B. When a similar reaction was interrupted after half the theoretical amount of carbon dioxide had been evolved, the product was shown to consist of a mixture of 1 (R = Cl), 1 (R = O-*t*-Bu), and 1 (R = I) in the ratio 1:2:7.

Irradiation of 1-Iodoadamantane (1, R = I). The iodide 1 (R = I) was irradiated with the 200-W lamp under the following conditions to give the products noted: (a) in Freon 113 alone, yielding 1 (R = Cl) almost quantitatively; (b) in Freon 113 containing *tert*-butyl alcohol to give a mixture of 1-chloroadamantane, 1-adamantanol, and 1-*tert*-butoxyadamantane.

Registry No. 1 (R = COOH), 828-51-3; 2 (R = COOH), 699-55-8; 2 (R = I), 931-98-6; 3 (R = COOH), 18720-30-4; 3 (R = I), 930-80-3; 4 (R = COOH), 64725-77-5; 4 (R = I), 74725-75-0; 5 (R = COOH), 53292-20-9; 5 (R = I), 74725-76-1; 6 (R = COOH), 53578-15-7; 6 (R = I), 74725-77-2; *t*-BuOI, 917-97-5.

Asymmetric Reductions with Chiral Alkoxy(acyloxy)borohydrides

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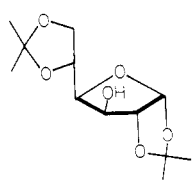
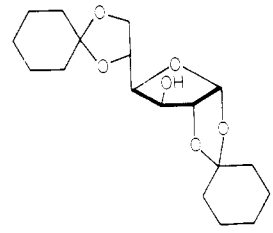
A number of modified lithium aluminum hydride reagents containing chiral ligands have been used to reduce unsymmetrical ketones asymmetrically.[1] Relatively little success, however, has been realized with chiral sodium borohydride derived systems.[2]

Recently, Yamazaki and co-workers described the asymmetric reduction of several ketones (but primarily propiophenone) with sodium borohydride in the presence of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (DIPGF) alone[3] and also sodium borohydride plus Lewis acids and DIPGF.[4] In the latter report as high as 88% ee was claimed although more typical values in the range of 25–55% were reported for propiophenone reductions. Unfortunately, in both papers the percent enantiomeric excess values for ethylphenylcarbinol are considerably higher than they should be because a "maximum rotation" value for the carbinol was used that is only about 63% of the true value.[5]

Independently, we have been investigating some related borohydride reducing systems. This paper will describe one that employs $NaBH_4$, a carboxylic acid, and 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose (DCHGF)[6] as ingredients. In THF solutions, variants of this system give percent enantiomeric excess values in the range of 35–50% for acetophenone and propiophenone reductions. These values are 2–3 times those obtained when the carboxylic acid is omitted from the recipe and are comparable to the true values obtained when $NaBH_4$ and Lewis acids are used with DIPGF.[4,5] Some of the features of this system have been explored, and the results suggest a hypothesis that may be helpful in the design of synthetic chiral borohydride modifiers.



DIPGF



DCHGF

Our general view of this process is that there is initial formation of an (acyloxy)borohydride,[7] which is soluble in THF. Addition of DCHGF or DIPGF (usually 2 equiv) results in the evolution of 1 equiv of dihydrogen over a period of 2–3 h, indicating addition of one hydroxy-monosaccharide unit to the (acyloxy)borohydride with formation of a mono-alkoxy(acyloxy) species. Then, somewhat more slowly, a second equivalent of dihydrogen is released as a bis[alkoxy(acyloxy)] intermediate is formed (Scheme I). Addition of 1 equiv of ketone along with the hydroxymonosaccharide or within the time period required for the release of the first equivalent of dihydrogen results in quantitative ketone reduction over a 48-h period and the production of an optically active carbinol.

Several variations on the above general scheme were examined by using acetophenone and propiophenone. In preliminary reactions we allowed $NaBH_4$ to react with 1 equiv of some chiral carboxylic acids and carried out reductions without adding any DCHGF. Such reagents, presumably chiral (acyloxy)borohydrides gave only a few percent asymmetric synthesis. Similarly, using chiral $PhCH(OH)CH_2OH$ as a secondary modifier gave no asymmetric induction. $NaBH_4$ and DCHGF (2 equiv) alone (no initial modification with carboxylic acid) gave about 18% ee and quantitative reduction with both acetophenone and propiophenone. Quantitative reductions and substantial increases in the percent enantiomeric excess were realized when both carboxylic acid and DCHGF modification were used. Table I shows some results.

