drogen sulfate containing H_2O (2 drops). After adding 50% aqueous NaOH (0.8 mL), the whole reaction mixture was stirred at 55 °C for 48 h. The reaction was quenched with H_2O, acidified with 5% aqueous HCl, extracted with ethyl acetate, washed with H_2O and brine, and concentrated to give ZK 96 480 (**4**) (42 mg, 86%) as a colorless viscous oil: $[\alpha]^{22}_D$ +138.25° (*c* 1.025, $CHCl_3$). Other spectral data were identical with those of an authentic sample.[1]

Registry No. **1**, 112741-41-0; **2**, 106937-28-4; **4**, 94079-80-8; **10**, 112741-21-6; **11** (R^4 = C_5H_{11}), 112741-22-7; **11** (R^4 = $CH_2CHMeCH_2CH_2CH{=}CMe_2$), 112741-23-8; **11** ($R^4$ = $CHMeCH_2C{\equiv}CEt$), 112741-24-9; **11** (R^4 = cyclohexyl), 112741-25-0; **11** (R^4 = CH_2OPh), 112741-26-1; (*E*)-**12** (R^4 = C_5H_{11}), 112741-27-2; (*Z*)-**12** (R^4 = C_5H_{11}), 112741-32-9; (*E*)-**12** (R^4 = (*R*)-$CH_2CHMeCH_2CH_2CH{=}CMe_2$), 112741-28-3; (*Z*)-**12** (R^4 = (*R*)-$CH_2CHMeCH_2CH_2CH{=}CMe_2$), 112835-57-1; **12** ($R^4$ = $CHMeCH_2C{\equiv}CEt$), 112741-29-4; (*E*)-**12** (R^4 = cyclohexyl), 112741-30-7; (*Z*)-**12** (R^4 = cyclohexyl), 112741-33-0; (*E*)-**12** (R^4 = CH_2OPh), 112741-31-8; (*Z*)-**12** (R^4 = CH_2OPh), 112741-34-1; **12** (R^4 = C_5H_{11}) (enone), 112741-35-2; **12** (R^4 = $CH_2CHMeCH_2CH_2CH{=}CMe_2$) (enone), 112741-36-3; **12** (R^4 = $CHMeCH_2C{\equiv}CEt$) (enone), 112741-37-4; **12** (R^4 = cyclohexyl) (enone), 112741-38-5; **12** (R^4 = CH_2OPh) (enone), 112741-39-6; **13**, 92134-25-3; **14**, 112495-28-0; **14** (methoxy deriv), 112763-20-9; **15**, 112636-34-7; **15** (aldehyde deriv), 112741-40-9; **16**, 112835-58-2; **17**, 106937-25-1; **17** (acetate), 106937-24-0; **17** (methyl ether), 112741-47-6; **17** (*tert*-butyloxycarbonylmethyl ether), 106937-26-2; **18**, 106937-27-3; **19**, 112741-42-1; **19** (THP ether), 106937-29-5; **20**, 112835-59-3; **20** (THP ether), 106975-02-4; **20** (oxidized), 112741-48-7; iii, 72657-23-9; iv (X = Cl), 112741-43-2; iv (X = Br), 112741-44-3; v, 112741-45-4; vi, 112741-46-5; vii, 112741-13-6; $MeOCH_2P^+Ph_3Cl^-$, 4009-98-7; $OHCC_5H_{11}$, 66-25-1; (*R*)-$OHCCH_2CHMeCH_2CH_2CH{=}CMe_2$, 2385-77-5; (*R*)-$OHCCHMeCH_2C{\equiv}CEt$, 112741-14-7; $PhOCH_2CHO$, 2120-70-9; $Br_2CHCOC_5H_{11}$, 14799-24-7; (*R*)-$Br_2CHCOCH_2CHMeCH_2CH_2CH{=}CMe_2$, 112741-15-8; (*S*)-$Br_2CHCOCHMeCH_2C{\equiv}CEt$, 112741-16-9; (*R*)-$Br_2CHCOCHMeCH_2C{\equiv}CEt$, 112741-17-0; $Br_2CHCOCH_2OPh$, 112763-19-6; $MeOCOC_5H_{11}$, 106-70-7; (*R*)-$MeOCOCHMeCH_2C{\equiv}CEt$, 112741-20-5; $PhOCH_2CO_2Me$, 2065-23-8; 2-methyl-4-heptynal, 112741-10-3; 1,1-dibromo-3-methyl-5-octyn-2-ol, 112741-11-4; 1,1-dibromo-3-methyl-5-octyn-2-one, 112741-12-5; cyclohexanecarboxaldehyde, 2043-61-0; (cyclohexylcarbonyl)dibromomethane, 112741-18-1; methyl 2-methyl-4-heptynoate, 112741-19-2; methyltriphenylphosphonium bromide, 1779-49-3; *tert*-butyl bromoacetate, 5292-43-3.

Chiral Synthesis via Organoboranes. 15. Selective Reductions. 42. Asymmetric Reduction of Representative Prochiral Ketones with Potassium 9-*O*-(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]-nonane

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Potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane (9-*O*-DIPGF-9-BBNH, K-glucoride), a new stable chiral borohydride reducing agent, was prepared by reaction of the corresponding borinic ester, 9-*O*-DIPGF-9-BBN, with potassium hydride in THF. The reagent provides high optical induction for asymmetric reduction of prochiral ketones, such as relatively hindered aliphatic ketones, alkyl aromatic ketones, and α-keto esters. In particular, the reduction of hindered α-keto esters provides the corresponding α-hydroxy esters with optical purities approaching 100% ee. Moreover, the reduction of relatively hindered aliphatic ketones such as 3,3-dimethyl-2-butanone, 2,2-dimethylcyclopentanone, spiro[4.4]nonan-1-one, and 2,2-dimethylcyclohexanone yields the corresponding alcohols in 70% ee, 84% ee, 82% ee, and 64% ee, respectively. The reduction of unhindered aliphatic ketones such as 2-butanone, 3-methyl-2-butanone, 2-octanone, and cyclohexyl methyl ketone provides the corresponding alcohols in relatively low optical purities, 3% ee, 39% ee, 27% ee, and 23% ee, respectively. Alkyl aromatic ketones are reduced to the corresponding alcohols, providing products in 78% ee for acetophenone, 92% ee for propiophenone, 87% ee for butyrophenone, 87% ee for isobutyrophenone, 85.4% ee for valerophenone, 97–100% ee for pivalophenone, and 91% ee for 2′-methylacetophenone. The reduction of α-keto esters provides the corresponding α-hydroxy esters in exceptionally high ee, such as 86% ee for methyl pyruvate, 86% ee for ethyl pyruvate, 87% ee for isopropyl pyruvate, 81% ee for *tert*-butyl pyruvate, 92% ee for ethyl 2-oxobutanoate, 94% ee for ethyl 2-oxopentanoate, 98% ee for methyl 3-methyl-2-oxobutanoate, 97% ee for ethyl 3-methyl-2-oxobutanoate, 97% ee for methyl 3,3-dimethyl-2-oxobutanoate, 98% ee for ethyl 3,3-dimethyl-2-oxobutanoate, 93% ee for ethyl 4-methyl-2-oxopentanoate, 92% ee for methyl benzoylformate, 94% ee for ethyl benzoylformate, 93% ee for isopropyl benzoylformate, and 96% ee for ethyl α-oxo-1-naphthaleneacetate. The reduction of relatively more hindered ketones such as 3,3-diethyl-2-pentanone, 2,2,2-triphenylacetone, 2,2,2-triethylacetophenone, 2,2,2-triphenylacetophenone, and 2′,4′,6′-trimethylacetophenone results in a serious decrease in optical purity, 25% ee, 7% ee, 34% ee, 4% ee, and 35% ee, respectively. 4-Chlorobenzophenone is reduced to 4-chlorobenzhydrol in only 11.5% ee. Ethyl 2,2-dimethylacetoacetate is reduced to ethyl 2,2-dimethyl-3-hydroxybutanoate in 43% ee. The reductions of alkyl heterocyclic ketones such as 2-acetylfuran, 2-acetylthiophene, and 3-acetylpyridine afford the corresponding alcohols with 42% ee, 42% ee, and 70% ee, respectively. The reductions of α-halo ketones, 2-chloroacetophenone and 2,2,2-trifluoroacetophenone, yield the corresponding halohydrins in 77% ee and 48% ee, respectively. *trans*-4-Phenyl-3-buten-2-one is reduced to the corresponding allylic alcohol in 60% ee. The reduction of 4-phenyl-3-butyn-2-one provides the corresponding acetylenic alcohol in 61% ee. The reagent also reduces representative cyclic and bicyclic ketones with high stereoselectivities to give the corresponding thermodynamically less stable alcohols, such as 98% for 2-methylcyclohexanone, 96% for 2-phenylcyclohexanone, 99.7% for 2-*tert*-butylcyclohexanone, 94% for 4-*tert*-butylcyclohexanone, 96% for norcamphor, and 96% for camphor.

