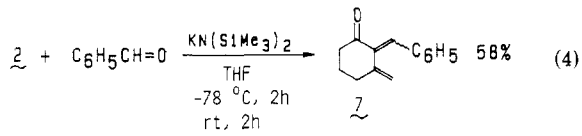
hexamethyldisilazide,[10] **2** reacts with an aldehyde at the α-position to afford the cyclohexanone **7** having two exo double bonds in good yield (eq 4). The reaction possibly



(4)

proceeds through a C=C bond isomerization of an initially formed aldolate followed by a Peterson-like elimination. Furthermore, these results apparently indicate that the fluoride-catalyzed reaction takes place in a charge-controlled manner like an enolate anion, which may support the generation of *naked enolate anion* from **2**[9,11] in this reaction.

As shown in the tables, the present procedure appears to be applicable to other cyclic enones as well.

Thus, with γ-silyl α,β-unsaturated enones, an appropriate choice of a catalyst or electrophile has allowed several types of synthetically useful regio- and chemoselective condensation reactions with carbonyl compounds or their derivatives.

Acknowledgment. This work is partially supported by a Grant from the Ministry of Education, Science, and Culture of the Japanese Government. We are also indebted to Toray Silicone Co. for the generous supply of chlorotrimethylsilane.

(10) In place of this base, use of lithium diisopropylamide gave much less satisfactory results.
(11) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598.

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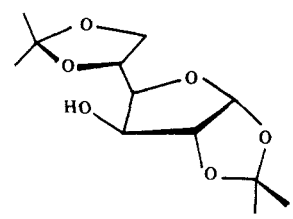
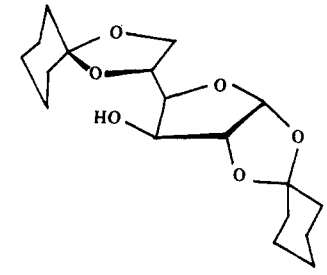
Potassium 9-*O*-(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane. A New, Effective Chiral Borohydride Reagent[1]

Summary: A convenient and simple synthesis of a new chiral borohydride reagent, potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo-[3.3.1]nonane, consisting of a single reducing species, is described. The new reagent is generally effective for the asymmetric reduction of alkyl phenyl ketones and hindered aliphatic ketones.

Sir: Among a wide variety of naturally occurring chiral synthons, monosaccharide derivative has been one of the most attractive chiral auxiliaries for the modification of sodium borohydride[2] or lithium aluminum hydride.[3] A successful use of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (DIPGF)[2d] or 1,2:5,6-di-*O*-dicyclohexylidene-α-D-glucofuranose (DCHGF)[2e] for modification of sodium borohydride in the presence of carboxylic acids was reported recently to achieve up to 83% enantiomeric excess (ee) in the reduction of propiophenone. Unfortunately, the authors report that their reagent appears to be a complex mixture and they could not assign a specific structure to the reagent which achieved this promising 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 auxiliary on the asymmetric yield achieved.



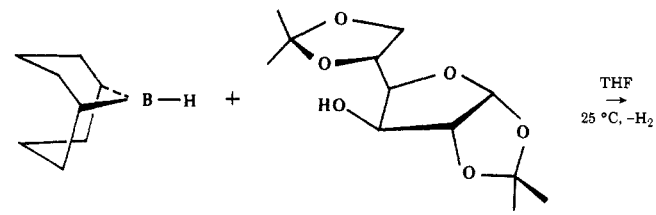
DIPGF



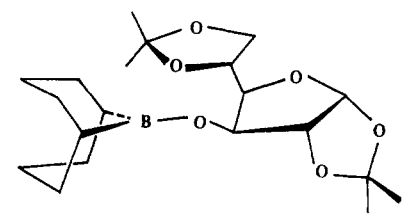
DCHGF

The recent development of a general synthesis of potassium 9-alkoxy-9-boratabicyclo[3.3.1]nonanes[4] by the reaction of potassium hydride with the corresponding borinic esters offered promise for the synthesis of such chirally modified borohydride reagents. Moreover, this class of borohydrides possesses 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.

