Asymmetric Reductions with Chiral Reagents from Lithium Aluminum Hydride and (+)-(2S,3R)-4-Dimethylamino-3-methyl-1,2-diphenyl-2-butanol[1,2]

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Stereoselectivity in reductions of carbonyl compounds by a chiral reagent prepared by adding the amino alcohol (+)-(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (6) to lithium aluminum hydride in ether is reasonably high and shows remarkable reversal depending upon age of the reagent from predominantly *R* product to predominantly *S* product. Reduction of acetophenone gives either (*R*)-(+)- or (*S*)-(−)-methylphenylcarbinol in 60–70% enantiomeric purity depending upon use of the reagent either immediately after its preparation (procedure A) or upon aging overnight or refluxing for a few minutes (procedure B). This reversal in stereoselectivity with age of reagent was observed with five different carbonyl substrates. The reduction of phenyltrifluoromethyl ketone did not show this reversal phenomenon, however. Procedure A for asymmetric reduction of phenyl alkyl ketones gives the *R* carbinol in excess in each case. Representative enantiomeric purities (% e.e., *R* isomer) of the carbinols, PhCHOHR, from reduction of the ketones, PhCOR, at 0° follow: R = Me, 68% e.e.; *n*-Pr, 61% e.e.; *i*-Pr, 30% e.e.; *t*-Bu, 36% e.e.; CF_3, 30% e.e. This series roughly conforms to a decrease in stereoselectivity as the size of the R group increases. The reagent prepared from 6 and lithium aluminum deuteride gave upon reaction with acetophenone the corresponding deuteriated (*R*)-phenylmethylcarbinol-α-*d*, 80% e.e., and upon reaction with benzaldehyde (*S*)-benzyl-α-*d* alcohol, 40% e.e. With this chiral reducing agent we have realized a generally useful method for asymmetric synthesis of carbinols with substantial enantiomeric purities.

The reduction of an achiral carbonyl compound by a chiral reducing agent to give unequal amounts of the enantiomeric secondary carbinols has been the subject of much study.[4] Most of such studies are of theoretical interest rather than of practical value for the synthesis of optically active materials. Landor and coworkers[5] have made a detailed study of modified monosaccharide–lithium aluminum hydride complexes and Červinka and his students[6] have studied carbonyl reduction by lithium aluminum hydride–chiral alkaloid complexes. For instance, the reduction of acetophenone (4) by a reagent (3) made by mixing lithium aluminum hydride (1) and quinine (2) in a 1:1 molar ratio gave (*R*)-(+)-phenylmethylcarbinol (5) in 48% excess over the racemate.[6a] The stereoselectivities observed in the reduction of other substrates by this chiral reducing agent were generally less than 30%.

$$\underset{1}{LiAlH_4} + \underset{2}{\text{quinine}} \longrightarrow \underset{3}{LiAlH_3\text{–quinine}} + H_2$$

$$\underset{3}{LiAlH_3\text{–quinone}} + \underset{4}{PhCOMe} \longrightarrow \longrightarrow$$

$$HO\triangleright\overset{Me}{\overset{|}{C}}\triangleleft H + H\triangleright\overset{Me}{\overset{|}{C}}\triangleleft OH$$
$$\qquad\quad Ph \qquad\qquad Ph$$
$$74\%\ R\text{-}(+)\text{-}5 \qquad 26\%\ S\text{-}(-)\text{-}5$$

A readily available chiral reagent which would achieve consistently high stereoselectivities for a wide spectrum of carbonyl compounds would constitute a valuable synthetic tool for the organic chemist. It seems likely that a superior chiral reducing agent might be designed based upon a systematic study of the structural variables of reagents of this type. We have begun such a study using the chiral amino carbinol (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol[7] of known configuration[7c] (6, R*OH)[8] for the reaction with lithium aluminum hydride in various molecular ratios to give a chiral reducing reagent represented by 7.

$$PhCH_2\overset{\overset{OH}{\triangledown}}{\underset{\underset{Ph}{\triangle}}{C}}\!\!-\!\!\overset{\overset{Me}{\triangledown}}{\underset{\underset{H}{\triangle}}{C}}H_2NMe_2$$

6, R*OH

$$\underset{1}{LiAlH_4} + n\underset{6}{R^*OH} \longrightarrow \underset{7}{LiAlH_{4-n}(OR^*)_n} + nH_2$$

This specific reagent was chosen because of a report[9] of reasonably high stereoselectivity using this chiral amino carbinol in the preparation of a reagent for the reduction of acetophenone and a subsequent promising preliminary study.[2] We have summarized the data we have collected in Tables I–III. Initial studies using acetophenone and a reagent prepared from lithium aluminum hydride and the chiral amino carbinol (6, R*OH, molar ratio 1.0:2.3) have shown that substantial stereoselectivities in the order of 40–75% e.e.[10] are obtained repeatedly (Table I). We have now carried out experiments designed to explore the effects of temperature, concentration, solvent, time, ratio of reactants, and

(1) We acknowledge with gratitude support of these studies by the National Science Foundation (NSF GP 27448).

(2) For a preliminary communication of a portion of this work, see S. Yamaguchi, H. S. Mosher, and A. Pohland, *J. Amer. Chem. Soc.*, **94**, 9254 (1972).

(3) On leave from Tohoku University, Sendai, Japan.

(4) This subject has been reviewed: J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1970, pp 160–218.