Over the past decades, the asymmetric reduction of carbonyl compounds has been actively investigated by organic chemists.[2] Most of the early experiments in this area, however, gave disappointingly low optical yields.[3]

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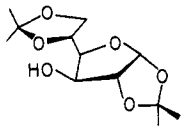
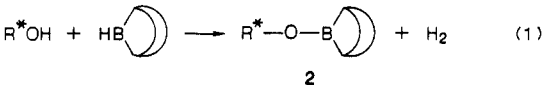
Recently, considerable success has been achieved in the asymmetric reduction area using both chirally modified lithium aluminum hydrides[4] and borane derivatives.[5] However, only limited success has been achieved for chirally modified borohydride reagents.[6]

It was reported that sodium borohydride modified with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (DIPGF, **1**)



DIPGF, 1

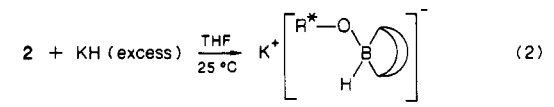
in the presence of isobutyric acid achieved up to 83% enantiomeric excess (ee) in the reduction of propiophenone.[6c] Unfortunately, the authors reported that their reagent appeared to be a complex mixture and they could not assign a specific structure to the reagent which achieved the asymmetric reduction. It appeared desirable to undertake the synthesis of a well-defined borohydride derivative which would permit a systematic study of the effect of the structure of the chiral auxiliaries on the asymmetric reduction achieved. Fortunately, we recently established a general synthesis of chiral dialkylmonoalkoxyborohydrides, specifically, potassium 9-alkoxy-9-boratabicyclo[3.3.1]nonanes, **3**, by the reaction of the corresponding chiral borinic esters, **2**, with excess potassium hydride (eq 1 and 2).[7]



(1)

2

where R*OH = selected optically active alcohols



(2)

3

The synthetic method provides a class of trisubstituted borohydrides consisting of a single, well-defined reducing species and possessing only one hydride per reagent molecule, which should be advantageous for understanding the asymmetric results achieved. With more than one hydride per borohydride unit, it is possible for the stereochemical results to vary with the different hydrides undergoing reaction. In the course of studying the asymmetric reduction with these chiral borohydrides, we discovered a highly promising asymmetric 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, **4**),[8] which provides very high optical yields (90–100% ee) in the reduction of typical prochiral ketones such as α-keto esters and pivalophenone.[9] In order to define the scope and limits of this reagent, K-glucoride,[8] **4**, in the asymmetric reduction of prochiral ketones, we undertook a detailed study of the asymmetric reduction of structurally different ketones bearing various functional groups such as acyclic ketones, cyclic aliphatic ketones, alkyl aromatic ketones, keto esters, a diaryl ketone, alkyl heterocyclic ketones, a conjugated enone, and a conjugated acetylenic ketone.

Results and Discussion

K-Glucoride, **4**, was prepared by the reaction of excess potassium hydride with the borinic ester **5**, which in turn was prepared by the reaction of 9-BBN with 1 (eq 3 and 4). The stability of the reagent was examined by ^{11}B NMR spectra and by measuring the number of moles of hydrogen evolved by hydrolysis of aliquots of the supernatant solution at appropriate time intervals.

The asymmetric reduction was carried out in tetrahydrofuran (THF) at −78 °C except for a few examples where the reaction was very sluggish at −78 °C. The product alcohols were obtained by a nonoxidative workup procedure[10] or alkaline hydrogen peroxide oxidation.[24] Optical purities of the product alcohols were determined by measuring the rotations of the alcohols obtained and

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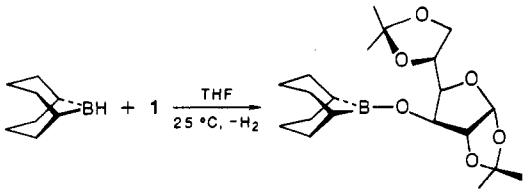
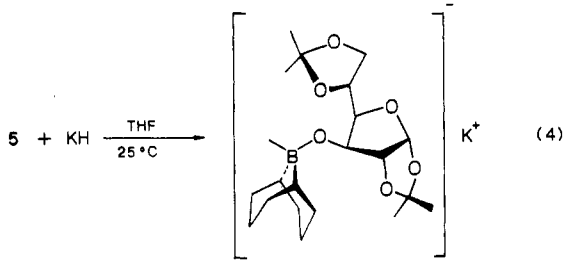


(3)

9-O-DIPGF-9-BBN, 5



(4)

K-glucoride, 4

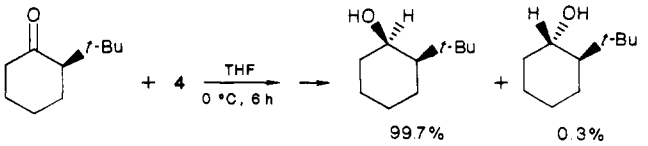
comparing the values with the maximum reported rotations. The enantiomeric excesses of these alcohols were also determined by capillary GC analysis of the MTPA ester derivatives.[27]

Preparation and Stability of K-Glucoride, 4. The borinic ester (9-*O*-DIPGF-9-BBN, **5**) was prepared by treatment of 9-BBN with 1. The reaction proceeded smoothly in THF at 25 °C with the evolution of 1 equiv of H_2 within 2 h (eq 3). The ^{11}B NMR spectrum of the resulting solution revealed the disappearance of 9-BBN (δ 28.0) with the appearance of only the desired borinic ester **5** (δ 56.30), which could be isolated by distillation. The borinic ester **5** was easily converted in essentially quantitative yield into the corresponding borohydride reagent **4** by vigorous stirring with a modest excess (1.1–1.5 equiv) of potassium hydride in THF at 25 °C (eq 4). In this reaction, a slightly exothermic reaction was observed following a short induction period of 10–30 min with completion of the reaction taking place within 2 h.

The reagent **4** exhibits the characteristic chemical shift in the ^{11}B NMR spectrum (δ 1.33, br s), the characteristic strong absorption at 2038 cm^{-1} attributed to the B–H stretching vibration in the IR spectrum, and a stoichiometric ratio of K:B:H as 1:1:1 by analysis.

The reagent **4** is stable toward disproportionation at room temperature for an extended period of time, especially when the solution in THF is stored over excess potassium hydride under a positive pressure of nitrogen.

Stereoselectivity in the Reduction of Cyclic and Bicyclic Ketones. Representative cyclic and bicyclic ketones such as 2-methylcyclohexanone, 2-phenylcyclohexanone, 2-*tert*-butylcyclohexanone, norcamphor, and camphor were reduced by K-Glucoride, **4**, at 0 °C and −78 °C. The reductions were complete within 6 h. As shown in Table I, the reagent **4** affords excellent stereoselectivities for the ketones examined, exhibiting 94–99.7% stereoselectivities favoring the thermodynamically less stable isomeric alcohols. Especially noteworthy is the reduction of the hindered cyclic ketone 2-*tert*-butylcyclohexanone to the corresponding cis alcohol in 99.7% isomeric purity, even at 0 °C (eq 5). The results are presumably due to the large steric requirements of the glucoride moiety.[10]



99.7% 0.3%

(5)

Table I. Stereoselective Reduction of Representative Cyclic and Bicyclic Ketones with K-Glucoride in THF[a]

ketone	temp, °C	time, h	yield,[b] %	less stable alcohol,[c] %
2-methylcyclohexanone	0	3	98	97
	−78	6	97	98
2-phenylcyclohexanone	0	3	97	95
	−78	6	96	96
2-*tert*-butylcyclohexanone	0	6	96	99.7
4-*tert*-butylcyclohexanone	0	3	98	92
	−78	6	98	94
norcamphor	0	3	97	94
	−78	6	94	96
camphor	0	24	90	96

[a] $[H^-]$:[cpd] = 1.1:1.0, [ketone] = 0.3 M. [b] By GC analysis. [c] By capillary GC analysis.