Accordingly, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (DIPGF, **2**) was selected for study as the chiral auxiliary. The 9-BBN derivative, 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-borabicyclo[3.3.1]nonane (9-*O*-DIPGF-9-BBN, **3**) was easily prepared by treating this compound with 9-borabicyclo[3.3.1]nonane (9-BBN, **1**) (eq 1). The borinic ester was converted into



9-BBN, 1 DIPGF, 2



(1)

9-*O*-DIPGF-9-BBN, 3

(1) This work was presented at the 190th National Meeting of the American Chemical Society, Chicago, September 1985.

(2) (a) Hirao, A.; Mochizuki, H.; Nakahama, S.; Yamazaki, N. *J. Org. Chem.* **1979**, *44*, 1720. (b) Hirao, A.; Nakahama, S.; Mochizuki, D.; Itsuno, S.; Ohowa, M.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1979**, 807. (c) Hirao, A.; Nakahama, S.; Mochizuki, H.; Itsuno, S.; Yamazaki, N. *J. Org. Chem.* **1980**, *45*, 4231. (d) Hirao, A.; Itsuno, S.; Owa, M.; Nagami, S.; Mochizuki, H.; Zoorov, H. H. A.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 900. (e) Morrison, J. D.; Grandbois, E. R.; Howard, S. I. *J. Org. Chem.* **1980**, *45*, 4229. (f) Review: Midland, M. M. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 2, and references cited therein.
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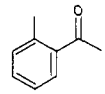
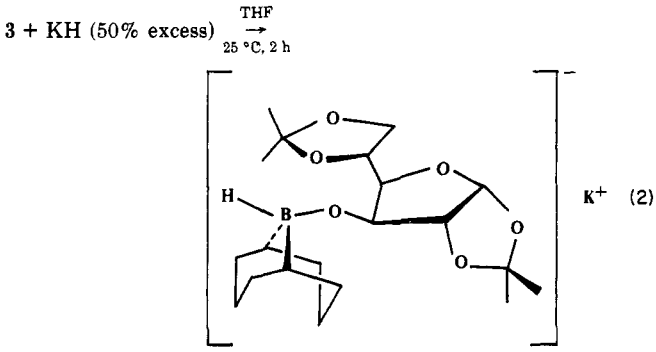
Table I. Reduction of Prochiral Aromatic Ketones with K 9-*O*-DIPGF-9-BBNH in THF at -78 °C[a]

ketones	K 9-*O*-DIPGF-9-BBNH time, h	yield,[e] %	$[\alpha]^{22}_D$, obsd, deg	config	% ee	% ee NB-Enantride[b]	% ee Binal-H[c]	% ee $NaBH_4$-IBA-DIPGF[d]
	16	95	+33.92 (neat)	*R*	78[f]	70	95	78
	16	93	+25.82 (neat)	*R*	92[g]		98	83
	36	96	+21.33 (neat)	*R*	87[h]		71	57
	40	93	+25.96 (*c* 2.2, benzene)	*R*	100[i] 97[j]		44	
	24	93	+50.46 (neat)	*R*[k]	91[j]			

[a] $[H^-]$:[ketone] = 1.1:1.0, [ketone] = 0.3 M. [b] Registered name of Aldrich Company, ref 6. [c] Reference 5. [d] Reference 2d and 2e. [e] By GC analysis. [f] Based on $[\alpha]_{D,max}$ 43.5° (neat), ref 7. [g] Based on $[\alpha]_{D,max}$ 28.1° (neat), ref 7. [h] Based on $[\alpha]_{D,max}$ 24.6° (neat), ref 8. [i] Based on $[\alpha]^{22}_{D,max}$ 25.9° (*c* 2.2, benzene), ref 7. [j] By capillary GC analysis of the MTPA esters. [k] Absolute configuration is probably *R*, based on the order of elution of MTPA derivatives in capillary GC analysis and (+) sign of rotation.

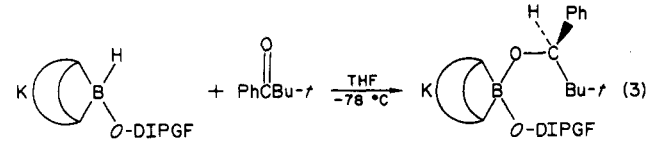
the corresponding borohydride reagent, potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane (K 9-*O*-DIPGF-9-BBNH, **4**) by treatment with potassium hydride, in essentially quantitative yield (eq 2).