(5) (a) S. R. Landor and A. R. Tatchell, *J. Chem. Soc. C*, 2280 (1966); (b) S. R. Landor, B. J. Miller and A. R. Tatchell, *ibid.*, 197 (1967).

(6) (a) O. Červinka, *Collect. Czech. Chem. Commun.*, **30**, 1684, 2403 (1965). (b) O. Červinka and O. Bělavský, *ibid.*, **30**, 2487 (1965); **32**, 3987 (1967). (c) O. Červinka, V. Suchan, O. Kotýnek, and V. Dudek, *ibid.*, **30**, 2484 (1965).

(7) (a) A. Pohland and H. R. Sullivan, *J. Amer. Chem. Soc.*, **75**, 4453 (1953); (b) A. Pohland and H. R. Sullivan, *ibid.*, **77**, 3400 (1955); (c) H. R. Sullivan, J. R. Beck, and A. Pohland, *J. Org. Chem.*, **28**, 2381 (1963); (d) A. Pohland, L. R. Peters, and H. R. Sullivan, *ibid.*, **28**, 2483 (1963).

(8) Throughout this paper we shall use R*O– to symbolize the specific chiral alkoxy group from (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (6). R*OH is the alcohol from which the analgesic Darvon is made.

(9) See ref 4, p 205, entry 14 in Table 5-11.

(10) By % e.e. we designate the enantiomeric excess, *i.e.*, the per cent excess of one enantiomer over the racemate. This was determined either by optical rotation or by use of relative areas of suitable signals from the diastereomeric α-methoxy-α-trifluoromethylphenylacetate (MTPA) derivatives.[11]

(11) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

TABLE I

ASYMMETRIC REDUCTIONS OF ACETOPHENONE (4) BY INSOLUBLE (A)[a] AND SOLUBLE (B)[a] CHIRAL REAGENTS FROM $LiAlH_4$ AND (+)-(2S,3R)-4-DIMETHYLAMINO-3-METHYL-1,2-DIPHENYL-2-BUTANOL (R*OH)[b]

PhCOMe + $LiAlH_n(OR^*)_{4-n}$ ⟶ ⟶ (+)-PhCHOHMe + (−)-PhCHOHMe

4 7 (R)-(+)-5 (S)-(−)-5

No.	Procedure[a]	Molar ratio[b,c] LiAlH4	Molar ratio[b,c] R*OH	Molar ratio[b,c] PhCOMe	Reaction temp, °C	Extent of reduction,[d] %	Stereoselectivity[e] Configuration	Stereoselectivity[e] % e.e.
1	A	1.0	0.77	0.70	rt	Q	R	29 (31)[f]
2	A	1.0	0.76	1.39	rt	Q	R	23 (24)[f]
3	B	1.0	0.76	2.10	rt	86	R	18 (18)[f]
4	A	1.0	0.77	0.64	0	Q	R	31
5	A	1.0	1.00	0.83	0	Q	R	52
6	B	1.0	1.00	0.83	0	Q	R	47[g]
7	A	1.0	1.54	0.70	rt	Q	R	41 (40)[f]
8	A	1.0	1.53	1.39	rt	Q	R	48 (46)[f,h]
9	A	1.0	1.54	0.64	0	Q	R	65, 66[i]
10	A	1.0	2.00	0.83	0	Q	R	40, 49[j]
11	A	1.0	2.00	1.66	0	59	R	21
12	A	1.0	2.30	0.70	rt	Q	R	58 (57)[f]
13	A	1.0	2.30	0.64	0	Q	R	68 (68)[f]
14	A	1.0	2.30	0.64	−65	Q	R	75 (75)[h]
15	A	1.0	3.00	0.83	0	Q	R	26
16	A	1.0	3.00	0.83	0	Q	R	28,[i] 27[i]
17	B	1.0	2.00	0.83	rt	29	S	49
18	B	1.0	2.00	1.67	rt	15	S	45
19	B	1.0	2.30	0.64	rt	40, 43[k]	S	66, 66[k]
20	B	1.0	2.30	0.32	rt	50	S	70
21	B	1.0	2.30	0.21	rt	77	S	75
22	B	1.0	2.30	0.64	0	35	S	53
23	B	1.0	2.30	0.64	−65	9	R	5
24	D[a]	1.0	2.30	0.64	0	Q	R	29
25	B	1.0	3.00	0.83	rt	27	S	71
26	B	1.0	3.00	0.83	0	24	S	60

[a] Procedures are given in the Experimental Section. Briefly they are as follows: A, an insoluble precipitate is formed upon adding an ethereal solution of R*OH to a filtered, standardized, ethereal $LiAlH_4$ solution (the heterogeneous reagent is used immediately); B, an aged homogeneous ether solution of the reagent as prepared in A is used; C uses an aged benzene solution of the reagent; D follows procedure A except that ten times the ether solvent is used and no precipitate is formed (the reagent is used immediately). [b] R*OH symbolizes the chiral alcohol 6. [c] The actual quantities used for each reaction ranged from 0.33 to 1.5 mmol. [d] The extent of reduction is based on glc-determined ratio of methylphenylcarbinol to acetophenone in the isolated product. Q means "almost quantitative"; *i.e.*, less than 2% of ketone detected in the product. [e] Enantiomeric excess (% e.e.) is the excess of one isomer over the racemate. Unless otherwise designated this was determined by optical rotation. [f] Alternative analysis on the same sample based upon the nmr relative peak heights of the *C*-methyl doublets of the diastereomeric MTPA derivatives. [g] The initial precipitate was heated in ether for 10 min and allowed to stand overnight but did not dissolve. Acetophenone was then added. [h] Alternate analysis on the same sample based upon relative areas of the OCH_3 nmr signals of diastereomeric MTPA derivatives in the presence of 0.1 *M* Eu(fod)$_3$ nmr shift reagent. [i] Duplicate runs both analyzed by optical rotation. [j] Duplicate runs except hydride concentration adjusted to the same as that in no. 9 by reducing the amount of ether accordingly. [k] Duplicate run which was refluxed for an additional 2 hr to see if the extent of reduction could be increased. Excess hydride was present at the end of the reaction, as evidenced by liberation of hydrogen upon hydrolysis.

