Asymmetric Syntheses. Part 2.[1] Reduction of Ketones with Chiral Sodium Borohydride-Lactic acid Derivative Systems

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Asymmetric reduction of acetophenone, propiophenone, and 2-acetylnaphthalene using chirally modified reagents prepared from sodium borohydride and optically active (*S*)-lactic acid derivatives produced the corresponding optically active (*R*) alcohols with enantiomeric excesses as high as 38.3%. The extent of asymmetric synthesis was dependent on the catalyst, the solvent, and the reaction conditions. ^{1}H and ^{13}C N.m.r. data for sodium borohydride chiral species are reported.

The utility of modified sodium borohydride reagents containing chiral ligands in the asymmetrical reduction of unsymmetrical ketones has been amply demonstrated, their potential for the synthesis of optically pure substances of biological significance being of particular interest. There has been much work on the asymmetric reduction of ketones with sodium borohydride under phase transfer conditions in the presence of various optically active onium salts, to afford optically active carbinols.[2]

Sugimoto *et al.*[3] described the asymmetric reduction of aromatic ketones with sodium borohydride in the presence of bovine serum albumin in an alkaline medium. This method has been extended successfully to heterocyclic ketones.[1] Enantiomeric excesses in the range 15—78% for the aromatic and heterocyclic alcohols produced, have been reported.

In contrast, there are fewer reports in the literature on asymmetric reduction in nonaqueous solutions of prochiral ketones with chiral sodium borohydride derived systems. Hirao and Yamasaki *et al.*[4] reported the asymmetric reduction of various ketones with sodium borohydride in the presence of hydroxymonosaccharide derivatives alone and also with modified reagents prepared from sodium borohydride plus carboxylic acids in the presence of monosaccharide derivatives. In the former case the enantiomeric excesses obtained were in the range 2—28%, in the latter 18—85%.

Morrison *et al.*[5] described the asymmetric reduction of several ketones with chiral alkoxy(acyloxy)borohydrides with enantiomeric excesses in the range 5—51%.

More recently, a chiral reducing agent prepared from $NaBH_4$ and (*S*)-(+)-mandelic acid in dioxane,[6] has been claimed to reduce acetophenone to 1-phenylethanol with an enantiomeric excess of 11.5%.

Independently, we have been investigating borohydride reducing systems that employ $NaBH_4$, the commercially available and inexpensive ethyl L-(−)-lactate and also the L-(−)-2-acetoxypropionic acid. The reducing agents have been tested in THF and benzene solutions on acetophenone, propiophenone, and also on 2-acetylnaphthalene. The enantiomeric excesses found in this study were better than those obtained with mandelic acid modified $NaBH_4$ but lower than those reported for the systems designed by Morrison and Hirao-Yamasaki. Here, we primarily describe and discuss the capacity for asymmetric reduction of the three systems $NaBH_4$–ethyl L-(−)-lactate, $NaBH_4$–L-(−)-2-acetoxypropionic acid, and $NaBH_4$–2L-(−)-acetoxypropionic acid–ethyl L-(−)-lactate.

Characterization of Species from the Reaction of $NaBH_4$ *and Lactic Acid Derivatives.*—The possible nature of the reducing systems from $NaBH_4$ and lactic acid derivatives responsible for the asymmetric reduction of ketones is tentatively assigned on the basis of the following data and considerations.

Preliminary experiments (four runs) showed that addition of 4 mol equiv. of ethyl lactate to the $NaBH_4$ suspended in benzene gave evolution of 0.6—1.0 mol equiv. of hydrogen within 30—60 min. Further hydrogen evolution could not be measured because of unavoidable leaks in the apparatus; this was ascertained by checking the variation of a known volume of hydrogen kept in the volumetric side of the eudiometer for fixed periods of time. In the reaction of $NaBH_4$ with 2-acetoxypropionic acid alone (Table 5) the hydrogen was evolved within 5 min. In contrast, the hydrogen production was slow and incomplete for the additions of ethyl lactate to the preformed acyloxy derivatives in the molar proportions shown in Table 6.