As expected, in view of the absence of any asymmetric induction with chiral acids alone, if a chiral acid is used along with DCHGF, the sugar derivative is the controlling influence. Thus, enantiomeric acids (runs 8 and 9 in Table I) gave the same direction and virtually the same degree of asymmetric reduction when used with DCHGF. Racemic 2-phenylbutanoic acid was often used as the acid component, but achiral lipophilic acids like 3-methylbutanoic (isovaleric) acid were equally effective.

An interesting difference was observed between 2-phenylbutanoic acid and (+)- or (−)-pinanecarboxylic acid. In reactions involving the former as a preliminary modifier, the reaction solution remained clear for about 20 h, and then a gelatinous precipitate formed. In contrast, reductions involving the pinanecarboxylic acid enantiomers remained homogeneous over the entire 48-h reaction period. We believe this is merely a reflection of the relative lipophilicities of the alkoxy(acyloxy) intermediates that are produced; but it reveals one consideration that might be applied to the choice of the acid modifier if completely

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(2) For examples and leading references see: (a) J. P. Masse and E. R. Parayre, *J. Chem. Soc., Chem. Commun.*, 438 (1976); (b) C. Innis and G. Lamaty, *Nouv. J. Chim.*, 1(6), 503 (1977); (c) T. Sugimoto, Y. Matsumura, S. Tanimoto, and M. Okano, *J. Chem. Soc., Chem. Commun.*, 926 (1978); (d) S. I. Goldgerg et al., *J. Am. Chem. Soc.*, **100**, 6768 (1978); (e) R. Kinishi, Y. Nakajima, J. Oda, and Y. Inouye, *Agric. Biol. Chem.*, **42**, 869 (1978); (f) S. Colonna and R. Fornasier, *J. Chem. Soc., Perkin Trans. 1*, 371 (1978).

(3) A. Hirao, H. Mochizuki, S. Nakahama, and N. Yamazaki, *J. Org. Chem.*, **44**, 1720 (1979).

(4) A. Hirao, S. Nakahama, D. Mochizuki, S. Itsuno, M. Ohowa, and N. Yamazaki, *J. Chem. Soc., Chem. Commun.*, 807 (1979).

(5) In ref 3 and 4 a maximum rotation for ethylphenylcarbinol (erroneously called 3-phenylpropanol in ref 4) of $[\alpha]^{20}_D$ +34.8° (c 8, ether) was used. The correct value is $[\alpha]^{20}_D$ 55.54° in ether [P. A. Levene and L. Mikeska, *J. Biol. Chem.*, **70**, 355 (1926)]. Thus, to obtain true percent enantiomeric excess values one should multiply the reported values by 0.63.

(6) R. C. Hockett, R. E. Miller, and A. Scattergood, *J. Am. Chem. Soc.*, **71**, 3072 (1949).

(7) G. W. Gribble, "Eastman Organic Chemicals Bulletin", **No. 51**, Eastman Chemical Co., 1979, p 1.

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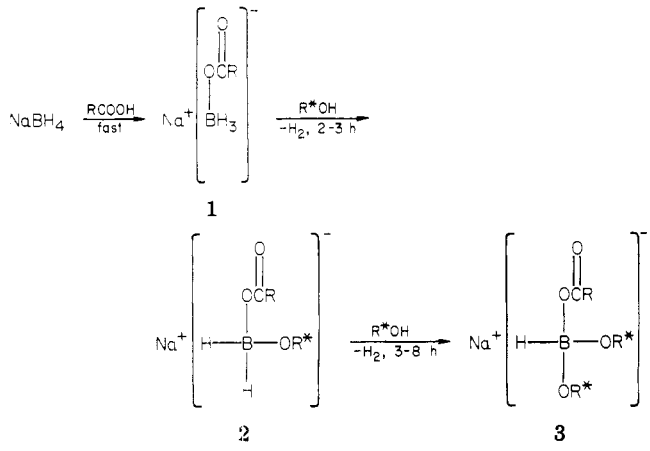
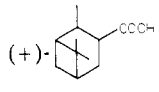
Scheme I[a]



[a] R*OH = DCHGF or DIPGF.

