Table I. $\delta(^{13}C)$ Values (in ppm, Relative to Me_4Si) of Reduced Azanaphthalenes[a]

	solvent	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
8	CD_3CN	56.2		36.0		140.8	141.2		132.4	155.2
9	CD_3CN	148.8		135.3		39.5	41.1		157.5	127.9
3	CD_3CN	42.0	42.0		115.3	118.9	118.9	115.3	135.0	135.0
6	CD_3OD	41.0	38.6		122.7	113.75	119.75		144.5	133.6
5	CD_3OD	149.0	147.6		138.9	126.6	154.8		151.4	138.9
4	CD_3CN	43.7		*128.8*	*125.6*	*119.4*	*120.4*	*127.2*	149.3	138.2

[a] Assignments based on additivity relationships and gated mode off-resonance splittings; preliminary assignments are italicized. Measurements were made at 25.05 MHz with a JEOL FX100 spectrometer. Internal Me_4Si served as a reference in all cases.

transformations which limit the synthetic usefulness of each method. Direct reduction by sodium borohydride and TFA circumvents each of these difficulties and provides a direct route to the tetrahydropteridines.

The structures assigned to the compounds reported herein were confirmed by proton magnetic resonance (^1H NMR), ^{13}C NMR (Table I), and mass spectrometric data. The reduction products can be easily distinguished by the characteristic upfield shift in the ^{13}C NMR spectrum of the newly formed sp^3 carbons and the overall simplification of the aromatic proton region in the ^1H NMR spectrum. These reduction products are relatively thermally stable and resistant to fragmentation so that molecular ions could be observed during mass spectrometric analysis.

Experimental Section

General Procedure for the Reduction of Azanaphthalenes. The nitrogen-containing aromatic (1.0 g) was dissolved in tetrahydrofuran (10 mL), and sodium borohydride (1.0 g) was added with stirring. Trifluoroacetic acid (10 mL) was added over 15 min without cooling, and the mixture was stirred an additional 45 min. Water (5 mL) was added and the pH adjusted with a 50% sodium hydroxide solution to pH 7. Dichloroethane (50 mL) was added to the solution, and vigorous stirring was begun. The organic layer was separated, dried (Na_2SO_4), and removed at reduced pressure, yielding an oil which solidified upon cooling.

1,2,3,4-Tetrahydroquinoxaline (3). The reaction of 1 (1 g) by the general procedure gave an oil which solidified when cooled. The solid, when recrystallized from ethyl acetate, gave 910 mg (90%) of colorless crystals: mp 95–96 °C (lit.[5] 96–97 °C); ^1H NMR (CD_3CN) δ 4.5 (4 H, s, CH_2), 5.4 (2 H, s, NH), 7.75 (4 H, m); mass spectrum, *m/e* 134, 110, 104, 92, 88, 87, 86.

1,2-Dihydroquinazoline (4). The reaction of **2** by the general procedure gave a solid which when recrystallized from ethyl acetate resulted in the formation of yellow waxy plates (860 mg, 85%): mp 168–169 °C dec; ^1H NMR (CD_3CN) δ 4.5 (2 H, s, CH_2), 6.8 (4 H, m), 7.3 (1 H, s, NH), 9.3 (1 H, s, =CH); mass spectrum, *m/e* 132, 105, 77, 76.

Pyrido[2,3-*b*]-1,2,3,4-tetrahydropyrazine (6). The reaction of **5** (1 g) by the general procedure gave a crude oil which when recrystallized from anhydrous ether gave 765 mg (75%) of a colorless solid: mp 128–129 °C; ^1H NMR (CD_3CN) δ 3.4 (1 H, m), 6.7 (3 H, m), 8.65 (2 H, s, br d); mass spectrum, *m/e* 132, 120, 107, 104, 93, 79, 77.