various substrates upon the stereoselectivity of this reduction. Pertinent observations are as follows.

(1) Of foremost interest is the previously communicated[2] observation that the sense of stereoselectivity is dependent upon the length of time that the reagent has been allowed to stand before its use for reducing the carbonyl substrate. When acetophenone was added to the reagent at 0° either 30 sec or 3 min after its preparation (by mixing **1** and **6** to form reagent **7**, $LiAlH_4$R*OH molar ratio of 1.0:2.3, procedure A), a near-quantitative yield of (*R*)-(+)-phenylmethylcarbinol [*R*-(+)-**5**] which was 68% enantiomerically pure was formed (Table I, example 13). However, when the reagent was allowed to stand overnight or was refluxed in ether for a few minutes before the same substrate was added (procedure B), then a 43% yield of the *S*-(−) enantiomer of **5**, which was 66% enantiomerically pure, was obtained (Table I, no. 19). This phenomenon is represented graphically in Figure 1.

This reversal of stereochemistry with age of the reagent is like that observed previously by Sandman, Mislow, *et al.*,[12] during the stereoselective additions of the "di-3-pinanylboron" reagent[13] to olefins.

(2) This reversal in stereoselectivity seems in part to be associated with a less soluble and more soluble form of reagent **7**. On initial preparation of this reagent, by the addition of a concentrated ether solution of amino carbinol **6** to the $LiAlH_4$ solution ($LiAlH_4$:R*OH molar ratio 1.0:2.3) there is an immediate liberation of the theoretical amount of hydrogen and formation of a precipitate which goes into solution upon

(12) D. J. Sandman, K. Mislow, W. P. Giddings, J. Dirlam, and G. C. Hanson, *J. Amer. Chem. Soc.*, **90**, 4877 (1968). These authors found a freshly prepared 1:1 THF solution of (+)-α-pinene and boron hydride treated with benzonorbornadiene followed by oxidation and acetylation to give (+)-*exo*-2-benzonorbornenyl acetate with 7.4% e.e. of the 1*S*,2*R* enantiomer. However, when the reagent was warmed and held for 21 hr before the benzonorbornadiene was added, the stereoselectivity was reversed with the formation, in comparable enantiomeric purity, of the 1*R*,2*S* enantiomer. The reason for this reversal in stereoselectivity with age of the "di-3-pinanylboron" reagent is unknown and may or may not be related to the phenomenon that we observe with the chiral $LiAlH_n(OR^*)_{4-n}$ reagent.

(13) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **81**, 247 (1959); **83**, 2544 (1961).

TABLE II

ASYMMETRIC REDUCTION OF SUBSTRATES BY INSOLUBLE (A)[a] AND SOLUBLE (B)[a] $LiAlH_4$–(2*S*,3*R*)-4-DIMETHYLAMINO-3-METHYL-1,2-DIPHENYL-2-BUTANOL (R*OH 6)[b] REAGENTS. $LiAlH_4$:R*OH:SUBSTRATE RATIO 1.3:3.0:1.0

No.	Substrate	Procedure[a]	Temp, °C	Solvent[c]	Extent of reduction,[d] %	Stereoselectivity[e] Configuration	Stereoselectivity[e] % e.e.
1	PhCOMe	A	0	ETH	Q	*R*	68
2		B	rt	ETH	46	*S*	62
3		C	rt	THF	90	*R*	13
4		C	rt	BENZ	40	*S*	43
5		C	0	PENT	43	*S*	30
6	$PhCOCF_3$	A	0	ETH	Q	*R*	29, 30[f]
7		B	0	ETH	96	*R*	30
8		C	rt	BENZ	95	*R*	29
9	PhCO-*n*-Pr	A	0	ETH	Q	*R*	60, 62,[f] 61[g]
10		B	0	ETH	50	*S*	59[f]
11		C	rt	BENZ	41	*S*	49
12	PhCO-*i*-Pr	A	0	ETH	Q	*R*	30, 28,[f] 30[g]
13		B	0	ETH	34	*S*	20
14		C	rt	BENZ	20	*S*	48
15	PhCO-*t*-Bu	A	0	ETH	Q	*R*	36, 35[f]
16		B	0	ETH	43	*R*	28
17		C	rt	BENZ	24	*S*	9
18	MeCO-*t*-Bu	A	0	ETH	Q	*R*	16, 28,[g] 28[h]
19		B	0	ETH	42	*S*	19,[i] 21[g]
20		C	rt	BENZ		*S*	4[i]