Table I. Ketone Reductions with Sodium Acyloxyborohydride Modified with DCHGF[a]

run	R in RC(O)Ph	RCOOH[b]	product % ee[c]
1	Me	(±)-PhCH(Et)COOH	44
2	Et		39[d]
3	CH_2Cl		25
4	$CH(CH_3)_2$		5
6[e]	Et		51
7	Me	$(CH_3)_2CHCH_2COOH$	46
8	Et	 (+)-[pinanecarboxylic acid]	39
9	Et	(−)-pinanecarboxylic acid	37

[a] 2 equiv (except for run no. 6; see footnote e). [b] 1 equiv. [c] All products had the *R* absolute configuration; all reductions in this table were quantitative (48 h). [d] A comparable experiment with DIPGF as the sugar gave 37% ee. [e] In this run a fivefold excess of reducing reagent **3** was used.

homogeneous reactions are desired.

The stereoselectivity of the (acyloxy)borohydride–sugar system [(±)-PhCH(Et)COOH and 2 equiv of DCHGF] toward two substituted cyclohexanones was also determined. Reduction of 4-*tert*-butylcyclohexanone gave 57% *cis*- and 43% *trans*-4-*tert*-butylcyclohexanol. Reduction of 2-methylcyclohexanone gave 60% *cis*- and 40% *trans*-2-methylcyclohexanol.

Asymmetric reduction was found to be highest for acetophenone and propiophenone [(±)-PhCH(Et)COOH/2 equiv of DCHGF system]. Other phenones gave lower percent enantiomeric excess values (Table I, runs 3–5). However, in related work with modified $LiAlH_4$ reagents and phenacyl chloride we have observed that there is extensive hydrogenolysis, so that along with the desired chlorohydrin reduction product a considerable amount of phenylmethylcarbinol is formed. With the (acyloxy)borohydride reagents, no hydrogenolysis was observed (run 3, Table I).

Increasing the waiting period after the addition of sugar derivatives was found to increase the percent enantiomeric excess. However, aging periods equal to or longer than the approximate time required for the evolution of 2 equiv of dihydrogen after the addition of hydroxymonosaccharide were counterproductive overall because the reduction yield was decreased drastically (Table II). We have observed that solutions aged more than 8 h after the addition of 2 equiv of DCHGF lose hydride (as measured by H_2 evolution on hydrolysis). This may be the result of some as yet unidentified side reaction of the dialkoxy(acyloxy)borohydride species.

Table II. Effect of Waiting Time after Addition of 2 Equiv of DCHGF to $NaBH_4$/(±)-PhCH(Et)COOH before the Addition of Propiophenone

waiting time, h	% reduction	% ee
0	100	35
1	100	38
2	100	39
8	49	42
45	28	41

A discussion of the precise character of this chiral reducing system is complicated by the fact that several potential reducing species exist simultaneously in reaction mixtures, and their relative contributions to the rate and stereoselectivity are hard to assess. Our current view is that under the reaction conditions most frequently used (1 equiv of RCOOH, then 2 equiv of R*OH, and then ketone addition after a 2-h waiting period) the following description is appropriate. As shown in Scheme I, the (acyloxy)borohydride **1** forms almost instantaneously. We have measured H_2 evolution to confirm this. In about 2 h another equivalent of H_2 is evolved as **2** forms. This is the point at which ketone has usually been added. From this point on our analysis is rather speculative. We believe that reduction by **2** is faster than reduction by **1**. When **2** reduces the ketone a new species, $Na^+[BH(OR^*)(OR')OOCR]^-$ (**4**), is introduced. Intermediate **4** is similar to **3** but contains one alkoxy group from the sugar derivative and one from the reduced ketone. Competition for **2** by the ketone and the second R*OH means that some, but not all, of the ketone will be reduced by **2**; the rest is reduced by either **3** or **4**. We believe that reduction by **2** is more rapid than that by **3** or **4**, the latter being quite hindered sterically, but that **2** gives a lower percent enantiomeric excess than **3**. In an experiment involving 2 equiv of DCHGF that was stopped after a 3-h reduction time, 41% reduction and 34% ee were observed. The percent reduction was *higher* than expected, suggesting that, indeed, **2** may reduce ketones relatively rapidly. However, the percent enantiomeric excess is *lower* than that observed when such a reaction is allowed to proceed for 48 h (39%). Also, a reduction system using only 1 equiv of DCHGF gave only 31% ee after 48 h. Both these experiments suggest that in systems using 2 equiv of DCHGF and 48-h reduction times there must be some reduction species other than **2** that gives a higher stereoselectivity than **2**. In such systems there should be some reduction by **3** and **4**, and we believe these reductions occur more slowly but with higher asymmetric bias than reduction via **2**, thereby boosting the overall percent enantiomeric excess. This is supported by the observation that aged solutions containing 2 equiv of DCHGF (Table II) give higher percent enantiomeric excess values (but as mentioned, low reduction yields). Such aged solutions should contain mainly **3** (and unknown decomposition products). Also, reduction with a solution containing a fivefold excess of **3** (run 6, Table I) gave complete reduction of propiophenone in 48 h and 51% ee. Again this suggests that there is higher asymmetric bias with species **3**.