Table II. Effect of Reaction Temperature on the Reduction of Propiophenone in THF[a]

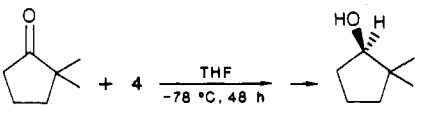
temp, °C	time, h	yield,[b] %	% ee[c]	confign
0	6	97	76	*R*
−25	10	98	80	*R*
−78	16	93	92	*R*

[a] See the corresponding footnotes in Table I. [b] See the corresponding footnotes in Table I. [c] By rotation.

These ketones exist as a pair of enantiomers. No attempt was made to examine the optical yields which might be achieved in these compounds.

Effect of Reaction Temperature on the Enantioselectivity. In order to examine the effect of reaction temperature on asymmetric reduction with K-Glucoride, **4**, the reduction of propiophenone was carried out in THF at various temperatures (0 °C, −25 °C, −78 °C, and −100 °C). As shown in Table II, the optical induction increases significantly at lower temperatures, giving 76% ee at 0 °C, 80% ee at −25 °C, and 92% ee at 78 °C. At −100 °C, the reaction was too slow to obtain the product alcohol.

Asymmetric Reduction of Aliphatic Ketones. The reduction of unhindered aliphatic ketones with **4** proceeded to completion in THF within 10 h, even at −78 °C. The asymmetric inductions realized for such ketones, however, were much less favorable, such as 3% ee for 2-butanone, 39% ee for 3-methyl-2-butanone, 27% ee for 2-octanone, and 23% ee for cyclohexyl methyl ketone, respectively. However, in the reduction of relatively hindered aliphatic ketones, high optical yields were achieved, such as 70% ee for pinacolone, 84% ee for 2,2-dimethylcyclopentanone, 82% ee for spiro[4.4]nonan-1-one, and 64% ee for 2,2-dimethylcyclohexanone, respectively (eq 6). Moreover,



84% ee

(6)

all of the alcohols obtained are consistently enriched in the *R* enantiomers. The results are summarized in Table III.

These optical yields for relatively hindered aliphatic and alicyclic ketones appear to be among the more favorable in the literature for these substrates. For unhindered ketones, however, NB-Enantride[6a] is much better. However, NB-Enantride provides only 2% ee in the reduction of pinacolone, a hindered aliphatic ketone,[6a] as compared to the present value of 70%.

Asymmetric Reduction of Alkyl Aromatic Ketones. As shown in Table IV, most of the prochiral alkyl aromatic ketones examined were reduced smoothly to the corresponding alcohols in THF, even at −78 °C, giving high

Table III. Asymmetric Reduction of Representative Aliphatic Ketones with K-Glucoride in THF[a]

ketone	temp, °C	time, h	yield,[b] %	$[\alpha]^{22}_D$, deg	% ee	abs confign
2-butanone	−78	6	99	−0.43 (neat)	3[c]	*R*
3-methyl-2-butanone	−78	6	98	−1.90 (neat)	36[d] (39)[c]	*R*
3,3-dimethyl-2-butanone	−78	16	95	−5.70 (neat)	70[f]	*R*
2-octanone	−78	6	97	−2.58 (neat)	27[g]	*R*
cyclohexyl methyl ketone	−78	10	95	−1.29 (neat)	23[h] (20)[e]	*R*
2,2-dimethylcyclopentanone	−78	48	88	−19.65 (*c* 4.16, PhH)	(84)[i]	*R*[j]
spiro[4.4]nonan-1-one	−78	96	75	−31.43 (*c* 0.56, PhH)	80[k] (82)[i]	*R*
2,2-dimethylcyclohexanone	−50	48	92	−3.43 (neat)	(64)[e,l]	*R*[j]

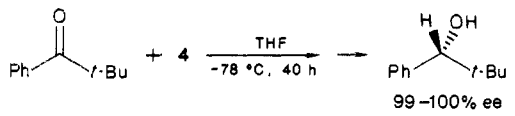
[a] See the corresponding footnotes in Table I. [b] See the corresponding footnotes in Table I. [c] Based on $[\alpha]_D$ 9.57° (neat): Cristol, S. J.; Franzus, B.; Shadan, A. *J. Am. Chem. Soc.* **1955**, *77*, 2512. [h] Based on $[\alpha]^{20}_D$ 5.68° (neat): Domleo, A.; Kenyon, J. *J. Chem. Soc.* **1926**, *129*, 1841. [i] By capillary GC analysis of *l*-menthyl carbonate derivatives. [j] Absolute configuration is unknown, but probably *R*, based on the order of elution of *l*-menthyl carbonate derivatives in capillary GC analysis and (−) sign of rotation. [k] Based on $[\alpha]^{25}_D$ 39.8° (*c* 1.5 PhH): Nakazaki, M.; Chikamatsu, M.; Asao, M. *J. Org. Chem.* **1981**, *46*, 1147. [l] ^{19}F NMR analysis of MTPA esters: Merck, E. M.; Lepoivre, J. A.; Lemiere, G. L.; Alderweireldt, F. C. *Org. Mag. Reson.* **1983**, *21*, 380.

Table IV. Asymmetric Reduction of Representative Alkyl Aromatic Ketones with K-Glucoride in THF at −78 °C[a]

ketone	time, h	yield,[b] %	$[\alpha]^{22}_D$, deg	% ee	abs confign
acetophenone	16	95	+33.92 (neat)	78[c] (78)[d]	*R*
propiophenone	16	93	+25.82 (neat)	92[e]	*R*
butyrophenone	20	95	+39.22 (*c* 4.82, PhH)	87[f]	*R*
isobutyrophenone	36	96	+21.33 (neat)	87[g]	*R*
valerophenone	20	94	+17.08 (neat)[h]	85.4[i]	*R*
pivalophenone	40	93	+25.98 (*c* 2.2, PhH)	100[j] (97)	*R*
2′-methylacetophenone	24	93	+50.46 (neat)	(91)	*R*[k]

[a] See the corresponding footnotes in Table I. [b] See the corresponding footnotes in Table I. [c] Based on $[\alpha]^{21}$ +43.5° (neat), ref 26. [d] The figures in parentheses indicate % ee determined by capillary GC analysis of MTPA esters. [e] Based on $[\alpha]^{22}_D$ +28.1° (neat), ref 26. [f] Based on $[\alpha]^{22}_D$ +45.2° (*c* 4.81, PhH), ref 4e. [g] Based on $[\alpha]^{25}_D$ −24.6° (neat): Napsipuri, D.; Sharker, G. J. *Indian J. Chem. Soc.* **1967**, *44*, 165. [h] α^{22}_D value. [i] Based on α^{22}_D −0.2° (neat, l 0.01), ref 4e. [j] Based on $[\alpha]^{22}_D$ +25.9° (*c* 2.24, PhH), ref 26. [k] Unknown, but probably *R*, based on the order of elution of MTPA esters in capillary GC analysis and (+) sign of rotation.

optical yields. Especially noteworthy is the reduction of pivalophenone to give essentially optically pure (*R*)-(+)-2,2-dimethyl-1-phenylpropanol (97–100% ee) (eq 7).