[a] The procedures are detailed in the Experimental Section. The abbreviations are the same as outlined in the notes to Table I. [b] R*OH symbolizes the chiral alcohol 6. [c] Solvents: ETH is diethyl ether, THF is tetrahydrofuran, BENZ is benzene, and PENT is pentane. [d] Based on the carbinol–ketone ratio as determined by glc analysis; Q represents essentially quantitative yield. [e] Stereoselectivity is designated by per cent excess of an enantiomer over the racemate (% e.e.). [f] This is an alternate analysis on the same sample obtained from the nmr relative peak areas for the OCH_3 signal from the diastereomeric MTPA derivative in the presence of 0.1–0.2 *M* Eu(fod)$_3$ shift reagent. [g] Calculated on relative areas of ^{19}F nmr signals of α-CF_3 group of diastereomeric MTPA derivatives. [h] Based on relative areas of *t*-Bu nmr resonances of diastereomeric MTPA derivatives in the presence of 0.2 *M* Eu(fod)$_3$. [i] Based on the relative heights of *tert*-butyl signals of diastereomeric MTPA derivatives.

TABLE III

ASYMMETRIC REDUCTIONS OF BENZALDEHYDE AND ACETOPHENONE BY $LiAlD_4$–(2*S*,3*R*)-4-DIMETHYLAMINO-3-METHYL-1,2-DIPHENYL-2-BUTANOL (R*OH, 6) REAGENT IN ETHER SOLVENT AT 0°

$$PhCOR + LiAlD_n(OR^*)_{4-n} \longrightarrow\longrightarrow (R)\text{-}PhC\overset{*}{D}OHR + (S)\text{-}PhC\overset{*}{D}OHR$$

No.	PhCOR R	Method[a]	Molecular ratio[b] $LiAlD_4$	Molecular ratio[b] R*OH	Molecular ratio[b] PhCOR	Per cent redn[b,c] $LiAlD_4$	Per cent redn[b,c] ($LiAlH_4$)	Stereoselectivity[d] Configuration	Stereoselectivity[d] $LiAlD_4$ % e.e.	Stereoselectivity[d] $LiAlH_4$ (% e.e.)
1	H	A	1.0	2.30	0.64	Q		*S*	43, 40[f]	
2	H	B	1.0	3.00	0.83	72		*S*	19	
3	Me	A	1.0	2.30	0.64	Q	(Q)	*R*	90, 81[h]	(68)[e]
4	Me	A	1.0	2.30	0.64	Q		*R*	80[g]	
5	Me	A	1.0	1.54	0.64	Q	(Q)	*R*	78, 79[h]	(66)[e]
6	Me	A	1.0	1.54	0.64	Q		*R*	79[g]	
7	Me	B	1.0	3.00	0.83	29	(24)	*S*	73	(60)[e]

[a] See Experimental Section for details. Procedure A essentially involves the insoluble form while procedure B is the aged, soluble reagent. [b] R*OH symbolizes the chiral alcohol 6. [c] Determined by glc and based on carbinol:unreduced substrate ratios; Q represents an essentially quantitative yield. Parentheses indicate data from Table I. [d] Stereoselectivity is given as per cent excess of one enantiomer over the racemate (% e.e.) based upon optical rotation unless otherwise indicated. [e] These are the directly comparable or most closely comparable $LiAlH_n$ reductions taken from Table I. [f] Stereoselectivities determined on the same sample by use of nmr signals of benzylic protons of MTPA in the presence of 0.4 *M* Eu(fod)$_3$. [g] Duplicate experiment. [h] Stereoselectivities determined on the same sample by use of nmr signals of OCH_3 protons of MTPA ester in the presence of 0.1 *M* Eu(fod)$_3$.

swirling in about 7–8 min (2–3 min in refluxing ether). If acetophenone (4) is added to this precipitated reagent at room temperature immediately after mixing (within the first 3 min), the precipitate immediately dissolves and *R*-(+)-**5** is obtained in 58% e.e. (Table I, no. 12). Addition of **4** to a sample of this reagent which has been stirred for 8 min after mixing gave *S*-(−)-**5** in 15% e.e. At this point in time the precipitate which was formed on initial mixing had just dissolved.

(3) An added complicating factor is that, although the per cent yields of reduction product are essentially quantitative when the reagent containing the precipitate is used (procedure A), the per cent yields with the aged, soluble reagent (procedure B) fall short of the theoretical, even in the presence of 1–3 *M* excess of the hydride reagent. Unreduced carbonyl compound is recovered even though active hydride still remains in the incomplete reduction mixture, as shown by the liberation of hydrogen upon the addition of water. A clear exception to this general observation is the reduction of phenyl trifluoromethyl ketone by either the insoluble or soluble reagent which gives high per cent yields and about 30% e.e. of *R* enantiomer under all conditions tried (Table II, no. 6–8). This behavior may

be related to the well-known ease of reduction of trifluoromethyl ketones.

(4) Evidence that the reversal in stereoselectivity is not simply a difference between heterogeneous *vs.* homogeneous reactions is given by the following. When the reagent is prepared in dilute solution by adding R*OH (**6**) to an 0.05 *M* ether solution of $LiAlH_4$ (instead of to the usual 0.5 *M* $LiAlH_4$ solution), a clear solution results without the formation of a precipitate as is observed when the concentration is approximately ten times this. The immediate addition of acetophenone to this dilute homogeneous solution results in its reduction to (*R*)-(+)-phenylmethylcarbinol, 29% e.e. (Table I, no. 24). This is a lower specificity but the same sense of asymmetric reduction as observed with the precipitated complex which results when the reagent is prepared in more concentrated form.