Tetrahydropteridines 8 and 9. Reduction of pteridine **7** (726 mg) gave 694 mg (94%) of an oil which was extracted with anhydrous ether (25 mL), and the residue was taken up in dichloromethane (25 mL). Each solution was evaporated at reduced pressure, and the residues were taken up in ethanol–cyclohexane (1:7). Each separate extract was chromatographed on Florisil following the method of Taylor and Sherman.[8] Washing the column with ethanol–cyclohexane (1:7) eluted **9**. **8** was eluted from the column with ethanol–hexane (3:2). The eluants for each compound were combined, and solvent was removed at reduced pressure with minimal heating. Recrystallization of each residue from carbon tetrachloride gave **9** (248 mg, 38%), mp 144–145 °C (lit.[9] mp 146 °C), and **8** (352 mg, 58%), mp 142–143 °C (lit.[8] mp 144–146 °C). ^1H NMR ($CDCl_3$) **9**: δ 3.65 (2 H, s), 5.95 (2 H, s), 7.55 (2 H). ^1H NMR ($CDCl_3$) **8**: δ 3.75 (4 H, s), 5.8 (2 H, s), 7.3 (1 H, s), 7.8 (1 H, s).

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Registry No.—**1**, 91-19-0; **2**, 253-82-7; **3**, 3476-89-9; **4**, 53378-34-0; **5**, 322-46-3; **6**, 35808-40-3; **7**, 91-18-9; **8**, 10593-78-9; **9**, 26538-74-9.

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Asymmetric Reduction of Ketones with Sodium Borohydride in the Presence of Hydroxymonosaccharide Derivatives

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Many chemists have attempted to prepare optically active compounds with chiral reagents, catalysts, and media. Of these investigations, the use of chirally modified metal hydrides to reduce prochiral ketones continues to be studied actively and some high enantiomeric excesses of chiral carbinols have now been achieved.[1] Among the metal hydrides, lithium aluminum hydride modified with chiral alcohols, amino alcohols, and amines has been mainly employed.[2] Little attention has been paid, however, to the use of sodium borohydride in asymmetric reduction.

Recently, asymmetric induction in the borohydride reduction of carbonyl compounds has been carried out in the presence of optically active catalysts under phase-transfer conditions.[3] Almost all prochiral ketones undergo borohydride reduction in the presence of various optically active "onium" salts as catalysts to afford chiral carbinols. The highest optical yield in the studies was 32% for phenyl *tert*-butyl ketone.[3c] In another study, carbinols in 5–10% enantiomeric excesses were obtained in the reduction of ketones with sodium borohydride in the presence of β-cyclodextrin in alkaline aqueous solution.[4]

In contrast to these systems using aqueous conditions, we now report asymmetric reduction of ketones with sodium borohydride in nonaqueous solution in the presence of various hydroxymonosaccharide derivatives, as shown in **1–6**, which are readily synthesized from the corresponding carbohydrates such as glucose and fructose.

Acetophenone and propiophenone are easily reduced with sodium borohydride in the presence of **1–6** to afford carbinols in relatively high optical yields. The results are summarized in Table I. Generally, the reduction of carbonyl compounds

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Table I. Reduction of Acetophenone and Propiophenone with Sodium Borohydride in Benzene or in Tetrahydrofuran (THF) in the Presence of Hydroxymonosaccharide Derivatives, 1–6, at 25 °C[a]

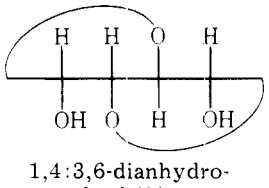
monosaccharides	registry no.	ketones	solvents	yield,[b] %	$[\alpha]^{20}_D$	optical yield, %	config
1	652-67-5	acetophenone[e]	THF	100	−3.11[c]	5.9	(−)-*S*[g]
2	641-74-7	acetophenone	THF	100	−4.01[c]	7.6	(−)-*S*
3	14686-89-6	acetophenone	benzene	64	+6.67[c]	12.7	(+)-*R*[h]
1		propiophenone[f]	THF	100	−6.54[d]	18.8	(−)-*S*[i]
2		propiophenone	THF	100	−6.70[d]	19.3	(−)-*S*
3		propiophenone	benzene	78	+13.68[d]	39.3	(+)-*R*[j]
4	23397-76-4	propiophenone	benzene	43	+12.19[d]	35.0	(+)-*R*
5	20880-92-6	propiophenone	benzene	100	−7.80[d]	22.4	(−)-*S*
6	4064-06-6	propiophenone	benzene	100	+2.32[d]	8.1	(+)-*R*

