNH, 1

In the course of a systematic study of the asymmetric reduction of representative prochiral ketones containing representative functional groups with the reagent 1, we discovered that methyl benzoylformate could be reduced at −78 °C in THF to methyl mandelate with *S* configuration in 92% ee. Encouraged by this result, we undertook to explore the asymmetric reduction of representative α-keto esters with this reagent, 1. In the reduction of α-keto esters, it seems reasonable that the degree of asymmetric induction should depend on the steric inequality of the two moieties attached to the carbonyl group. Accordingly, we examined the effect of variations in the steric bulk of both these moieties in a systematic manner. For the *R* groups, we selected methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl, phenyl, and 1-naphthyl groups (eq 1). The reductions were carried out at −78 °C in THF using a 10% excess of 1.

The reductions of the α-keto esters we studied were all

R = Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, *t*-Bu, Ph, 1-naphthyl (1)

complete within 10 h. Thus, ethyl pyruvate (2, R = Me) underwent rapid reduction (<6 h) to give (*S*)-(−)-ethyl lactate (3, R = Me), 86% ee. The reduction of ethyl 2-oxobutanoate (2, R = Et), ethyl 2-oxopentanoate (2, R = *n*-Pr), and ethyl 4-methyl-2-oxopentanoate (2, R = *i*-Bu) increased significantly, affording 92–94% ee. Surprisingly, the reduction of even more hindered α-keto esters such as ethyl (or methyl) 3-methyl-2-oxobutanoate (2, R = *i*-Pr) and ethyl (or methyl) 3,3-dimethyl-2-oxobutanoate (2, R = *t*-Bu) gave essentially 100% optical induction. Similarly, in the reduction of aromatic α-keto esters, high optical yields were obtained, such as 94% for ethyl benzoylformate (2, R = phenyl) and 96% ee for ethyl α-oxo-1-naphthaleneacetate (2, R = 1-naphthyl). The results are summarized in Table I. To facilitate comparison we also list the results recently realized with Alpine-Borane (neat).[6b,c]

To our knowledge, this is the first time that such high optical yields have been realized for the reduction of ethyl 2-oxobutanoate, ethyl 2-oxopentanoate, methyl 3-methyl-2-oxobutanoate, ethyl 3-methyl-2-oxobutanoate, ethyl 4-methyl-2-oxopentanoate, methyl 3,3-dimethyl-2-oxobutanoate, ethyl 3,3-dimethyl-2-oxobutanoate, and ethyl α-oxo-1-naphthaleneacetate. The direction of reduction was consistent. All of the α-hydroxy esters obtained were enriched in the *S* enantiomer.

In the reduction of α-keto esters by neat Alpine-Borane, we observed that increases in the steric requirements of the alkoxy group resulted in an increase in the optical yield realized.[6b,c] However, in the present case, such variation in the steric requirements of the alkoxy group, OR, in the ester, $MeCOCO_2R$, and $PhCOCO_2R$, failed to improve the optical yield.

The following procedure for the reduction of methyl

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3,3-dimethyl-2-oxobutanoate (2, R = *t*-Bu) is representative. An oven-dried, 50-mL long-necked 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. The flask was charged with the THF solution (0.43 M, 26 mL) of the reagent 1 (11 mmol) and cooled to −78 °C. Into the flask was added 1.44 g of methyl 3,3-dimethyl-2-oxobutanoate (10 mmol) in 7 mL of THF precooled to −78 °C via a double-ended needle.[9] After the reaction mixture was stirred, the mixture was maintained at −78 °C for 10 h. The excess of hydride was then destroyed by an addition of 2 mL of methanol precooled to −78 °C. After the volatiles were pumped off at aspirator pressure, the residue was dissolved in 25 mL of ethyl ether. The mixture was cooled to 0 °C and oxidized with 3 mL of 30% hydrogen peroxide in 4 mL of pH 7 phosphate buffer solution at 0 °C for 3 h. The ether layer was separated and the aqueous layer was extracted with 3 × 25 mL portions of ethyl ether. The combined extract was washed once with saturated brine solution (15 mL), dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated. Distillation of the residue provided 1.11 g of methyl 3,3-dimethyl-2-hydroxybutanoate (3, R = *t*-Bu) (76%, bp 77–80 °C/18 mmHg, GC yield 85%) containing a small amount of impurities. The alcohol was further purified by preparative GC (20% Carbowax 20M, 6 ft × $^1/_2$ in. column, 100 °C) and the rotation was measured: $[\alpha]^{22}_D$ +40.37° (*c* 3.22, $CHCl_3$), 113% based on the maximum reported rotation $[\alpha]^{20}_D$ −35.8° (*c* 3.16, $CHCl_3$).[10] Capillary GC analysis (Supelcowax, 15 M) of MTPA esters[11] of the product alcohol revealed a composition of 98.5% *S* + 1.5% *R* (i.e., 97% ee).