(5) Empirical studies indicate that the highest stereoselectivities for both precipitated and soluble forms of the reagent were obtained with $LiAlH_4$:R*OH ratios from approximately 1.0:2.3 to 1.0:1.5 (68 and 66%, respectively, Table I, no. 13 and 9 at 0° for procedure A). The exact ratio for the production of reasonably high *R* stereoselectivity according to procedure A does not appear to be critical. The original rationale for using the $LiAlH_4$:R*OH ratio of 1.0:2.3 was that this represented a modest excess of $LiAlH_4$ over that required for a reagent with the empirical formula of $LiAlH(OR^*)_3$. In fact this ratio corresponds to a mixture represented by $LiAlH(OR^*)_3 \cdot 2LiAlH_2(OR^*)_2$.[14] However, with an $LiAlH_4$:R*OH ratio of 1:1, corresponding to $LiAlH_3(OR^*)$, the precipitate formed in ether does not go into solution on standing or refluxing. This 1:1 reagent affords high stereoselectivity of the *R* enantiomer, whether the freshly prepared or aged reagent is used (47 *vs.* 52% e.e., respectively, Table I, no. 6 and 5). However, addition of extra ether, which causes solution of some of this 1:1 complex, results in a reagent with reduced *R* stereoselectivity (21% e.e. *R*).

(6) The addition of an ether solution of R*OH, **6**, to $LiAlH_4$ ($LiAlH_4$:R*OH molar ratio 1.0:2.3) results in the formation of a precipitate which begins to deposit when approximately one half of the R*OH has been added. However, when the order of mixing is reversed, no precipitate is formed. Immediate use of the resulting solution, from this reverse order of mixing, for reduction of acetophenone gives the *R*-(+) enantiomer of **5**, but with low (10% e.e.) stereoselectivity in 92% yield. Longer standing of such a solution leads to a reagent which gives high *S*-(−) stereoselectivity.

(7) The stereoselectivity of the reduction by the insoluble complex was found to increase with decreasing temperature: 20°, 57% *R*; 0°, 68% *R*; −65°, 75% *R*; the percentage yield was nearly quantitative in each case (Table I, no. 12, 13, 14). The stereoselectivity of the soluble reagent seems to decrease with lower reaction temperature: 20°, 66% e.e. *S*; 0°, 53% e.e. *S*; −65°, 5% e.e. *R* (Table I, no. 19, 22, and 23).

(8) When the reagent was prepared in benzene instead of ether solution it was soluble under all conditions tried and the *S*-(−) enantiomer of **5** formed in reasonably high stereoselectivities (40-55% e.e.) in analogy with the soluble reagent in ether solution (Table II). Similarly, the reagent in pentane, using a $LiAlH_4$:R*OH ratio of 1:2.3, was soluble and afforded the *S* enantiomer of **5** (30% e.e.). Repetition in tetrahydrofuran solvent gave a homogeneous solution of the reagent which reduced acetophenone to **5** to give the *R* enantiomer with low stereoselectivity (13% e.e.), contrary to the results in benzene, pentane, and ether solution (Table II).

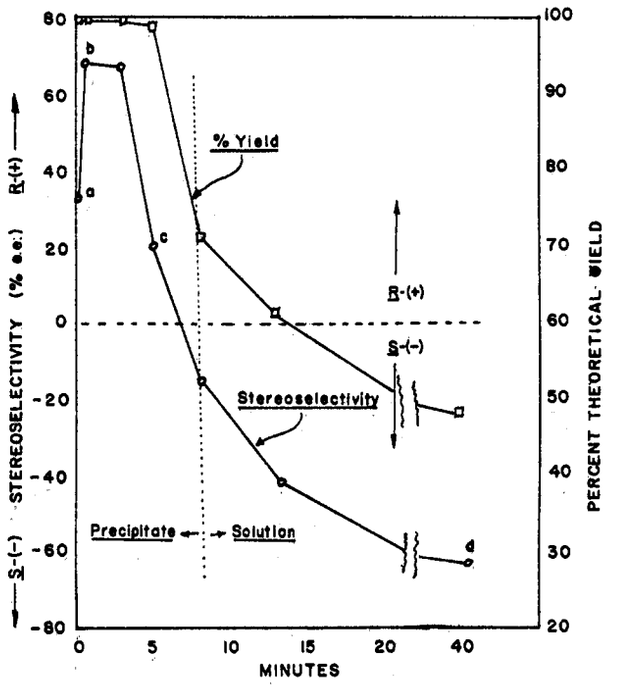


Figure 1.—Change in stereoselectivity (O—O left ordinate) and in percent yield (□—□ right ordinate) with age of reagent ($LiAlH_4$; R*OH ratio 1.0:2.3) in ether solvent at room temperature. (a) Zero time corresponds to results when acetophenone and R*OH in ether were added to $LiAlH_4$. (b) Acetophenone added to reagent 30 sec after mixing. (c) After 8 min of shaking the initial precipitate had just dissolved, at which point acetophenone was added. (d) This sample was refluxed in ether for 3 min as well as standing for 40 min before acetophenone was added.