These results indicate that reaction of $NaBH_4$ with the hydroxy group of ethyl lactate (R*OH) proceeds to a mono- or at most a di-alkoxyborohydride stage according to equations (1) and (2). In the case of 2-acetoxypropionic acid (R^*CO_2H),

$$NaBH_4 + R^*OH \longrightarrow NaBH_3OR^* + H_2 \quad (1)$$

$$NaBH_3OR^* + R^*OH \longrightarrow NaBH_2(OR^*)_2 + H_2 \quad (2)$$

$NaBH_4$ may simply react with the carboxylic function according to the following equation (3), in the same way of

$$NaBH_4 + R^*CO_2H)_n \longrightarrow NaBH_{4-n}(R^*CO_2)_n + nH_2 \quad (3)$$
$$n = 1—4$$

previously reported similar cases. Finally, the reaction of $NaBH_4$ with known molar quantities of 2-acetoxypropionic acid and subsequent addition of ethyl lactate is represented by equations (4) and (5).

$$NaBH_4 + (R^*CO_2H)_n \longrightarrow NaBH_{4-n}(R^*CO_2)_n + nH_2 \quad (4)$$

$$NaBH_{4-n}(R^*CO_2)_n + R^*OH \longrightarrow NaBH_{4-n+1}(R^*CO_2)_n(R^*O) + H_2 \quad (5)$$

The species shown in equation (5) is just one of those possible for the reacting molecules involved. Unfortunately, the species present in the three types of reaction mixtures are not quite as simple as might appear from the equations, although the species shown might well be involved. We made a preliminary study in order to obtain ^{1}H n.m.r., ^{13}C n.m.r., and i.r. data of the possible hydroborate complexes.

^{1}H *N.m.r. Study.*—Equimolar proportions of sodium tetrahydroborate and ethyl lactate were stirred in dry deuteriobenzene under nitrogen until gas evolution stopped (*ca.* 1 h). The mixture was then filtered and the benzene solution taken into an n.m.r. tube for analysis. No unchanged ethyl lactate was detected by g.c. analysis of the benzene solution. The ^{1}H n.m.r. spectrum was very similar to those of the alkoxy derivatives of $NaBH_4$, the multiplicities of which resemble those of ethyl lactate.

Thus, while the signal of the CH_3 group of the lactic acid moiety is indistinguishable from those of other species, the CH_3, CH_2, and CH patterns of the lactate forms in equations (1)—(5) absorb at higher fields than the corresponding protons of the free ethyl lactate. However, when the benzene sample was treated with little water, the multiplicities disappeared to leave an n.m.r. spectrum of the free ethyl lactate. No B–H proton of sodium tetrahydroborate derivatives could be seen in these n.m.r. spectra. However, the absence of B–H protons in these spectra, has previously been reported as characteristic of many B–H containing compounds, the explanation being, that partial decoupling of the boron from the hydrogen by quadrupole induced ^{11}B and ^{10}B relaxation occurs.[7] It is this mechanism which explains the lack of any observable proton coupling to boron.

^{1}H N.m.r. data consistent with the proposed formation of acyloxy hydroborate were observed for the reaction products of 2-acyloxypropionic acid with sodium tetrahydroborate. The peak absorption of the acyl entities of the acyloxy hydroborates is broadened and, as expected, there are no signals due to unchanged acid.

^{13}C *N.m.r. Study.*—^{13}C N.m.r. analysis of the reaction between $NaBH_4$ and ethyl lactate gave the best evidence of the reactivity of the hydroxy group of ethy lactate towards $NaBH_4$: it showed that more than one alkoxy derivative of sodium borohydride of the type shown in equations (1) and (2) is formed, and confirmed the presence of ethanol as a by-product (Table 1). In the Figure are shown the spectra of ethyl lactate and ethyl lactate–$NaBH_4$ derivatives: the latter species cannot be identified at present but it is clear that they are formed in different amounts. N.m.r. spectra taken at various intervals of time showed that the $NaBH_4$ alkoxy derivatives first formed do not change with ageing and no disproportionation reaction between the species takes place in the solution. A control experiment with addition of a little D_2O to the reaction solution caused complete hydrolysis of the sodium borohydride alkoxy derivatives and re-formation of ethyl lactate whose identity was confirmed by ^{13}C n.m.r. spectroscopy. The effect of altering the ethyl lactate:$NaBH_4$ ratio was examined. Thus, the use of 0.5 mol of $NaBH_4$ instead of the standard amount (1:1 ratio), influenced only the ethanol signals which appeared to be less than for experiments with smaller amounts of lactate. Also in these experiments, addition of water regenerated the free ethyl lactate which was identified by g.c. and ^{13}C n.m.r. spectroscopy. spectroscopy.