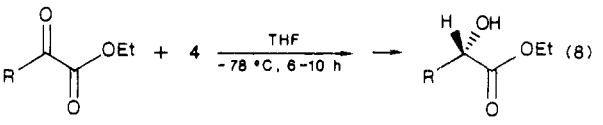


(7)

Similarly, in the reduction of a series of alkyl aromatic ketones, consistently high optical yields were obtained, such as 78% ee for acetophenone, 92% ee for propiophenone, 87% ee for butyrophenone, 87% ee for isobutyrophenone, 85.4% ee for valerophenone, and 91% ee for 2′-methylacetophenone. Again, all of the alcohol products obtained were consistently enriched in their *R* enantiomers. It is noteworthy that the optical yields obtained by K-glucoride **4** in the reduction of more hindered alkyl phenyl ketones, such as 97–100% ee for pivalophenone and 87% ee for isobutyrophenone, are considerably higher than the values (44% ee and 71% ee, respectively) obtained by the recently reported highly promising Binal-H reagent.[4e] To the best of our knowledge, this is the first time such a high optical yield (97–100% ee) for the asymmetric reduction of pivalophenone has been achieved.

Asymmetric Reduction of α-Keto Esters. In the asymmetric reduction of α-keto esters, it appears that the degree of asymmetric induction should depend on the steric inequality of the two moieties attached to the carbonyl group.[11] Accordingly, we examined the effect of variations of the steric bulk of both these moieties in a systematic manner.

For a variation of the R groups, we selected methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl, phenyl, and 1-naphthyl groups (eq 8). All of the reductions of the



(8)

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

α-keto esters examined were complete within 10 h in THF at −78 °C. Varying the steric bulk of the R groups had a predictable effect on increasing the optical induction. Thus, ethyl pyruvate (**6**, R = Me) underwent rapid reduction (<6 h) to give (*S*)-(−)-ethyl lactate (**7**, R = Me) in 86% ee. Significantly improved asymmetric inductions were achieved for the reduction of ethyl 2-oxobutanoate (**6**, R = Et), ethyl 2-oxopentanoate (**6**, R = *n*-Pr), and ethyl 4-methyl-2-oxopentanoate (**6**, R = *i*-Bu) (92–94% ee). Moreover, the reduction of a hindered α-keto ester, ethyl (or methyl) 3,3-dimethyl-2-oxobutanoate (**6**, R = *t*-Bu) provided essentially 100% optical induction. This contrasts strongly with the 11% ee realized in the reduction of **6** (R = *i*-Pr) with neat Alpine-Borane, one of the most promising reagents available for asymmetric reduction of α-keto esters.[11b] Similarly, in the reduction of aromatic α-keto esters, high optical yields were obtained, such as 94% ee for ethyl benzoylformate (**6**, R = Ph) and 96% ee for ethyl α-oxo-1-naphthaleneacetate (**6**, R = 1-naphthyl). To our knowledge, this is the first time 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, and ethyl α-oxo-1-naphthaleneacetate. The direction of the induction is consistent. All of the α-hydroxy esters obtained are enriched in the *S* enantiomers.

(11) (a) Brown, H. C.; Pai, G. G.; Jadhav, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 1531. (b) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384. (c) Midland, M. M.; Zderic, S. A. *J. Am. Chem. Soc.* **1982**, *104*, 525.

Table V. Asymmetric Reduction of Representative α-Keto Esters with K-Glucoride in THF at -78 °C[a]

ketone	time, h	yield,[b] %	α-hydroxy ester		
			opt rottn, deg	% ee	abs confign
methyl pyruvate	6	80	α^{22}_D -7.79 (neat)	86[c] (82)[d]	S
ethyl pyruvate	6	75	$[\alpha]^{22}_D$ -9.74 (neat)	85[e] (86)	S
isopropyl pyruvate	8	78	$[\alpha]^{22}_D$ -9.13 (neat)	(87)	S
tert-butyl pyruvate	8	72	$[\alpha]^{22}_D$ -7.46 (neat)	79[f] (81)	S
ethyl 2-oxobutanoate	6	80	$[\alpha]^{24}_D$ -7.21 (neat)	90[g] (92)	S
ethyl 2-oxopentanoate	6	81	α^{22}_D -5.6 (neat)	111[h] (94)	S
methyl 3-methyl-2-oxobutanoate	8	83	$[\alpha]^{22}_D$ +20.09 (*c* 1.12, CCl_4)	113[i] (98)	S
ethyl 3-methyl-2-oxobutanoate	8	85	α^{22}_D +1.85 (neat)	99[j] (97)	S
methyl 3,3-dimethyl-2-oxobutanoate	10	85	$[\alpha]^{22}_D$ +40.37 (*c* 3.22, $CHCl_3$)	113[k] (97)	S
ethyl 3,3-dimethyl-2-oxobutanoate	10	87	$[\alpha]^{22}_D$ +27.7 (*c* 3.4, $CHCl_3$)	(98)	S[l]
ethyl 4-methyl-2-oxopentanoate	6	83	$[\alpha]^{22}_D$ -10.06 (neat)	93[m] (93)	S
methyl benzoylformate	10	85[n]	$[\alpha]^{22}_D$ +155.1 (*c* 0.58, $CHCl_3$)	89[q] (92)	S
ethyl benzoylformate	10	80[n]	$[\alpha]^{22}_D$ +97.33 (*c* 1.01, EtOH)	93[p] (94)	S
isopropyl benzoylformate	10	83[n]	$[\alpha]^{22}_D$ +103.55 (*c* 0.62, $CHCl_3$)	92[q] (93)	S
ethyl α-oxo-1-naphthaleneacetate	10	78[n]	$[\alpha]^{24}_D$ +153.51 (*c* 2.68, $CHCl_3$)	(96)	S[l]

[a] See the corresponding footnotes in Table I. [b] See the corresponding footnotes in Table I. [c] Based on α^{25}_D -4.54° (neat) (*l* 0.5): Mislow, K.; O'Brien, R. E.; Schafer, H. *J. Am. Chem. Soc.* **1962**, *84*, 1940. [d] The figures in parentheses indicate % ee determined by capillary GC analysis of MTPA esters. [e] Based on $[\alpha]^{23}_D$ +11.29° (neat): Kenyon, J.; Phillips, H.; Turley, H. G. *J. Chem. Soc.* **1925**, *127*, 411. [f] Based on $[\alpha]^{20}_D$ +9.48° (neat): Wood, C. E.; Such, J. E.; Scarf, F. J. *J. Chem. Soc.* **1926**, 1928. [g] Based on $[\alpha]^{24.2}_D$ -8.0° (neat): 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): 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): Caglioti, L.; Misiti, D.; Mondelli, R.; Selva, A.; Arcamone, F.; Cassinelli, G. *Tetrahedron* **1969**, *25*, 2193. [j] Based on α^{20}_D +1.87° (neat): 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 28. [l] The absolute configuration is unknown, but probably *S*, based on the order of elution of MTPA derivatives and the sign of rotation. [m] Based on $[\alpha]^{23}_D$ -10.8° (neat): Mori, K. *Tetrahedron* **1969**, *25*, 2193. [n] Isolated yield. [o] Based on $[\alpha]^{25}_D$ +174.2° (*c* 0.58, $CHCl_3$): Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126. [p] Based on calculated $[\alpha]^{25}_D$ -104.4° (*c* 1.75, EtOH): Seki, M.; Baba, N.; Oda, J.; Inouye, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4613. [q] Based on calculated $[\alpha]^{27}_D$ +112.4° (*c* 1, $CHCl_3$), ref 11b.

This represents a significant difference between the behavior of Alpine-Borane and K-glucoride in the reduction of aralkyl ketones such as acetophenone and keto esters such as ethyl pyruvate. Alpine-Borane [from (+)-α-pinene)] yields *S* products in the reduction of both classes of ketones. On the other hand, K-glucoride yields *R* products with aralkyl ketones and *S* products with α-keto esters. The behavior of Alpine-Borane is consistent with the transition-state model for the reduction by the reagent.[11c] Unfortunately, there is at present no really satisfactory model for the transition state for reductions by K-glucoride.

Subsequently, we examined the effect of the steric requirements of the alkoxy groups, OR′, in the α-keto esters, $MeCOCO_2R'$ and $PhCOCO_2R'$, on the optical induction achieved in asymmetric reduction with **4**. Variation of the R′ groups, from methyl to ethyl, isopropyl, and *tert*-butyl, achieved insignificant variation in the optical induction realized. These results contrast strongly with those produced by Alpine-Borane.[11] The results are summarized in Table V.