(9) The reduction of three additional phenyl alkyl ketones (excluding phenyl trifluoromethyl ketone) showed generally decreased stereoselectivities as the size of the alkyl group increased (Table II). The aliphatic ketone, methyl *tert*-butyl ketone, showed the lowest order of stereoselectivity of these substrates. In each of these cases the heterogeneous reagent (procedure A) gave the *R* enantiomer in excess while the homogeneous reagent (procedure B) gave the *S*. However, phenyl trifluoromethyl ketone gave excess *R* enantiomer in good yield (Table II, no. 1–3) with both heterogeneous and homogeneous reagents.[15]

(10) A soluble chiral reagent prepared from sodium aluminum hydride and **6** in ether gave relative low stereoselectivities of the (*R*)-**5** enantiomer (5% e.e. with $NaAlH_4$:R*OH ratio of 1:2 and 17% e.e. with 1:3 ratio); the same reagent in benzene was soluble

(14) Throughout we shall represent the reagents as $LiAlH(OR^*)_3$, $LiAlH_2(OR^*)_2$, $LiAlH(OR^*)_3$, and $LiAl(OR^*)_4$. By these formulas we wish to designate only the ratio of the $LiAlH_4$ and R*OH used in the preparation of these reagents; we specifically do not imply that these formulas represent either the structure or state of aggregation of the reagent. These experiments were done in relatively small amounts and the exact ratios in any one experiment may easily be off by 0.1.

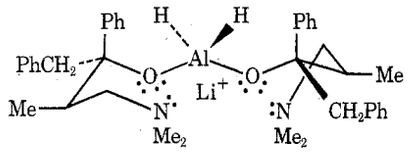
(15) It should be pointed out that because of the *R*–*S* nomenclature rules (*R*)-phenyltrifluoromethylcarbinol is configurationally related to (*S*)-phenylmethylcarbinol, where the methyl group is replaced by the trifluoromethyl group. Thus the departure from the regular pattern in the reduction of phenyl trifluoromethyl ketone by procedure A (precipitated reagent) was to give the *R* enantiomer instead of the *S*.

and gave 12% e.e. (*R*)-**5** when prepared with a 1:2.7 molar ratio of $NaAlH_4$ to R*OH. It is interesting that the soluble form of the sodium aluminum hydride reagent gives (*R*)-(+)-**5** in excess whereas the soluble form of the lithium aluminum hydride reagent gives (*S*)-(−)-**5** in excess.

(11) Several experiments were designed to obtain some information concerning the nature of the isolated precipitate. At 0°, $LiAlH_4$ and R*OH were mixed in 1.0:2.3 molar ratio and the mixture was immediately centrifuged. The supernatant layer was removed and the solid was twice washed with anhydrous ether. The resulting solid did not dissolve in ether on standing at room temperature; upon addition of acetophenone it gave (*R*)-(+)-**5** in 70% e.e. Another sample of this solid was vacuum dried and hydrolyzed to give 90–94% (duplicate runs) of the theoretical amount of hydrogen based on the formula $LiAlH_2(OR^*)_2$. Again the chiral reagent was made by mixing $LiAlH_4$ and R*OH in 1.0:2.3 molar ratio but this time the mixture was refluxed for a short time until the precipitate went into solution. It was centrifuged free of a slight amount of turbidity and the supernatant liquid was evaporated to dryness to give a white, silky solid which was completely soluble in pentane. Addition of acetophenone to this pentane solution resulted in a 43% yield of (*S*)-(−)-**5** with 30% e.e. Thus the soluble form which gives *S* stereoselectivity does not revert to the insoluble form which gives *R* stereoselectivity upon evaporation of solvent.

Discussion

We would like to be able to interpret these results from a mechanistic standpoint, *i.e.*, to postulate transition-state stereochemistries which would account for the observed configurations and generally high stereoselectivities of the products and which would explain the phenomenon of reversal in stereochemistry, depending upon the age of the reagent. We had anticipated that the stereoselectivities might be high based upon rather speculative models for this reaction involving a structure such as **8** which is held in a tight



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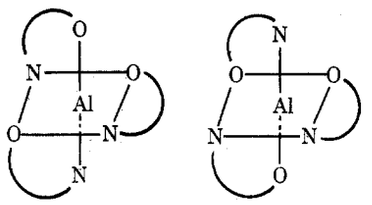
complex by coordination of the heteroatoms to the lithium cation. However, the reversal in stereoselectivity with age of the reagent was totally unexpected. This complication renders any interpretation doubly difficult.

Important parallels can be drawn between the complexities of these asymmetric reductions and asymmetric hydroborations by "di-3-pinanylborane." Attempts to rationalize the stereochemistry of asymmetric hydroborations by this chiral reagent have led to the postulation of a series of six speculative transition-state models, each one of which tried to improve on the previous model in order to accommodate some additional observation.[16] All but the last of these models were proposed before the observation on the reversal in stereoselectivity with age of this reagent.[12] None, including the last of these proposed models, attempted to account for such a reversal.

One can speculate that the state of association of the chiral reagent, for instance $[LiAlH_2(OR^*)_2]_n$, is involved in this observed reversal of stereochemistry with age of reagent. The reactivity of aluminum isopropoxide in the Meerwein–Ponndorf–Verley reduction has been studied with respect to association of the reagent. It is now established[17] that the stable form of aluminum isopropoxide in solution is the tetramer, while the active reducing species is the trimer which is in equilibrium with the tetramer. One can easily imagine that a monomer of a reagent such as **7** might have considerably different stereoselectivity from its dimer or trimer.