The initial success observed with DCHGF and (acyloxy)borohydrides suggests the following rational approach to the chiral modification of $NaBH_4$. Our hypothesis is that $NaBH_4$ should first be converted to a lipophilic modification that is soluble in nonhydroxylic organic solvents and more reactive toward hydroxyl groups than

$NaBH_4$ itself (the acyloxy intermediate). Then a secondary modifier that has two capabilities should be used. It must be able to covalently attach itself to the boron and also must be a polydentate ligand able to coordinate the sodium cation. Cation complexing is presumed to "lock" the chiral ensemble, and the resulting rigidity enhances the discrimination in the hydride-transfer process between the enantiotopic faces of the ketone.[8,9]

Experimental Section

General Procedure for Small-Scale Reductions (Runs 1–5 and 7–9 in Table I). To a stirred, nitrogen-blanketed suspension of $NaBH_4$ (0.38 g, 10 mmol) in THF (5 mL) was added a solution of the carboxylic acid (10 mmol) in THF (15 mL, followed by another 5-mL rinse). Almost at once 1 equiv of dihydrogen was evolved. Then a solution of DCHGF (usually 20 mmol in 15 mL of THF followed by a 10-mL rinse) was added all at once. There was another, but slower, evolution of dihydrogen: after 2–3 h, 1 equiv; after 5–8 h, 2 equiv. The ketone (10 mmol in 10 mL of THF) was added at various times relative to the DCHGF addition (see Table II), but for quantitative reduction in 48 h with 1 equiv of reagent it is best to add it after about 2–3 h. Waiting drastically lowers the yield but does not significantly affect the percent enantiomeric excess. The workup procedure is detailed in the following description of a larger scale propiophenone reduction.

Preparative-Scale Reduction of Propiophenone. To a 1-L oven-dried, three-necked flask equipped with a magnetic stirrer and a 250-mL addition funnel were added, under nitrogen, oven-dried $NaBH_4$ (3.78 g, 100 mmol) and THF (50 mL). To the resulting suspension was added racemic 2-phenylbutanoic acid (16.42 g, 100 mmol) in 150 mL of THF (plus a 50-mL THF rinse). A rapid gas evolution ensued. After the mixture was stirred for 15 min, a solution of DCHGF (68.08 g, 200 mmol) in 150 mL of THF (plus a 100-mL THF rinse) was added. The reaction mixture was then stirred for 2 h under nitrogen (gas evolution). Propiophenone (13.42 g, 100 mmol) was then added in 50 mL of THF (followed by a 50-mL THF rinse), and the reaction was stirred for 48 h. After about 20 h a white precipitate began to appear and then slowly thickened to a white gelatinous mass.

The reaction mixture was hydrolyzed with 250 mL of 1 M hydrochloric acid (considerable gas evolution). Two clear layers formed. The aqueous layer was extracted with ether (3 × 250 mL), and the combined organic layers were divided into two equal portions. Each was extracted with 5% NaOH solution (2 × 250 mL) and washed with water (2 × 250 mL). Then they were recombined, dried over Na_2SO_4 (48 h), filtered, and concentrated to give a white solid residue (86 g). The residue was triturated with cold pentane. Vacuum evaporation of the pentane gave a pale yellow oil (13.74 g). Vacuum distillation [61–62 °C (0.3 mm)] gave 9.20 g (68%) of ethylphenylcarbinol (no propiophenone detectable by GC): $[\alpha]_D$ +21.5° (c 9.375, ether); 39% ee (based on lit.[5] max $[\alpha]_D$ 55.54°); neat rotation $[\alpha]_D$ +11.5°; 39% ee (based on lit.[10,11] max $[\alpha]_D$ 29.16°).