[a] Conditions: Reactions for 120 h in benzene and 48 h in THF. $NaBH_4$, 30 mmol; ketones, 30 mmol; monosaccharides **1–2**, 30 mmol, and **3–6**, 60 mmol. Total volume of the solvent, 60 mL. [b] Determined based on relative peak areas of carbinol and unreacted ketone in GC. [c] Optical yield was determined by optical rotation. Maximum value of phenylmethylcarbinol for $[\alpha]^{23}_D$ −52.5 (*c* 2.27, CH_2Cl_2).[11] [d] Maximum value of phenylethylcarbinol for $[\alpha]^{20}_D$ +34.8 (*c* 8, diethyl ether).[12] [e] Registry no. 98-86-2. [f] Registry no. 93-55-0. [g] Registry no. 1445-91-6. [h] Registry no. 1517-69-7. [i] Registry no. 613-87-6. [j] Registry no. 1565-74-8.

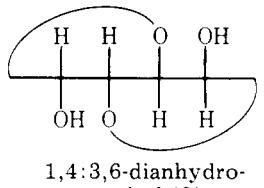
Table II. Asymmetric Reduction of Various Ketones with Sodium Borohydride in the Presence of 1 at 25 °C[a]

ketones	registry no.	solvents	yield,[b] %	$[\alpha]^{20}_D$	optical yield, %
$CH_3CO(i\text{-}C_4H_9)$	108-10-1	THF	100	+0.61[c]	3.0[g]
$CH_3COC_6H_4$		THF	100	−3.11	5.9
$C_2H_5COC_6H_5$		THF	100	−6.54	18.8
$C_2H_5COC_6H_5$		1,4-dioxane	100	−4.78	13.7
$C_2H_5COC_6H_5$		benzene/THF 1/1 (v/v)	100	−3.46	9.9
$C_2H_5COC_6H_5$		pyridine	100	−1.99	5.7
$n\text{-}C_3H_7COC_6H_5$	495-40-9	THF	100	−4.48[d]	4.1[h]
$i\text{-}C_3H_7COC_6H_5$	611-70-1	THF	100	−4.62[e]	9.7[i]
β-Naph-COC_6H_5	644-13-3	THF	100	+0.78[f]	1.9[j]

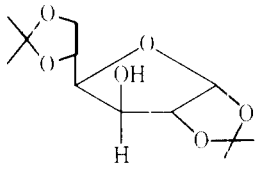
[a] Conditions: Reactions for 48 h. $NaBH_4$, 30 mmol; ketones, 30 mmol; **1**, 30 mmol. Total volume of the solvent, 60 mL. [b] Determined based on relative peak areas of carbinol and unreacted ketone in GC. [c] Maximum value for $[\alpha]^{20}_D$ −20.54 (neat).[13] [d] Maximum value for $[\alpha]^{20}_D$ −108.7 (neat).[14] [e] Maximum value for $[\alpha]^{20}_D$ +47.7 (*c* 6.8, $C_2H_5OC_2H_5$).[15] [f] Maximum value for $[\alpha]^{20}_D$ −41.9 (*c* 5, C_2H_5OH).[16] [g] Registry no. 16404-54-9. [h] Registry no. 22135-49-5. [i] Registry no. 34857-28-8. [j] Registry no. 69454-61-1.