These uncertainties in state of aggregation of the reagent are in addition to those due to the multiple conformations that one species may assume during actual reaction with the substrate. Furthermore, in the present case, coordination number of the aluminum in solution is not known. Speculative models might be based on either a tetrahedral or octahedral aluminum geometry where coordination could be either with heteroatoms of the reagent or with solvent. If octahedral geometry is involved there is the added complication of cis *vs.* trans isomerism, **9a** *vs.* **9b**, as well as the overall chirality, *i.e.*, **9a** or **9b** *vs.* the mirror images.



9a **9b**

The chiral reducing complex resulting from reaction of $LiAlH_4$ with R*OH has the possibility of three different stoichiometries, $LiAlH_3(OR^*)$, $LiAlH_2(OR^*)_2$, or $LiAlH(OR^*)_3$, each of which could have different stereoselectivities in asymmetric reductions. The rate of reduction of such species will also differ; thus if a mixture contains more than one such species the stereoselectivity during the initial phase of the reaction should be different from that during the final stages of reduction. This complexity is compounded in that the transfer of the first active hydrogen of $LiAlH_2(OR^*)_2$ produces a new chiral reagent $LiAlH(OR^*)_2(OR'^*)$ with the reduced substrate as a ligand. This reagent should be capable of further transfer of hydrogen and should have a stereoselectivity in further reductions which would be different from that of $LiAlH_2(OR^*)_2$ or $LiAlH(OR^*)_3$. Thus the possible complexities of the reaction reported here considerably surpass those of the chiral "di-3-pinanylborane" hydroboration reaction. We are convinced that it is premature to attempt to interpret our present results in terms of transition-state models.

An initial hypothesis which we entertained was that the "*R*" reagent (*i.e.*, the reagent with *R* stereoselectivity toward acetophenone) was $LiAlH_2(OR^*)_2$ which was formed very rapidly upon mixing $LiAlH_4$ and R*OH, while the "*S*" reagent, which was formed by a slower subsequent reaction, was $LiAlH(OR^*)_3$. The

(16) The evolution of these transition state models has been reviewed in ref 4, pp 220–240.

(17) V. J. Shiner and D. Whittaker, *J. Amer. Chem. Soc.*, **85**, 2337 (1963).

change in stereoselectivity with time according to this hypothesis follows the rate of the conversion according to the following equations.

$$LiAlH_4 + R^*OH \longrightarrow LiAlH_3OR^* + H_2$$

$$LiAlH_3OR^* + R^*OH \longrightarrow LiAlH_2(OR^*)_2 + H_2$$

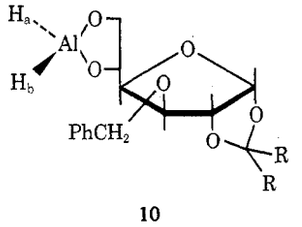
$$LiAlH_3(OR^*) + R^*OH \longrightarrow LiAlH(OR^*)_3 + H_2$$

This hypothesis is untenable, because upon adding 3 molar equiv of the alcohol (R*OH) to the $LiAlH_4$ solution 90-94% of the 3 molar equiv of hydrogen are liberated immediately, not 2 mol rapidly and a third mole much more slowly, as would be required by such a postulate.

At least two distinct reagents must be postulated, one with *R* and the other with *S* stereoselectivity with respect to acetophenone reduction; both reagents probably have the same empirical formula although not necessarily the same molecular formula. We will refer to these as the *R* and the *S* reagent. We assume that the initially formed *R* reagent is produced rapidly and that this changes more slowly into the more stable *S* reagent. This change might be an isomerization, as represented by the difference in **9a** and **9b**, or it might be a conversion from one state of aggregation into another as in the interconversion of aluminum isopropoxide trimer and tetramer.[17] However, it is not an isomerization of the skeleton of the chiral alcohol, since the R*OH is recovered unchanged in high yield from these reductions.

Superficially it might appear that the *R* reagent is the initial precipitate and that the *S* reagent is its soluble form with the reversal in stereoselectivity being a reflection of the difference between a heterogeneous *vs.* homogeneous reaction. This is readily discounted by the results obtained from a reagent prepared according to procedure A but using ten times the amount of ether solvent which gives a solution rather than a precipitate but still shows predominant *R* stereoselectivity in the reduction of acetophenone when used immediately after preparation (Table I, no. 24). Furthermore, the reagent used for the experiments reported in Figure 1 become homogeneous after 7–8 min of swirling whereas the maximum *S* stereoselectivity is not developed until longer standing.

In the studies by Landor, *et al.*,[5b] on chiral reducing agents derived from $LiAlH_4$ and monosaccharide derivatives such as **10**, it was found that one of the two available active hydrogens reacted much faster than the other to give predominant *S* stereoselectivity in the reduction of acetophenone. When 1 equiv of ethanol was added to reagent **10** the resulting new reagent **11**, which had one reactive hydrogen left, gave *R* stereoselectivity.