Asymmetric Reduction of Some Other Ketones. As noted previously, K-glucoride (**4**) provides excellent optical inductions for hindered aliphatic ketones and alkyl aromatic ketones. Moreover, the reagent gives highly favorable results for the asymmetric reduction of α-keto esters. Accordingly, it appeared desirable to investigate the generality and limitations of K-glucoride (**4**) in the asymmetric reduction of other representative prochiral carbonyl compounds. Consequently, the asymmetric reduction of more hindered aliphatic and aromatic ketones, a diaryl ketone, a β-keto ester, alkyl heterocyclic ketones, and α,β-unsaturated ketones was studied.

The reduction of highly hindered ketones such as 3,3-diethyl-2-pentanone, 2,2,2-triphenylacetone, 2,2,2-triethylacetophenone, and 2′,4′,6′-trimethylacetophenone required the use of elevated temperatures (-25 °C, 0 °C, and 25 °C) and provided only low optical yields (4–35% ee). The decreased optical inductions observed for those ketones possessing alkyl groups bulkier than the *tert*-butyl group may be in part due to the relatively elevated reaction temperatures required for the reductions. Thus, K-glucoride appears to operate best for ketones of intermediate steric requirements which can be reduced at lower temperatures.

Not surprisingly, only low optical induction (11.5% ee) was observed for the reduction at -78 °C of 4-chlorobenzophenone, a ketone with two substituents of essentially identical steric requirements.

Unlike α-keto esters, the reduction of a β-keto ester, ethyl 2,2-dimethylacetoacetate, provided a significantly lower optical yield (43% ee).

The reduction of alkyl heterocyclic ketones such as 3-acetylfuran, 2-acetylthiophene, and 3-acetylpyridine proceeds readily at -78 °C to yield the corresponding alcohols in 42–70% ee.

Among the α-halo ketones examined, 2-chloroacetophenone was reduced to the corresponding alcohol in 77% ee. However, a considerably lower optical induction was observed in the reduction of 2,2,2-trifluoroacetophenone (48% ee).

The reductions of *trans*-4-phenyl-3-buten-2-one and 4-phenyl-3-butyn-2-one provides the corresponding α,β-unsaturated alcohols in 60% ee and 61% ee, respectively.

All of the results are summarized in Table VI.

Conclusion

The present study provides a convenient and simple synthesis of a highly effective chiral borohydride reagent, K-glucoride, containing a single hydride per molecule and consisting of a single characterized reducing species. The reagent affords high optical inductions for the reduction of prochiral ketones such as hindered aliphatic ketones, alkyl aromatic ketones, and α-keto esters. In particular, the reduction of hindered α-keto esters yields the corresponding α-hydroxy esters with optical purities approaching 100% ee. Moreover, the directions of the asymmetric inductions are consistent, with the reductions providing the corresponding alcohols enriched in the *R* enantiomers for both aliphatic and alkyl aromatic ketones and the corresponding α-hydroxy esters enriched in the *S* enantiomers for α-keto esters.

Table VI. Asymmetric Reduction of Some Other Ketones with K-Glucoride in THF[a]

ketone	temp, °C	time, h	yield,[b] %	$[\alpha]^{22}_D$, deg	% ee	abs confign
3,3-diethylpentanone	0	60	88	not measured	(25)[c]	*d*
2,2,2-triphenylacetone[e]	25	48	87[c]	+0.213 (*c* 2.35, $CHCl_3$)	7[f]	*S*
2,2,2-triethylacetophenone	0	60	75	not measured	(34)	*d*
2,2,2-triphenylacetophenone[e]	25	48	85	+2.27 (*c* 1, acetone)	4[g]	*R*
5′,4′,6′-trimethylacetophenone	−25	60	50	+18.08 (*c* 1.55, EtOH)	35[h]	*R*
4-chlorobenzophenone	−78	48	88	+1.84 (*c* 6.75, $CHCl_3$)	11.5[i]	*d*
ethyl 2,2-dimethylacetoacetate	−78	8	80	−3.24 (neat, *l* = 1)	(43)	*d*
2-acetylfuran	−78	12	98	−10.56 (neat, *l* = 0.5)	103[j] (42)	*S*[k]
2-acetylthiophene	−78	12	97	+10.02 (neat, *l* = 1)	42[l]	*R*[k]
3-acetylpyridine	−78	12	97	+28.15 (*c* 1.06, MeOH)	70[m]	*R*
2-chloroacetophenone	−78	12	82[n]	−35.88 (*c* 1.14, PhH)	77[o]	*S*
2,2,2-trifluoroacetophenone	−78	12	95	+15.15 (neat, *l* = 1)	48[p]	*S*[q]
trans-4-phenyl-3-buten-2-one	−78	10	92	+23.8 (*c* 5.78, $CHCl_3$)	60[r]	*R*
4-phenyl-3-butyn-2-one	−78	10	95	+23.13 (*c* 4.69, EtOH)	58[s] (61)	*d*

[a] See the corresponding footnotes in Table I. [b] See the corresponding footnotes in Table I. [c] The figures in parentheses indicate % ee determined by capillary GC analysis of MTPA esters. [d] Absolute configuration is unknown. [e] Dark red color formation during reaction. [f] Based on $[\alpha]^{22}_D$ −29.1° (*c* 2.4, $CHCl_3$), ref 29. [g] Based on $[\alpha]^{20}_D$ +61° (*c* 1, acetone): Ellison, L.; Kenyon, J. *J. Chem. Soc.* **1954**, 779. [h] Based on $[\alpha]^{20}_D$ +52° (*c* 1.538 EtOH), ref 29. [i] Based on $[\alpha]^{25}_D$ −16.0° ($CHCl_3$), ref 30. [j] Based on α^{18}_D +10.29° (neat, *l* = 0.5): Duveen, D. I.; Kenyon, J. *J. Chem. Soc.* **1936**, 621. [k] Cervinka, O.; Belovsky, O.; Koralova, L. *Z. Chem.* **1969**, 448. [l] Based on $[\alpha]^{20}_D$ −23.7° (nerat, *l* = 1): Anderson, I. G.; Balfe, M. P.; Kenyon, J. *J. Chem. Soc.* **1950**, 1866. [m] Based on $[\alpha]^{20}_D$ −40.2° (*c* 0.87, MeOH), ref 31. [n] GC yield of styrene oxide. [o] By conversion to styrene oxide. Based on calculated $[\alpha]^{18}_D$ +46.84° (*c* 1.08, PhH), ref 32. [p] Based on $[\alpha]^{26}_D$ 31.85° (neat, *l* = 1): Feigl, D. M.; Mosher, H. S. *J. Org. Chem.* **1968**, *33*, 4242. [q] Peters, H. M.; Feigl, D. M.; Mosher, H. S. *J. Org. Chem.* **1968**, *33*, 4245. [r] Based on calculated $[\alpha]^{20}_D$ 39.6° (*c* 5.26, $CHCl_3$), ref 33. [s] Based on the newly observed calculated values, α_D +89.8° (neat) and $[\alpha]^{22}_D$ +39.95° (*c* 5.17, EtOH), which were determined by the rotation of the sample whose % ee was analyzed by capillary GC of MTPA esters (unpublished research of Dr. P. V. Ramachandran). These are higher than the calculated value determined by use of an NMR shift reagent: Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

Experimental Section

General Methods. All glassware was dried at 140 °C overnight, assembled hot, and cooled to room temperature in a stream of nitrogen. All reactions involving air-sensitive materials were carried out under a static pressure of nitrogen. The liquids were transferred with dry syringes or double-ended needles.

Spectra. ^1H NMR spectra were recorded on a Varian T-60 spectrometer with Me_4Si as internal standard. ^{11}B NMR spectra were obtained on a Varian FT-80A instrument. The chemical shifts are reported in δ relative to $BF_3{\cdot}Et_2O$. ^{19}F spectral analysis of the MTPA esters was performed by using a Varian XL-200 spectrometer. IR measurements were conducted on a Perkin-Elmer 1420 ratio recording spectrophotometer equipped with a Perkin-Elmer 3600 IR data station. Mass spectra were recorded on a Finnegan GC/mass spectrometer. Optical rotations were measured on a Rudolph polarimeter Autopol III.