K 9-*O*-DIPGF-9-BBNH, **4**

The new reagent, K 9-*O*-DIPGF-9-BBNH, **4**, proved relatively stable toward disproportionation, especially when the solution in THF was stored over excess potassium hydride under a positive pressure of nitrogen. The reagent **4** exhibited the characteristic chemical shift in the ^{11}B NMR (δ 1.33, br s), the characteristic B–H stretching absorption in the IR (ν_{B-H} = 2038 cm^{-1}), and analyzed for the stoichiometric ratio of K:B:H = 1:1:1. This reagent is the first example of a well-defined chiral borohydride reagent containing a monosaccharide as the chiral auxiliary.

The reagent **4** reduces ketones smoothly even at -78 °C in THF. Reduction of pivalophenone with the reagent yields 97–100% optically pure (*R*)-(+)-2,2-dimethyl-1-phenylpropanol (eq 3). To our knowledge, this is the first time that such a high optical yield has been achieved for the asymmetric reduction of this particular substrate.



K 9-*O*-DIPGF-9-BBNH, **4** 97-100% ee, *R*

Similarly, in the reduction of a series of alkyl phenyl ketones, consistently high optical yields are obtained, such as 78% for acetophenone, 92% for propiophenone, 87% for isobutyrophenone, and 91% for 2'-methylacetophenone (Table I). It is noteworthy that the optical yields obtained by the new reagent in the reduction of more hindered alkyl phenyl ketones, such as 97–100% for pivalophenone and 87% for isobutyrophenone, are considerably higher than the values obtained (44% and 71%, respectively) by the recently reported highly promising Binal-H reagent.[5] Moreover, the reagent appears to give highly consistent results. All of the alcohols obtained were enriched in the *R* enantiomers.

Reductions of aliphatic ketones were also carried out with the new reagent **4**. However, the reductions of unhindered ketones were much less favorable, achieving only limited optical yields, such as 3% for 2-butanone and 36% for methyl isopropyl ketone, respectively. For the reduction of such ketones, NB-Enantride[6] is much more favorable. However, the reduction of pinacolone, which is relatively hindered, provides a moderately high optical yield, 70%, much better than that provided by NB-Enantride, 2%. Similarly, in the reduction of a series of relatively hindered alicyclic ketones, high optical yields are obtained, such as 84% for 2,2-dimethylcyclopentanone, 82% for spiro[4.4]nonan-1-one, and 64% for 2,2-dimethylcyclohexanone, respectively. These optical yields obtained by asymmetric reduction of relatively hindered aliphatic and alicyclic ketones appear to be among the best reported in the literature for these substrates. Again, all of the alcohol products obtained were consistently enriched in their *R* enantiomers.

The following procedure served for the synthesis of the reagent **4**. All of the operations were performed under N_2 atmosphere. To a slurry of 9-BBN, **1** (32.3 g, 265 mmol), suspended in THF (200 mL) was added the solution (330 mL) of DIPGF, **2** (69 g, 265 mmol), in THF dropwise via a double-ended needle with vigorous stirring. Evolution of H_2 ceased within 1 h, and the mixture was stirred for an additional 2 h to ensure completion. Evaporation of solvent, followed by distillation under vacuum, yielded highly viscous 9-*O*-DIPGF-9-BBN, **3** (89 g, 88% yield): bp 198–201 °C/0.5 torr; ^{11}B NMR δ 56.30 (s); MS, M^+ 380.

(5) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.
(6) Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2495.