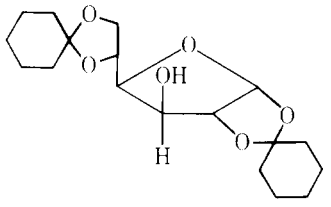
1,4:3,6-dianhydro-D-sorbtol (**1**)



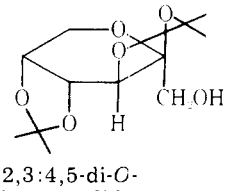
1,4:3,6-dianhydro-D-mannitol (**2**)



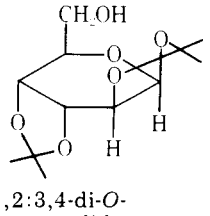
1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (**3**)



1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose (**4**)



2,3:4,5-di-*O*-isopropylidene-D-fructopyranose (**5**)



1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**6**)

with sodium borohydride has been conducted in alcoholic solutions. In the present asymmetric reduction, however, the reactions were carried out in benzene or tetrahydrofuran (THF) in order to increase the interaction between sodium borohydride and monosaccharide derivatives, possibly in their OH moieties.

In all cases examined here, asymmetric induction is at work. Among the monosaccharide derivatives tested, **3** led to the highest stereoselectivity observed and **4** was almost as effective. In fact, **3** afforded (*R*)-(+)-carbinol in an optical purity of 39.3% in benzene in the reduction of propiophenone. The presence of **3**, **4**, and **6** produced (*R*)-(+)-carbinols, whereas **1**, **2**, and **5** gave the opposite (*S*)-(−)-carbinol isomers. Propiophenone seems to be preferable to acetophenone in the asymmetric reduction under the same conditions.

In contrast, Červinka and co-workers[5] have reported that the reduction of acetophenone with lithium aluminum hydride, modified with **3** and **5** carried out in diethyl ether, afforded two (*R*)-(+)-phenylmethylcarbinols, which were 4 and 9% optically pure.

Among the asymmetric reduction of various ketones in the presence of **1** examined, the asymmetric reduction of propiophenone produced the highest optical yield (Table II). It looks like the more bulky groups are reduced in lower optical yields, i.e., naphthyl and $n\text{-}C_3H_7$ are lower than methyl, ethyl, or $i\text{-}C_3H_7$.

The role of the monosaccharide derivatives in the present system with sodium borohydride may be clearly different from chiral alcohols in the reductions with lithium aluminum hydride reported elsewhere.[2] In the case of lithium aluminium hydride, chiral alcohols readily react with the metal hydride to convert into chiral metal alkoxy hydrides which can be used in asymmetric reactions. Hydroxymonosaccharide derivatives, **1–6**, however, do not react with sodium borohydride at all, but

seem to interact strongly or to make coordinated complexes with sodium borohydride. Finally, in the presence of monosaccharides, sodium borohydride was found to be dissolved to some extent in THF in benzene and the reduction proceeded smoothly in either THF or benzene solution. In the absence of **1–6**, sodium borohydride was only slightly soluble in THF (ca. 0.1 g/100 mL at 25 °C) and insoluble in benzene and hence the reaction was extremely sluggish in the former and did not take place in the latter solution.

Optically active additives, **1–6**, are considered to be involved as chiral ligands or media in the present asymmetric reduction. These do not function as modified reagents but only enter into the reaction as intermediate complexes or solvates.

Experimental Section

Reagents. Ketones used here were purified by drying over CaH_2 and subsequent distillation in an atmosphere of nitrogen. THF and benzene were heated under reflux over sodium wire and distilled over $LiAlH_4$ in a nitrogen atmosphere. Sodium borohydride was purified twice by recrystallization from 2,5,8-trioxanonane. The hydroxymonosaccharide derivatives, 1,4:3,6-dianhydro-D-sorbitol (**1**),[6] 1,4:3,6-dianhydro-D-mannitol (**2**),[6] 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (**3**),[3] 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose (**4**),[8] 2,3:4,5-di-*O*-isopropylidene-β-D-fuructopyranose (**5**),[9] and 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**6**),[10] were prepared according to previous methods.