GC Analysis. All GC analyses were carried out with Hewlett-Packard 5730A and 5890 gas chromatographs equipped with a Hewlett-Packard 3390A integrator/plotter. Optical purities (% ee) and stereoselectivities were determined by capillary GC analysis using a Hewlett-Packard 5890 gas chromatograph equipped with 15-m Supelcowax or 50-m methyl silicone capillary columns.

Materials. 9-Borabicyclo[3.3.1]nonane (9-BBN), potassium hydride, and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (DIPGF, diacetone α-D-glucose) were purchased from the Aldrich Chemical Company. Tetrahydrofuran (THF) was distilled over benzophenone ketyl and stored under a nitrogen atmosphere in an ampule. Commercially available carbonyl compounds were used without further purification. 3,3-Diethyl-2-pentanone,[12] 2,2,2-triphenylacetone,[13] spiro[4.4]nonan-1-one,[14] 2,2-dimethylcyclohexanone,[15] pivalophenone,[16] 2,2,2-triethylacetophenone,[17] and 2,2-dimethyl-α-tetralone[18] were prepared by known methods. Isopropyl pyruvate[19] was prepared by the oxidation of isopropyl lactate. *tert*-Butyl pyruvate,[20] ethyl 2-oxobutanoate,[21] ethyl 2-oxopentanoate,[21] methyl 3-methyl-2-oxobutanoate,[21] ethyl 3-methyl-2-oxobutanoate,[21,22] isopropyl benzoylformate,[21] and ethyl α-oxo-1-naphthaleneacetate[21,23] were prepared by esterification of the corresponding acid. (*R*)-(+)-MTPA[27a] was purchased from the Aldrich Chemical Company and was converted to the acid chloride[27b] and distilled. *l*-Menthyl chloroformate was purchased from Aldrich Chemical Company and used without further purification.

Preparation of 9-*O*-(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane (K 9-*O*-DIPGF-9-BBNH, K-Glucoride, 4). To a slurry of 9-BBN (32.3 g, 265 mmol) suspended in THF (200 mL) was added the solution (330 mL) of DIPGF (1) (69 g, 265 mmol) in THF dropwise via a double-ended needle with vigorous stirring. After evolution of the hydrogen ceased (~1 h), the mixture was stirred for an additional 2 h to ensure completion. Evaporation (25 °C, 14 Torr) of the solvent, followed by distillation under vacuum, gave highly viscous 9-*O*-DIPGF-9-BBN, **5** (89 g, 88% yield): bp 198–201 °C/0.5 Torr; ^{11}B NMR δ 56.30 (s); MS, M^+ 380. An oil suspension of potassium hydride, transferred to a flask, was allowed to settle and most of the oil removed with a double-ended needle. Then the potassium hydride was washed with *n*-pentane (3 × 100 mL). After evaporation (25 °C, 14 Torr) of *n*-pentane, THF was added to the oil-free potassium hydride. To this suspension of oil-free potassium hydride (12 g, 300 mmol) in THF (150 mL) was added a THF solution (250 mL) of **5** (76 g, 200 mmol) slowly via a double-ended needle with vigorous stirring. The reaction became slightly exothermic after a 10–30-min induction period. The reaction was monitored both by hydrolysis of centrifuged aliquots and by ^{11}B NMR. It was complete within 2 h, producing the addition compound, K 9-*O*-DIPGF-9-BBNH, **4** (0.48 M, 96% yield): ^{11}B NMR δ 1.33 (br, s): IR ν_{B-H} 2038 cm^{-1}. Hydride and potassium were determined as H_2 and KOH following hydrolysis; boron was estimated by GC analysis of 1,5-cyclooctanediol following oxidation by alkaline hydrogen peroxide: $[H^-]$ = 0.48 M; $[K^+]$ = 0.48 M; [B] = 0.50 M. Therefore, a stoichiometry of K:B:H of 1:1:1 was established. The hydride solution of **4** in THF can be stored over excess potassium hydride under positive nitrogen

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pressure at room temperature for at least 6 months without any disproportionation or loss of hydride activity.

Stereoselective Reduction of Cyclic and Bicyclic Ketones with K-Glucoride in THF. The reduction of 2-*tert*-butylcyclohexanone is representative. An oven-dried, 50-mL flask containing a side arm and a magnetic stirring bar was cooled under a stream of nitrogen and connected to a mercury bubbler. Into the flask was added 5.5 mmol of **4** dissolved in THF (0.48 M, 11.5 mL). The flask was maintained at 0 °C with an ice bath. To this was added 5 mmol of 2-*tert*-butylcyclohexanone dissolved in THF (1.0 M, 5 mL). The reaction mixture was stirred at 0 °C for 6 h. The reaction was then quenched by the addition of 4 mL of 3 N HCl at 0 °C and the aqueous layer saturated with anhydrous potassium carbonate. Capillary GC analysis (Supelcowax, 15 m, 100 °C, isothermal) of the organic layer revealed the presence of 96% 2-*tert*-butylcyclohexanol containing 99.7% of the cis isomer. The results are summarized in Table I.

Asymmetric Reduction of Carbonyl Compound with 4. Standard Method. An oven-dried 50-mL, long-necked, round-bottom flask equipped with a septum-capped side arm, a magnetic stirring bar, and a stopcock adaptor was cooled to room temperature under a stream of nitrogen. The flask was charged with 11 mmol of a solution of **4** in THF and cooled to −78 °C. To this was added 10 mmol of a THF solution of the carbonyl compound precooled to −78 °C via a double-ended needle.[24] The reaction mixture was maintained at −78 °C. The concentration of carbonyl compound was made to be 0.3 M. At appropriate time intervals, the reaction mixture was quenched by the addition of anhydrous HCl in ethyl ether or anhydrous methanol at −78 °C. The product alcohols were isolated by the following procedures.

Procedure A. The reaction mixture was treated with 20 mmol of anhydrous methanol precooled to −78 °C. The mixture was stirred at −78 °C for 1 h to destroy unreacted hydride and then warmed to room temperature. The volatiles were evaporated under reduced pressure (14 mmHg, 25 °C). The residue was dissolved in 25 mL of *n*-pentane and treated with 8 mL of 3 N HCl at room temperature for 2 h. The reduction product was extracted with *n*-pentane (2 × 25 mL) after conversion of the borinic acid moiety into the "ate" complex using aqueous NaOH.[10] The pentane layer was washed with brine (2 × 20 mL), dried over anhydrous $MgSO_4$, and filtered. The product was isolated by fractional distillation. The alcohol product was further purified by preparative GC or column chromatography.

Procedure B. The procedure is exactly the same as described in procedure A, except for using 20 mmol of anhydrous HCl in ethyl ether instead of methanol. The product was isolated by bulb-to-bulb distillation after evaporation of solvent.

Procedure C. The unreacted hydride was destroyed by the same method as described in procedure A. The solvent was pumped off under reduced pressure (14 mmHg, 25 °C). The residue was dissolved in ethyl ether (25 mL) and oxidized with 8 mL) of 3 N NaOH and 4 mL of 30% hydrogen peroxide for 6 h at 25 °C. The aqueous layer was saturated with anhydrous potassium carbonate and extracted with ethyl ether (2 × 25 mL). After the combined ethereal solvent was evaporated, the product alcohol was isolated by bulb-to-bulb distillation or column chromatography. The volatile alcohol product was further purified by preparative GC or column chromatography.

Procedure D. This procedure is exactly the same as described in procedure C, except for using 4 mL of pH 7 phosphate buffer solution instead of 3 N NaOH and oxidizing with 30% hydrogen peroxide at 0 °C for 3 h.