The reaction of carboxylic acids with $NaBH_4$ was confirmed by the clear spectrum obtained in the reaction with 2-acetoxypropionic acid (Table 2).

Definitive evidence for the formation of acyloxyalkoxy–sodium borohydride derivatives was obtained by allowing $NaBH_4$ to react with 2-acetoxypropionic acid and then adding ethyl lactate (1:1:1 molar ratio of reactants): the pertinent ^{13}C n.m.r. data are gathered in Table 3.

Beside the direct reaction of ethyl lactate with $NaBH_4$, ethyl lactate oxyhydroborates were prepared by treatment of sodium tetrahydroborate with ethyl pyruvate according to the procedure of Kayser *et al.*[8] We found that the reaction occurred smoothly in dry benzene and the ^{1}H n.m.r. spectrum of the product was nicely superimposable with that of the compounds obtained from the direct reaction of $NaBH_4$ with ethyl lactate. These findings were completely consistent with i.r. results for the substances under scrutiny.

^{1}H N.m.r. and g.c. analyses of the reaction products of $NaBH_4$ with ethyl lactate both in benzene and in tetrahydrofuran showed that ethanol was formed along with the sodium hydroborate derivatives. It is logical to assume that

Table 1. ^{13}C N.m.r. chemical shifts of $MeCHCO_2CH_2Me$ (lactate) and its complexes with $NaBH_4$ in C_6D_6[a]

	Lactate	Lactate–$NaBH_4$
C-1	176.11	180.35; 177.10
C-2	67.48	72.21; 70.87; 70.15; 68.66
C-3	20.77	21.80; 21.11; 20.16
C-4	61.51	67.15; 61.39; 61.00; 57.27
C-5	14.41	14.53

[a] Signals at 57.81 and 18.98 of CH_2 and CH_3 of ethanol are also present.

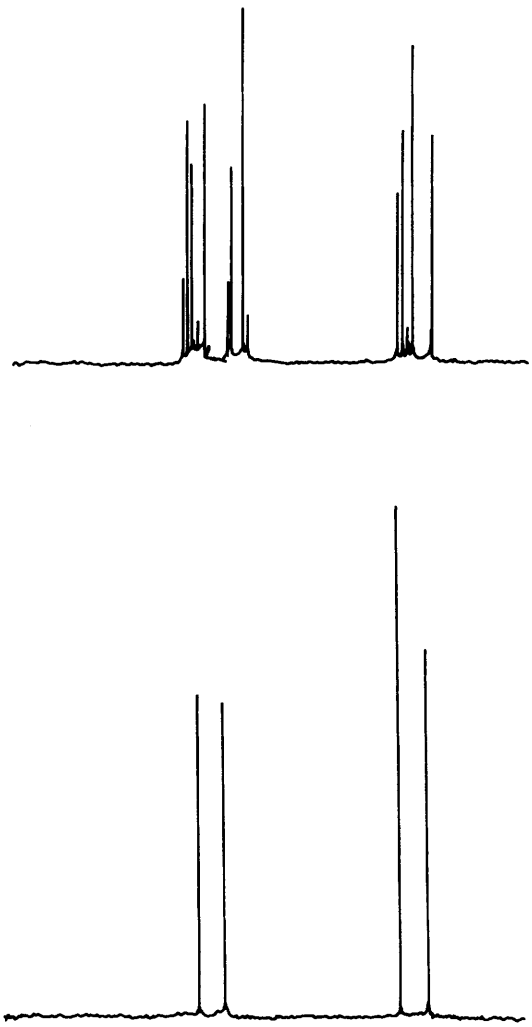

Figure. ^{13}C N.m.r. spectra of sodium borohydride–ethyl lactate derivatives (top) and ethyl lactate (bottom) as described in the text. Chemical shifts in Table 1

ethanol could originate from hydrolysis, while reduction or condensation (lactide formation) reactions of ethyl lactate brought about by $NaBH_4$, should be discarded since we were unable to detect (n.m.r. and g.c.) the presence of the expected substances in the reaction mixtures.