All the materials described were stored under a nitrogen atmosphere prior to use.

Instruments. Rotation were taken on a Zeiss Visual polarimeter with readings to ±0.02°. Gas chromatographic determination was made on a Simazu GC-6A using a Silicone SE-30 prepared column.

Procedures. Under a nitrogen atmosphere, a benzene solution of the monosaccharide (30 mmol for **1** and **2** and 60 mmol for **3–6** in 50 mL of benzene) was added to sodium borohydride (30 mmol) in benzene. After stirring for 3 h at 25 °C, the ketone (30 mmol) was added and the mixture was stirred for 120 h. The mixture was hydrolyzed with 1 N hydrochloric acid. The ether extracts were washed (H_2O, three times), dried ($NaSO_4$), and concentrated (water aspirator) to give a colorless oil. The crude product was purified by distillation under reduced pressure. No monosaccharide was detected by TLC. Reaction procedure in THF solution was conducted in the same way. Reaction time in THF was 48 h.

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Bimolecular Reductions of Aromatic Ketones and Aldehydes with the *n*-Butyllithium–$Fe_4S_4(SPh)_4$ System

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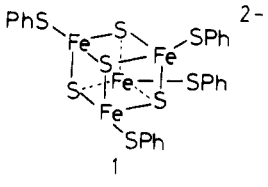
Although a tetrakis(mercapto-μ_3-sulfido-iron) cluster[1] is attractive as a model for a biological reducing agent of the ferredoxin type,[2] detailed descriptions as to function of the cluster are lacking. Recent studies have disclosed that the cluster catalyzes the transfer of electrons from external reductants to a nitrogen complex of molybdenum.[3] We have tried to utilize the cluster as an electron transfer carrier in a general organic redox reaction and found that $[Fe_4S_4(SPh)_4](n\text{-}Bu_4N)_2$ (**1**) mediates the transfer of electrons from



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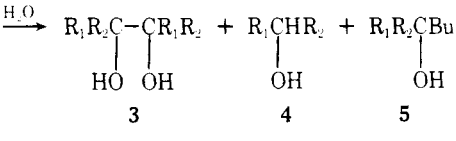
n-butyllithium to fluorenone.[4] Herein, we wish to describe our findings that the *n*-butyllithium–**1** system is effective as a reducing system for the bimolecular reductions of several aromatic ketones and aldehydes.

The *n*-butyllithium–**1** system was prepared by treating the cluster **1** under argon with *n*-butyllithium in degassed hexane–diethyl ether at 0 °C for 30 min. The reactions of ketones and aldehydes with the *n*-butyllithium–**1** system proceeded under mild conditions to give the corresponding pinacols **3**, hydrols **4**, and 1,2-addition products **5**. In these reactions,



2 3 4 5

n-butyllithium was oxidized to octane, butane, and 1- and 2-butenes. The cluster **1** was regenerated in over 97% purity on addition of benzenethiol instead of water to the reaction mixtures after the reaction.[5] In the iron ion–substrate molar ratio of 1:1, the yields of the products were dependent on the amount of *n*-butyllithium added. The optimum *n*-butyllithium–iron ion molar ratios to form predominantly pinacols are summarized in Table I. In the reduction of fluorenone having less negative reduction potential [$E_{1/2}$ (vs. SCE) = −1.29 and −1.95 V][6] than those of other ketones and aldehydes described in Table I, the formation of the fluorenone pinacol was observed in the *n*-butyllithium–iron ion molar ratio of 2:1 (entry 1). When the reduction of fluorenone was carried out in the molar ratio of 4:1, however, fluorenol was formed as a major product by a two-electron reduction.[4] In the cases of benzophenone, acetophenone, and benzaldehyde which have the first reduction potentials near the second reduction potential of fluorenone,[7] the *n*-butyllithium–iron ion molar ratio of

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