Asymmetric Reduction of Aliphatic Ketones. The reduction of 2,2-dimethylcyclopentanone is representative. According to the standard method, 10 mmol of 2,2-dimethylcyclopentanone (1.0 M, 10 mL) was reacted with 11 mmol of K-glucoride in THF (0.48 M, 22.9 mL) at −78 °C. After 48 h, the reaction mixture was worked up by procedure B or C and the yield of product alcohol was determined by GC analysis (10% Carbowax, 6 ft, 95 °C, isothermal). The analysis revealed the formation of 88% 2,2-dimethylcyclopentanol. The product alcohol was isolated by bulb-to-bulb distillation: yield, 0.85 g; bp 76–78 °C/40 mmHg. It was further purified by preparative GC (20% Carbowax, 6 ft, 90 °C, isothermal): $[\alpha]^{22}_D$ −19.65° (*c* 4.16, benzene). Since both optical rotation and absolute configuration of the alcohol are unknown, the optical purity was determined by capillary GC analysis (Supelcowax, 15 m, 150 °C, isothermal) of the *l*-menthyl carbonate derivatives of the alcohol prepared by the reaction of *l*-menthyl chloroformate (MCF, 0.2 mmol) and the alcohol (0.1 mmol) in toluene (0.4 mL) in the presence of pyridine (0.1 mL) at 25 °C.[25] The analysis indicated 84% ee. Its absolute configuration is assumed to be *R*, based on the order of elution of the *l*-menthyl carbonate derivatives in capillary GC analysis and the (−) sign of optical rotation observed. The workup procedure for the reduction of 2-butanone, 3-methyl-2-butanone, and 3,3-dimethyl-2-butanone was procedure A. For the other aliphatic ketones, procedures B or C were used. The results are summarized in Table III.

Asymmetric Reduction of Alkyl Aromatic Ketones. The reduction of pivalophenone is representative: 10 mmol of pivalophenone (1.0 M, 10 mL) was added to 11 mmol of K-glucoride in THF (0.48 M, 22.9 mL) at −78 °C by using the standard method. After 40 h, procedures B or C were followed. The ethereal extract was concentrated in vacuo (14 mmHg, 25 °C). Then bulb-to-bulb distillation of the residue provided 1.42 g of (*R*)-(+)-2,2-dimethyl-1-phenylpropanol (92% yield, bp 114–118 °C/16 mmHg) containing a small amount of starting ketone. The alcohol product was further purified by preparative GC (20% Carbowax 20M, 6 ft, 150 °C, isothermal) and the rotation was measured: $[\alpha]^{22}_D$ +25.96° (*c* 2.2, benzene), 100% ee, based on the maximum reported rotation $[\alpha]^{22}_D$ +25.9° (*c* 2.24, benzene).[26] Capillary GC analysis (Supelcowax, 15 m, 180 °C, isothermal) of MTPA esters[27a] of the product alcohol revealed a composition of 98.4% *R* + 1.6% *S* (i.e., 96.8% ee), in close agreement with the optical rotation measurement. The results are summarized in Table IV. The workup procedure followed for all of the alkyl aromatic ketones in Table IV was either procedure B or C.

Asymmetric Reduction of α-Keto Esters. The reduction of methyl 3,3-dimethyl-2-oxobutanoate is representative. According to the standard method, 10 mmol of methyl 3,3-dimethyl-2-oxobutanoate (1.0 M, 10 mL) was reacted with 11 mmol of K-glucoride in THF (0.48 M, 22.9 mL) at −78 °C. After 10 h, the unreacted hydride was destroyed by addition of 2 mL of anhydrous methanol. Then, workup by procedure D was followed. The ethereal extract was concentrated in vacuo (14 mmHg, 25 °C). Distillation of the residue provided (*S*)-(+)-methyl 3,3-dimethyl-2-hydroxybutanoate (yield, 1.11 g, bp 77–80 °C/18 mmHg, GC yield, 88%) containing a small amount of impurities. The alcohol was further purified by preparative GC (20% Carbowax 20M, 6 ft, 100 °C, isothermal) and the rotation was measured: $[\alpha]^{22}_D$ +40.37° (*c* 3.22, $CHCl_3$), 113% ee based on the maximum reported rotation value $[\alpha]^{20}_D$ −35.8° (*c* 3.16, $CHCl_3$).[28] Capillary GC analysis (Supelcowax, 15 m, 180 °C, isothermal) of MTPA esters of the product alcohol indicated the formation of 98.5% *S* + 1.5% *R* (i.e., 97% ee). The results are summarized in Table V. The workup procedure for all the α-keto esters examined in Table V was procedure D.

Asymmetric Reduction of Other Ketones. The following procedure was followed for the reduction of 2′,4′,6′-trimethylacetophenone, 4-chlorobenzophenone, ethyl 2,2-dimethylacetoacetate, 3-acetylpyridine, 2-chloroacetophenone, and *trans*-4-phenyl-3-buten-2-one.

2′,4′,6′-Trimethylacetophenone. The ketone (10 mmol) was treated with 11 mmol of K-glucoride in THF at −25 °C. (The reduction was extremely sluggish at −78 °C.) After 60 h, the mixture was worked up by procedure B. By GC analysis, a 50% yield of the product alcohol was realized. The product was isolated by bulb-to-bulb distillation: bp 80–85 °C/0.1 mmHg; yield 1.5 g (a mixture of the ketone and the product alcohol). It was further

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purified by preparative GC (20% Carbowax, 6 ft, 150 °C, isothermal): $[\alpha]^{22}_D$ +18.08° (c 1.55, ethanol), 35% ee, R, based on $[\alpha]^{20}_d$ +52° (c 1.53, ethanol).[29]

4-Chlorobenzophenone. The ketone (10 mmol) was treated with 11 mmol of K-glucoride in THF at −78 °C. After 48 h, GC analysis (10% SP-2100, 1 ft, 160 °C) indicated the formation of 88% 4-chlorobenzhydrol. The pentane extract worked up by procedure B was concentrated. Then the residue was purified by column chromatography (silica gel, 60–200 mesh) using cyclohexane–ethyl acetate (1:1) as eluent. The fraction containing pure 4-chlorobenzhydrol was concentrated and the pure alcohol was obtained: mp 56–58 °C [lit.[30] mp 54–56 °C)]; $[\alpha]^{22}_D$ +1.87° (c 6.75, $CHCl_3$); 11.5% ee, based on $[\alpha]^{25}_D$ −16.0° ($CHCl_3$).[30]

Ethyl 2,2-Dimethylacetoacetate. The ketone (10 mmol) was treated with K-glucoride (11 mmol) in THF at −78 °C by using the standard method. After 8 h, the mixture was worked up by procedure D. GC analysis (10% Carbowax 20M, 14 ft, 130 °C, isothermal) indicated the presence of 80% product alcohol. The product alcohol was isolated by bulb-to-bulb distillation. Yield: 1.1 g, bp 82–86 °C/18 mmHg. The alcohol was further purified by preparative GC (20% Carbowax 20M, 6 ft, 100 °C, isothermal): $[\alpha]^{22}_D$ −3.24° (neat), 43% ee, determined by capillary GC analysis (Supelcowax, 15 m, 160 °C, isothermal) of the MTPA esters.

3-Acetylpyridine. The reaction was followed by the standard method. After 12 h, the reaction mixture was worked up by procedure B, where chloroform was used as solvent for extraction. GC analysis (10% Carbowax 20M, 14 ft, 180 °C, isothermal) revealed the presence of 97% of the product alcohol. The product was isolated by bulb-to-bulb distillation. Yield: 1.1 g, bp 146–150 °C/17 mmHg. It was further purified by preparative GC (20% Carbowax 20M, 6 ft, 160 °C, isothermal): $[\alpha^{20}_D$ +28.15° (c 1.06, methanol), R, 70% ee based on $[\alpha]^{20}_D$ −40.2° (c 0.87, methanol).[31]

2-Chloroacetophenone. The ketone (10 mmol) was treated with 4 (11 mmol) in THF according to the standard method. After 12 h, the reaction mixture was quenched by the addition of anhydrous HCl (20 mmol) in ethyl ether precooled to −78 °C. The mixture was stirred at −78 °C for 1 h and then brought to room temperature. All of the ethereal solvent was pumped off in vacuo (14 mmHg, 25 °C). The residue was dissolved in 25 mL of ethyl ether–n-pentane (1:1). To this was added 7 mL of 2 N HCl, and the mixture was stirred at 25 °C for 0.5 h. Then the organic layer was separated and cooled to 0 °C. To this was added 8 mL of 3 N NaOH, and the mixture was stirred at 0 °C for 2 h. The aqueous layer was extracted with ethyl ether (25 mL × 2). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. The product styrene oxide was isolated by bulb-to-bulb distillation. Yield: 0.8 g, bp 85–87 °C/18 mmHg, GC ield, 82%. It was further purified by column chromatography (silica gel, 60–200 mesh) using cyclohexane–ethyl acetate (90:10) as eluent and then distillation: $[\alpha]^{22}_D$ −35.88° (c 1.14, benzene), S, 77% ee, based on calculated $[\alpha]^{18}_D$ +46.8° (c 1.08, benzene).[32]