To achieve completely anhydrous conditions for the reaction some benzene was distilled off (benzene–water azeotrope) from the solution already containing the ethyl lactate, but before the addition of oven-dried $NaBH_4$: no ethanol was then detected in the reaction of $NaBH_4$ with 2-acetoxypropionic acid and ethyl lactate.

Asymmetric Reduction Systems.—Asymmetric reduction of acetophenone and propiophenone at room temperature in benzene and in tetrahydrofuran were carried out in a variety of reaction systems. The procedure was to add varying quantities (1—4 multiples of 5 mmol) of ethyl lactate and ketone simultaneously to a benzene suspension of $NaBH_4$ (5 mmol) and to allow the mixture to react for varying periods of time (Table 4). Evolution of hydrogen was observed in all the runs with the gradual disappearance of the $NaBH_4$ to give clear solutions that, in some instance, turned gelatinous with time. (The runs reported in Table 4 and following are a choice of a number of experiments three times larger.) We believe that these changes merely reflect the insolubility of $NaBH_4$ in benzene and the relative lipophilicity of the alkoxy intermediates that are produced during the reaction processes. The results in Table 4 show that reduction is little affected by the amount of ethyl lactate, while stereoselectivity was found to be optimal for the stoicheiometric quantities of run 2. Sluggish reduction of propiophenone and lower e.e. were observed for a reaction in which both ratios lactate:$NaBH_4$ and ketone:$NaBH_4$ were high (run 4 of Table 4).

In the reduction of acetophenone in tetrahydrofuran the best results were obtained for ratios lactate:$NaBH_4$ and ketone:$NaBH_4$ equal to 3:1 and 1:1, respectively. The reduction percentage was 95 and the e.e. 7.3%, the latter value being, however, lower than the average value found for the reductions in benzene. Results for runs 6—8 of Table 4 show that the effect of waiting time before addition of acetophenone is to decrease the percent enantiomeric excess. In order to understand this unexpected result, we advance the following tentative explanation. The initially formed and most reactive mono- and di-substituted sodium borohydrides react further with ethyl lactate to give more substituted systems which are then unable to reduce the ketone (in the reaction period considered) both because of steric hindrance and/or because of their scanty solubility in the reaction medium. Although lowering the ratio lactate: $NaBH_4$ to 1:1 brings about a quantititative reduction of ketone it also gives rise to the lowest e.e. value. The latter may be the result of ketone reduction by unsubstituted $NaBH_4$ dissolved in tetrahydrofuran.

2-Acetoxypropionic acid reacts smoothly with $NaBH_4$ in benzene with quantitative evolution of dihydrogen to give a clear solution in a very short time: the results for three experiments are shown in Table 5. The synthetic yields were low while the selectivity values were higher the larger the ratios 2-acetoxypropionic acid–$NaBH_4$. A waiting time of 15 min affected both the reduction and e.e. yields in a negative fashion.

The results summarized in Table 6 show that the addition of 2-acetoxypropionic acid and ethyl lactate to $NaBH_4$ at different times, provided better results than using the two chiral agents

Table 2. ^{13}C N.m.r. chemical shifts of $MeCHCO_2H$ and $NaBH_4$–acetoxypropionic acid in C_6D_6

5 2 1
OCOMe
3 4

	Acid	$NaBH_4$–acid
C-1	175.65	174.87
C-2	69.15	71.18
C-3	171.72	171.66
C-4	16.89	17.17
C-5	20.50	20.89

Table 3. ^{13}C N.m.r. chemical shifts of the complex of $NaBH_4$ with $MeCHCO_2H$ and $MeCHCO_2CH_2Me$ in C_6D_6[a]

5 2 1 3 2 1 4 5
OCOMe OH
3 4

$NaBH_4$

	Acid	Lactate
C-1	174.59	178.35; 172.72
C-2	71.00	73.30; 72.03; 68.8
C-3	171.05	21.51; 20.07; 18.14
C-4	17.29	61.18
C-5	20.89	14.50

[a] No signals of ethanol were observed.