An oil suspension of potassium hydride, transferred to a flask, was allowed to settle and most of the oil decanted with a double-ended needle. Then the potassium hydride was washed with pentane (3 × 100 mL). To this oil-free potassium hydride (12 g, 300 mmol) suspended in THF (150 mL) was added a THF solution (250 mL) of **3** (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 2038 cm^{-1} (s). Hydride and potassium were determined as H_2 and KOH following hydrolysis; boron was estimated as 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 following procedure for the reduction of pivalophenone to (*R*)-(+)-2,2-dimethyl-1-phenylpropanol is representative of the asymmetric reductions. The THF solution (1.0 M, 10 mL) of pivalophenone (10 mmol), precooled to −78 °C, was added to the solution (0.48 M, 23 mL) of the reagent **4** (11 mmol) at −78 °C via a double-ended needle. After 40 h, unreacted hydride was quenched by injecting anhydrous HCl in ee precooled to −78 °C. Then the mixture was raised to 25 °C, and the reduction product was extracted with pentane after hydrolysis by dilute HCl followed by conversion of the borinic acid moiety into the "ate" complex[4a] using aqueous NaOH. The pentane layer was washed with brine, dried ($MgSO_4$), and filtered, and the solvent was evaporated. Distillation of the residue provided 1.42 g of (*R*)-(+)-2,2-dimethyl-1-phenylpropanol (92% yield, bp 114–118 °C/16 torr, [lit.[5] bp 130–140 °C/20 torr] containing a small amount of starting ketone). The alcohol product was further purified by preparative GLC (20% Carbowax 20M, 6 ft × $^1/_2$ in. column, 150 °C), and the rotation was measured: $[\alpha]^{22}_D$ +25.96° (*c* 2.2, benzene), 100% ee based on the maximum reported rotation $[\alpha]_{D,max}$ +25.9° (*c* 2.2, benzene).[7] Capillary GLC analysis (Supelcowax, 15 m) of MTPA esters[9] of the product alcohol revealed a composition of 98.4% *R* + 1.6% *S* (i.e., 96.8% ee), in close agreement with optical rotation measurement.

In conclusion, the present study provides a convenient and simple synthesis of an effective chiral borohydride reagent containing a single hydride per molecule and consisting of a single characterized reducing species. The new reagent reduces prochiral alkyl phenyl ketones and relatively hindered aliphatic ketones, effectively providing high optical yields of the corresponding alcohols consistently enriched in their *R* enantiomers. This study can be extended to the synthesis of a variety of simple, stable, and characterized chiral borohydride reagents incorporated with various chiral auxiliaries. Consequently, one should be able to design improved chiral borohydride reagents by systematic studies of the effect of the chiral moiety on the asymmetric induction. Such systematic studies are underway.

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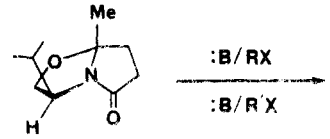
An Asymmetric Synthesis of Chiral 4,4-Disubstituted Cyclohexenones in High Enantiomeric Purity

Summary: An efficient approach to the title compounds in >95% ee has been accomplished by metalation and alkylation of chiral bicyclic lactams derived from δ-keto acids and (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol.

Sir: Our recent successes in reaching chiral compounds containing a quaternary stereocenter[1] has led to 3,3-disubstituted cyclopentenones **3**.[2] Thus, dialkylation of the readily available bicyclic lactam **1** by successive treatment with LDA and two different alkyl halides to **2**, followed by reduction and hydrolysis, gave **3** in >99% ee. It was



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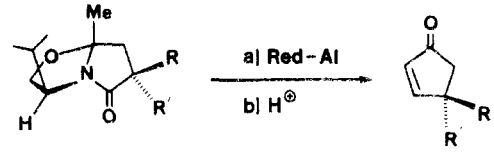
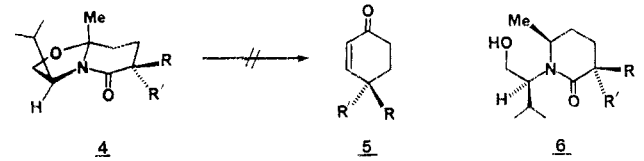


2 3

assumed that the homologated bicyclic lactam **4**, under similar conditions, would provide the chiral cyclohexenone, **5**. However this was not to be the case since all attempts to reduce the lactam carbonyl to aldehyde gave unwanted side products, the major one being the piperidone **6**. The



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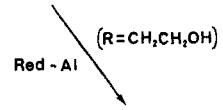

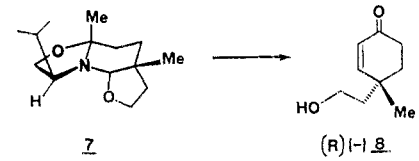

7 (R)-(-)-8

latter arises from reductive cleavage of the oxazolidine ring.

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