***trans*-4-Phenyl-3-buten-2-one.** The ketone (10 mmol) was treated with K-glucoride (11 mmol) in THF at −78 °C following the standard method. After 12 h, the reaction mixture was worked up by procedure C. GC analysis (10% Carbowax 20M, 14 ft, 180 °C, isothermal) indicated the formation of 92% *trans*-4-phenyl-3-buten-2-ol without any 1,4-reduction products. The product was isolated by bulb-to-bulb distillation. Yield: 2.5 g (~50% pure by GC). It was further purified by column chromatography (silica gel, 60–200 mesh) using cyclohexene–ethyl acetate (80:20) as eluent. The fractions containing the product alcohol were combined and concentrated in vacuo (14 mmHg, 25 °C), and the pure compound was obtained: $[\alpha]^{22}_D$ +23.8° (c 5.78, chloroform), R, 60% ee., based on calculated $[\alpha]^{20}_D$ 39.6° (c 5.26, chloroform).[33] The results are summarized in Table VI. The workup procedure for the reduction of the other ketones in Table VI was either procedure A or B, except for procedure C for 2-acetylfuran and 4-phenyl-3-butyn-2-one.

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Registry No. 1, 582-52-5; 4, 101696-41-7; 5, 101711-32-4; 9-BBN, 280-64-8; 2-methylcyclohexanone, 583-60-8; 2-phenylcyclohexanone, 1444-65-1; 2-*tert*-butylcyclohexanone, 1728-46-7; 4-*tert*-butylcyclohexanone, 98-53-3; norcamphor, 497-38-1; camphor, 76-22-2; *cis*-2-methylcyclohexanol, 7443-70-1; *cis*-2-phenylcyclohexanol, 16201-63-1; *cis*-2-*tert*-butylcyclohexanol, 7214-18-8; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; bicyclo[2.2.1]-heptan-2-ol, 1632-68-4; 1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol, 10385-78-1; propiophenone, 93-55-0; (*R*)-1-phenyl-1-propanol, 1565-74-8; 2-butanone, 78-93-3; 3-methyl-2-butanone, 563-80-4; 3,3-dimethyl-2-butanone, 75-97-8; 2-octanone, 111-13-7; cyclohexyl methyl ketone, 823-76-7; 2,2-dimethylcyclopentanone, 4541-32-6; spiro[4.4]nonan-1-one, 14727-58-3; 2,2-dimethylcyclohexanone, 1193-47-1; (*R*)-2-hydroxybutane, 14898-79-4; (*R*)-3-methyl-2-butanol, 1572-93-6; (*R*)-3,3-dimethyl-2-butanol, 1572-96-9; (*R*)-2-octanol, 5978-70-1; (*R*)-α-methylcyclohexanemethanol, 3113-99-3; (*R*)-2,2-dimethylcyclopentanol, 109530-56-5; (*R*)-spiro[4.4]nonan-1-ol, 21945-23-3; (*R*)-2,2-dimethylcyclohexanol, 112575-61-8; acetophenone, 98-86-2; butyrophenone, 495-40-9; isobutyrophenone, 611-70-1; valerophenone, 1009-14-9; pivalophenone, 938-16-9; 2′-methylacetophenone, 577-16-2; (*R*)-1-phenylethanol, 1517-69-7; (*R*)-1-phenyl-1-butanol, 22144-60-1; (*R*)-2-methyl-1-phenyl-1-propanol, 14898-86-3; (*R*)-1-phenyl-1-pentanol, 19641-53-3; (*R*)-2,2-dimethyl-1-phenyl-1-propanol, 23439-91-0; (*R*)-1-(2-methylphenyl)ethanol, 42070-90-6; methyl pyruvate, 600-22-6; ethyl pyruvate, 617-35-6; isopropyl pyruvate, 923-11-5; *tert*-butyl pyruvate, 76849-54-2; ethyl 2-oxobutanoate, 15933-07-0; ethyl 2-oxopentanoate, 50461-74-0; methyl 3-methyl-2-oxobutanoate, 3952-67-8; ethyl 3-methyl-2-oxobutanoate, 20201-24-5; methyl 3,3-dimethyl-2-oxobutanoate, 38941-46-7; ethyl 3,3-dimethyl-2-oxobutanoate, 5333-74-4; ethyl 4-methyl-2-oxopentanoate, 26073-09-6; methyl benzoylformate, 15206-55-0; ethyl benzoylformate, 1603-79-8; isopropyl benzoylformate, 31197-66-7; ethyl α-oxo-1-naphthaleneacetate, 33656-65-4; (*S*)-methyl 2-hydroxypropanoate, 27871-49-4; (*S*)-ethyl 2-hydroxypropanoate, 687-47-8; (*S*)-isopropyl 2-hydroxypropanoate, 63697-00-7; (*S*)-*tert*-butyl 2-hydroxypropanoate, 13650-70-9; (*S*)-ethyl 2-hydroxybutanoate, 88271-13-0; (*S*)-ethyl 2-hydroxypentanoate, 88945-70-4; (*S*)-methyl 3-methyl-2-hydroxybutanoate, 24347-63-5; (*S*)-ethyl 3-methyl-2-hydroxybutanoate, 63674-18-0; (*S*)-methyl 3,3-dimethyl-2-hydroxybutanoate, 103499-39-4; (*S*)-ethyl 3,3-dimethyl-2-hydroxybutanoate, 103499-40-7; (*S*)-ethyl 4-methyl-2-hydroxypentanoate, 60856-85-1; (*S*)-methyl α-hydroxybenzeneacetate, 21210-43-5; (*S*)-ethyl α-hydroxybenzeneacetate, 13704-09-1; (*S*)-isopropyl α-hydroxybenzeneacetate, 53439-96-6; (*S*)-ethyl α-hydroxy-1-naphthaleneacetate, 103499-41-8; 3,3-diethylpentanone, 17535-47-6; 1,1,1-triphenylacetone, 795-36-8; 2,2,2-triethylacetophenone, 50390-35-7; 2,2,2-triphenylacetophenone, 466-37-5; 2′,4′,6′-trimethylacetophenone, 1667-01-2; 4-chlorobenzophenone, 134-85-0; ethyl 2,2-dimethylacetoacetate, 597-04-6; 2-acetylfuran, 1192-62-7; 2-acetylthiophene, 88-15-3; 3-acetylpyridine, 350-03-8; 2-chloroacetophenone, 532-27-4; 2,2,2-trifluoroacetophenone, 434-45-7; *trans*-4-phenyl-3-buten-2-one, 1896-62-4; 4-phenyl-3-butyn-2-one, 1817-57-8; 3,3-diethyl-2-pentanol, 66793-94-0; (*S*)-1,1,1-triphenyl-2-propanol, 102282-60-0; 2,2-diethyl-1-phenyl-1-butanol, 5336-68-5; (*R*)-1,2,2,2-tetraphenylethanol, 21003-63-4; (*R*)-1-(2,4,6-trimethylphenyl)ethanol, 1517-71-1; α-phenyl-4-chlorobenzenemethanol, 119-56-2; ethyl 3-hydroxy-2,2-dimethylbutanoate, 7505-94-4; (*S*)-1-(2-furyl)-ethanol, 112653-32-4; (*R*)-1-(2-thienyl)ethanol, 86527-10-8; (*R*)-1-(3-pyridyl)ethanol, 7606-26-0; (*S*)-2-chloro-1-phenylethanol, 70111-05-6; (*S*)-2,2,2-trifluoro-1-phenylethanol, 340-06-7; (*R*)-*trans*-4-phenyl-3-buten-2-ol, 62413-47-2; 4-phenyl-3-butyn-2-ol, 5876-76-6.

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