DCHGF (59 g, 87%) was recovered from the pentane trituration residue.

Reduction of Propiophenone with an Excess of 3 (Run 6, Table I). A solution of (±)-2-phenylbutanoic acid (8.2 g, 50 mmol) in THF (75 mL plus a 25-mL wash) was added all at once to a stirred suspension of $NaBH_4$ (1.9 g, 50 mmol) in THF (25 mL). About 3 min later a solution of DCHGF (33.9 g, 100 mmol) in THF (75 mL plus a 50-mL wash) was added all at once. The resulting mixture was stirred for 2 h at room temperature (during which time it became a slightly cloudy solution). A solution of propiophenone (1.34 g, 10 mmol) in THF (25 mL plus a 25-mL wash) was added, and the reaction was stirred at room temperature for 48 h.

(8) Cation coordination may also promote the reaction of the hydroxyl group with the (acyloxy)borohydride intermediate, that is, assist in the process by binding the sugar derivative in a borohydride complex prior to reaction.

(9) We cannot exclude the possibility that there is some degree of asymmetric induction due to nonspecific, "noncovalent" interactions of the chiral sugar modifier and the reducing species present, for example, chiral media phenomena or cation coordination effects alone.[3]

The reaction was stirred for 10 min with 250 mL of 1 M HCl solution (gas evolution) and worked up as described above (preparative-scale reduction): crude yield 4.3 g; distilled yield 0.67 g [63–73 °C (0.25–0.30 mm)]; GC showed 100% carbinol, $[\alpha]^{23}_D$ +14.9°; 51% ee [based on $[\alpha]^{23}_D$ max 29.16° (l = 1, neat)].[10,11]

Acknowledgment. This research was supported by the Ventron Division of Thiokol. We thank Mr. Robert C. Wade for his encouragement and for enlightening discussions.

Registry No. 1,2:5,6-Di-*O*-isopropylidene-D-glucofuranose, 582-52-5; sodium borohydride, 16940-66-2; 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose, 23397-76-4; isovaleric acid, 503-74-2; (±)-2-phenylbutanoic acid, 7782-29-8; (+)-pinanecarboxylic acid, 58096-27-8; (−)-pinanecarboxylic acid, 58096-29-0; 4-*tert*-butylcyclohexanone, 98-53-3; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; 2-methylcyclohexanone, 583-60-8; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; acetophenone, 98-86-2; propiophenone, 93-55-0; (*R*)-(+)-ethylphenylcarbinol, 1565-74-8; chloroacetophenone, 532-27-4; 2-methyl-1-phenylpropan-1-one, 611-70-1; trifluoroacetophenone, 434-45-7; (*R*)-α-methylbenzenemethanol, 1517-69-7; (*R*)-α-(chloromethyl)benzenemethanol, 56751-12-3; (*R*)-2-methyl-1-phenylpropan-1-ol, 14898-86-3; (*R*)-α-(trifluoromethyl)benzenemethanol, 10531-50-7.

(10) S. H. Wilen, "Tables of Resolving Agents and Optical Resolutions", University of Notre Dame Press, Notre Dame, IN, 1972, p 204.

(11) Even a small amount of propiophenone enhances the neat rotation of phenylethylcarbinol significantly. Therefore, if there is incomplete reduction the propiophenone cannot be considered an innocuous achiral diluent; it must either be removed before rotations are measured or its effect must be determined via a calibration curve.

Asymmetric Reduction of Prochiral Aromatic Ketones with Modified Reagents Prepared from Sodium Borohydride and Carboxylic Acids in the Presence of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose

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Asymmetric reductions of prochiral ketones with the use of chirally modified metal hydrides continue to be studied actively.[1] By use of chiral hydride reagents prepared from lithium aluminium hydride (LAH), (*S*)-(−)-2,2'-dihydroxy-1,1'-binapthyl, and ethanol, enantiomeric excesses as high as 100% have been observed for the reduction of acetophenone.[2] Many studies, mostly based on the use of LAH derivatives modified by chiral alcohols,[3] amino alcohols,[4] and amines,[5] have been conducted, altering both

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