In conclusion, the present study provides a new, highly efficient method for the chiral synthesis of optically active α-hydroxy esters in optical purities approaching 100% ee by reduction of α-keto esters with the new chiral reducing agent, K 9-*O*-DIPGF-9-BBNH, 1. The reagent affords α-hydroxy esters consistently enriched in their *S* enantiomers.

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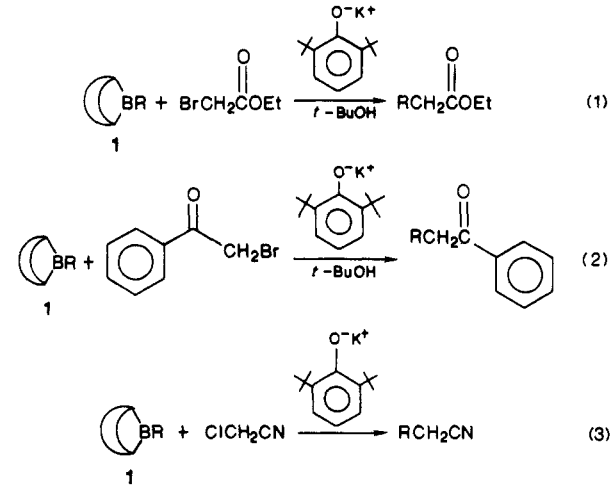
Herbert C. Brown,* Byung Tae Cho[1a,b]
Won Suh Park[1a]

Richard B. Wetherill Laboratory
Purdue University
West Lafayette, Indiana 47907
Received June 10, 1986

Base-Induced α-Alkenylation of Ethyl Bromoacetate, Phenacyl Bromide, and Chloroacetonitrile via *B*-*trans*-1-Alkenyl-9-borabicyclo[3.3.1]nonanes

Summary: *B*-*trans*-1-Alkenyl-9-borabicyclo[3.3.1]nonanes, easily and quantitatively prepared by the reaction of 9-BBN with various 1-alkynes in tetrahydrofuran, undergo facile reaction with α-halo carbanions generated from ethyl bromoacetate, phenacyl bromide, and chloroacetonitrile in the presence of potassium 2,6-di-*tert*-butylphenoxide, providing the corresponding β,γ-unsaturated esters, ketones, and nitriles in good yield.

Sir: Alkylations α to a carbonyl group still present a major challenge to the synthetic organic chemist.[1] A variety of ingenious methods have, however, been developed to achieve such transformations. Reaction of trialkylboranes with α-diazo ketones,[2] nitriles,[3] and aldehydes[4] provides good yields of the α-alkylated products. Use of dialkylchloroboranes[3,5] in a modified procedure allows an exceptionally facile α-alkylation of ethyl diazoacetates. We previously reported the base-induced α-alkylation of α-halo esters,[6] ketones,[7] and nitriles.[8] α-Alkylation of α-phenoxyacetic acid[9] under the influence of a base represents another approach. In all of these reactions, only one of the three groups of trialkylborane is utilized. This limitation could constitute a major difficulty in cases where it is desired to apply these homologation reactions to valuable intermediates. Fortunately, the use of *B*-alkyl-9-BBN derivatives 1 circumvented this difficulty for the base-induced synthesis of esters,[10] ketones,[11] and nitriles[9] (eq 1–3). In these reactions the alkyl group migrates preferentially over the cyclooctyl ring.



Since nucleophilic displacements on sp^2 hybridized carbons are achieved only with great difficulty, alkenyla-

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