Table 4. Optical and chemical yields for the reduction of acetophenone and propiophenone with the reagents derived from $NaBH_4$ and ethyl lactate at various molar ratios and according to different addition time in benzene and in tetrahydrofuran

			1-Phenylethanol				1-Phenylpropanol			
Run	$\frac{MeCH(OH)CO_2Et}{NaBH_4}$[a]	$\frac{Ketone}{NaBH_4}$	Waiting[b] time (min)	Reaction (time (h)	% Reduction	% e.e.	Waiting[b] time (min)	Reaction time (h)	% Reduction	% e.e.
In benzene										
1	1	1	0	29	96	11.3	0	25	79	13.6
2	3	1	0	96	75	13.0	0	24	80	15.2
3	4	1	0	30	72	8.6	0	26	76	13.9
4	4	4					0	25	26	7.0
In tetrahydrofuran										
5	3	1	9	24	95	7.3				
6	3	1	10	24	28	4.7				
7	3	1	45	24	17	3.9				
8	1	1	75	24	100	2.1				

[a] The standard reference amount was 5 mmol. [b] Time after addition of ethyl lactate to $NaBH_4$ before the addition of the ketone.

Table 5. Optical and chemical yields for the reduction of acetophenone with the reagents derived from $NaBH_4$ and 2-acetoxypropionic acid at various molar ratios and according to different addition times in benzene

Run	$\frac{MeCH(OAc)CO_2H}{NaBH_4}$[a]	$\frac{Acetophenone}{NaBH_4}$	Waiting[b] time (min)	Reaction time (h)	% Reduction	% e.e
1	2	1	0	24	38	5.4
2	3	1	0	24	20	10.6
3	3	1	15	24	15	9.8

[a] The standard amount was 5 mmol. [b] Time after addition of 2-acetoxypropionic acid to $NaBH_4$ before the addition of the ketone.

Table 6. Optical and chemical yields for the reduction of acetophenone and propiophenone with the reagents derived from $NaBH_4$, 2-acetoxypropionic acid and ethyl lactate at various molar ratios and according to different addition times in benzene and in tetrahydrofuran

	$\frac{MeCH(OAc)CO_2H}{NaBH_4}$	$\frac{MeCH(OH)CO_2Et}{NABH_4}$[a]	Waiting time[b]		1-Phenylethanol		1-Phenylpropanol	
Run			t_1 (min)	t_2 (min)	% Reduction	% e.e.	% Reduction	% e.e.
In benzene								
1	0.5	0.5	15	15			48	23.8
2[c]	1	1	15	15	33	28.7	30	33.1
3	1	2	15	15	11	24.9	22	38.3
4	1	1	0	15	19	12.4		
5	0.5	0.5	15	0	50	16.7	62	21.2
6	1	1	15	0	61	19.4		
7[d]	1	1	15	15			39	33.1
8[e]	1	1	15	15			57	32.8
In tetrahydrofuran								
9	0.5	0.5	15	15			95	1.2
10	1	1	15	15			17	22.7
11[f]	1	1	15	15			13	9.3
12[e]	1	2	15	0			65	25.9

[a] The standard reference amount was 5 mmol and the whole reaction time period was 24 h. [b] t_1 = Time after addition of 2-acetoxypropionic acid to $NaBH_4$ before the addition of ethyl lactate; t_2 = time after addition of ethyl lactate to reaction products before the addition of ketone. [c] An experiment on 2-acetylnaphthalene under the reaction conditions of run 2 gave the following results: reduction, 47%; e.e., 26.8%. [d] Ketone was added to the reaction mixture along with 1 mmol of ethanol. [e] The volume of the solvent was half that of the other experiments. [f] $NaBH_4$ was 10 mmol, that is twice the usual amount.

simultaneously. Those systems gave 1-phenylethanol and 1-phenylpropanol with stereoselectivities up to 28.7 and 38.3, respectively, in the reduction of the phenone precursors. In benzene it is clear that the optical yields increase with increasing amounts of ethyl lactate (runs 2,3), whilst there is a concomitant lowering of the reduction percentages. A further feature of relevance in this system is the sharp drop in both chemical and e.e. yields when the two chiral models are added simultaneously to the suspension of $NaBH_4$ in benzene (run 4). The simultaneous addition of ethyl lactate and ketone to the acyloxyborohydride, resulted in an increased reduction while the e.e. were little affected (runs 5,6).

The results from runs 9—12 also show that for these systems tetrahydrofuran is an inferior solvent compared with benzene for the enantioselective reduction of the two prochiral ketones under investigation. The results for run 9 (*i.e.* is high reduction percentage with a very low e.e. yield), confirm the solubility of $NaBH_4$ as such in tetrahydrofuran; it may, therefore, attack the ketone before being modified by the chiral molecules. Simultaneous addition of the ketone and ethyl lactate to the $NaBH_4$–2-acetoxypropionic acid derivative, gives good chemical and e.e. yields.

We have also investigated the effect of the presence of ethanol in benzene and found neither chemical nor optical purity yield changes (run 7, Table 6). In THF, the addition of t-butyl alcohol and ethanol gave quantitative chemical yields combined with e.e. values in the range 3—6%.

In conclusion, the major results of the present study are as follows. (i) Ethyl lactate and 2-acetoxypropionic acid which are suitable chiral modifiers for the preparation of modified $NaBH_4$ derivatives are completely eliminated during work-up of the reaction products because of their complete or very high solubility in water.

(ii) The hydroxylic group of ethyl lactate has been found to react both in benzene and in tetrahydrofuran with $NaBH_4$ to give alkoxy borohydrides capable of reducing asymmetrically unsymmetrical ketones.

(iii) Asymmetrical acyloxyborohydrides, readily obtained from 2-acetoxypropionic acid and $NaBH_4$, asymmetrically reduce prochiral ketones.

(iv) Acyloxy(alkoxy)borohydrides obtained from 2-acetoxypropionic acid and ethyl lactate with $NaBH_4$ are the most effective compounds studied for the unsymmetrical reduction of prochiral phenones. The effects of the two lactic acid derivatives are cumulative.

(v) Benzene is superior to tetrahydrofuran in the asymmetric reduction system, mainly because of the complete insolubility of the underivatized $NaBH_4$ in the former solvent. No traces of 1-phenylethanol could be detected in a 24 h experiment in which methyl phenyl ketone was allowed to react in a suspension of

$NaBH_4$ in benzene. In fact, it underwent greater reduction in tetrahydrofuran (ratio ketone:$NaBH_4$ = 1:1).

(vi) In all the cases *R*-alcohols were formed. The lactic acid derivatives used with $NaBH_4$ were: L-(−)ethyl lactate and L-(−)2-acetoxypropionic acid, both belonging to the *S* series.

(vii) Reductions with different concentrations of reactants gave results that argue against asymmetric induction arising from non-specific interactions between the ketone to be reduced and unchanged lactic derivatives or sodium borohydride derivatives.

Thus the chiral reducing systems discussed are moderately effective in enantioselective reduction of alkyl aryl ketones.[4–6] Similar, but better enantioselective asymmetric reductions have been reported,[1,3,13,14] whilst other reagents that have been used are chiral boranes[15] and chiral lithium aluminium hydrides.[16]

Experimental

All experiments were carried out under nitrogen. Benzene and tetrahydrofuran were either C. Erba or Fluka anhydrous solvents. Acetophenone, propiophenone, and L-(−)-lactic acid were Fluka purum grade reagent; L-(−)-ethyl lactate was purchased from EGA Chemie; Fluka sodium borohydride was oven dried before any experiments. The purity of all reagents, solvents, and products were checked by g.l.c., t.l.c., or ^1H n.m.r. spectroscopy. N.m.r. spectra were measured with a Bruker WP80SY instrument.

G.l.c. analyses were performed on a C. Erba Fractovap 2400T instrument with f.i.d. detector using a glass column (2 m × 3 mm) packed with LAC 728, 10% (CWLA 60/80) with nitrogen as carrier gas. Operation conditions: injection port 180 °C; column temperature 100—170 °C, 5 °C/min. The ratios of alcohols and unchanged ketones were determined by their peak areas.

Optical rotations were taken on a Perkin-Elmer Model 141 polarimeter using a 1-cm thermostatted microcell with readings to ±0.02°. I.r. spectra were measured with a Perkin-Elmer Model 257 instrument. T.l.c. was performed on silica gel 60 GF_{254} precoated plates (Merck) with chloroform as the mobile phase. Spots were detected by spraying the plates with a 3% CrO_3 sulphuric acid (1:1) and charring at 120 °C. Evolution of hydrogen was measured by connecting the reaction vessel to a graduated pipette (or eudiometer tube).

L-(−)-2-*Acetoxypropionic Acid.*—This compound was prepared as reported[9] by adding, with ice-bath cooling, lactic acid (0.54 mol) to an excess of acetyl chloride (1.2 mol) and leaving the mixture overnight at room temperature. The excess of acetyl chloride was eliminated on a rotary evaporator and the residue distilled under reduced pressure. The pure 2-acetoxypropionic acid was collected as a colourless liquid, b.p. = 135—140 °C at 16 mmHg (80% yield), $[\alpha]_D$ −52.8° (neat) (lit.,[9] $[\alpha]^{18}_{546.1}$ −47.8).

General Procedure for Asymmetric Reduction of Acetophenone and Propiophenone with the Reagents described in Tables 4—6.—Benzene (10 ml) or tetrahydrofuran were introduced into a 50-ml three-necked flask equipped with a magnetic stirrer and an addition funnel. A stream of nitrogen was passed through for 15 min and then oven-dried $NaBH_4$ (0.19 g, 5 mmol) was added. A solution of the chiral modifier (5 mmol or multiple of 5, see Tables) in 10 ml of solvent (plus 2—3 ml rinse) was added dropwise to the resulting suspension. Evolution of hydrogen ensued, rapid in the case of acid 2-acetoxypropionic acid, slow with ethyl lactate. When the addition was too rapid, the mixture tended to warm up. Depending on the nature and final concentration of the chiral $NaBH_4$ modifier added, the suspension of sodium borohydride changed into a cloudy or, more often, into a clear solution from which, in some instances, a white gelatinous precipitate would separate and then occasionaly disappear again. On the addition of the ketone (for timing and quantities see Tables) dissolved in the same solvent as the $NaBH_4$ reagent a white precipitate formed in some cases. After a period of time, usually 24 h, the reaction mixture was hydrolysed with hydrochloric acid 1M (considerable gas evolution). Two clear layers formed in the case of benzene. When the solvent was tetrahydrofuran, the hydrolysed mixture was extracted three times with ether (20, 15, 15 ml). The organic phase was washed with dilute aqueous NaOH to pH neutral and then dried (Na_2SO_4), filtered, and concentrated to give an oily residue. This was then subjected to column chromatography on silica gel 60 H (Merck) using chloroform as eluant. The products were characterized by i.r. and ^1H n.m.r. spectroscopy and were homogeneous on g.l.c.; they were uncontaminated by lactic acid derivatives. The optical yields were calculated by the observed optical rotations and the known maximum rotation of 1-phenylethanol, $[\alpha]_D$ −52.5° (*c* 2.27° in CH_2Cl_2),[10] 1-phenylpropanol, $[\alpha]_D$ +55.54° (in ether),[11] 1-(1-naphthyl)ethanol, $[\alpha]_D$ +74.39° (in absolute ethanol).[12] In a few cases, optical purities were determined by 80 MHz ^1H n.m.r. chiral shift measurements using tris{3-(trifluoromethylhydroxymethylene)-(−)-camphorato}europium(III), [Eu(tfc)$_3$]. The signals resolved were those of the tertiary H on the carbon bearing the hydroxy group. The e.e. values gained by using this technique were in good agreement with those from optical rotation measurements.

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