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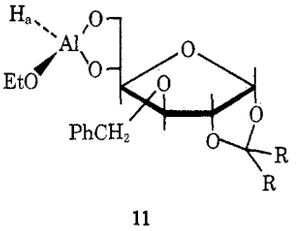

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A similar explanation in this form cannot rationalize our data, since we obtain either *R* or *S* stereoselectivity from a reagent with the same composition in which the $LiAlH_4$:R*OH ratio was unchanged, the only difference being the age of this reagent. Furthermore, we obtained this reversal in stereoselectivity with time whether the reagent had the composition $LiAlH_2(OR^*)_2$ or $LiAlH(OR^*)_3$. We have in fact carried out comparable experiments where the reagent $LiAlH_2(OR^*)_2$ was made according to procedure A and within 3 min 1 equiv of methanol (or phenol) was added in order to give a new reagent, $LiAlH(OR^*)_2(OR')$. Hydrogen was evolved upon the addition of methanol (or phenol) and the initial precipitate did *not* dissolve. Acetophenone was then added within 30 sec, with the result that (*R*)-(+)-**5** was formed in about 52% e.e (with phenol, 64% e.e.). Thus utilization of one of the two remaining available hydrogens did not result in a reversal of stereoselectivity.

However, it must be significant that *R* stereoselectivity is higher when there is sufficient $LiAlH_2(OR^*)_2$ reagent so that only one hydrogen needs to be utilized (Table I, no. 10, 40–49% e.e. *R*, quantitative yield) as compared to the experiment where both hydrogens must be used for complete reduction (Table I, no. 11, 21% e.e. *R*, 59% yield). The aged reagent with this same composition gave *S* stereoselectivity but in reduced per cent yield (Table I, no. 17 and 18, 49-45% e.e. *S*, 29–15% yield). The reduced chemical yields using the soluble reagent which gives *S* stereoselectivity is a troublesome point. It would thus seem that a large part of the active hydrogen in the soluble reagent with *S* stereoselectivity is rendered inactive toward reduction of acetophenone upon aging, perhaps by being "buried" in a relatively inaccessible position within the reagent molecule. This phenomenon is not noted with the initial insoluble reagent with *R* stereoselectivity.

Reduction of benzaldehyde by procedure A using $LiAlD_2(OR^*)_2$ instead of $LiAlH_2(OR^*)_2$ gave (*S*)-benzyl-α-*d* alcohol (40, 43% e.e., Table III, no. 1) with lower stereoselectivity than observed in the reduction of acetophenone to give (*R*)-phenylmethylcarbinol-α-*d* under comparable conditions (*ca.* 80% e.e., Table III, no. 3 and 4). These carbinols correspond in both cases to attack by deuteride on the *si* face of the respective carbonyl groups. Thus the steric course of these reductions is the same although the configurational designations of the products are opposite. A surprising observation was that the stereoselectivity was uniformly higher than the protio reagent (compare Table I, no. 9, 13, 19, and 20 and Table III, no. 3–7).

As a final point we would like to note that this asymmetric reduction system constitutes a reasonable method for obtaining either (*R*)-(+) or (*S*)-(−)-methylphenylcarbinol in approximately 70% enantiomeric purity. The same is true for the reduction of butyrophenone and to a lesser extent the other ketones tested. This is the method of choice for obtaining (*S*)-benzyl-α-*d* alcohol (40% e.e.) and presumably other α-deuterio chiral primary alcohols as well. Finally, these preliminary results point to the very real possibility of developing a superior reducing agent of the

same general type with even higher stereoselectivity.

Experimental Section

Instruments.—Optical rotations on small samples were taken on a Perkin-Elmer 141 electronic spectropolarimeter with digital read-out using 1-dm, center-filled water-jacketed cells thermostated at 20.0°; readings were ±0.002°. Rotations on larger samples were occasionally taken on a Zeiss visual polarimeter with readings to ±0.02°. Routine proton nmr determinations were made on a Varian T60 instrument; analytical determinations were made on a Varian HR-100 instrument ($CDCl_3$; solvent, TMS standard). ^{19}F determinations on MTPA diastereomeric esters[9] were made on a Varian XL-100 instrument ($CDCl_3$; solvent, trifluoroacetic acid external standard). Gas–liquid chromatographic (glc) determination were made on a Varian Aerograph at 40 ml/min, He flow rate, thermoconductivity detector, polyethylene glycol 20M, 5 ft × 0.25 in. column.

Reagents.—The (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol[7] (**6** R*OH), $[\alpha]^{27}D$ +8.09° (*c* 9.63, EtOH), mp 55–57°, was obtained by regeneration from the hydrochloride[18] and was stored in a desiccator over P_2O_5. This alcohol was recovered and repeatedly reused. Ether, tetrahydrofuran (THF), and benzene were distilled over $LiAlH_4$ and stored over a Linde 4A molecular sieve. A stock lithium aluminum hydride solution in ether was passed through a glass filter under nitrogen and stored in a flask closed with a rubber septum. It was analyzed immediately prior to use. Aliquots were removed by syringe as needed.

Determination of Stereoselectivity by Optical Rotation.—The enantiomeric excess, % e.e.,[10] was obtained from the observed optical rotation and the known maximum rotations of the carbinols according to the following data by assuming a linear relationship between rotation and concentration, *i.e.*, % e.e. $100 \times [\alpha]D_{obsd}/[\alpha]D_{max}$: (*R*)-$PhCHOHCH_3$,[19] $[\alpha]^{20}D$ +43.1° (*c* 7.19, cyclopentane); (*R*)-$PhCHOHCF_3$,[20] $[\alpha]^{20}D$ −14.9° (*c* 15, benzene); (*R*)-*n*-PrCHOHPh,[21] $[\alpha]^{20}D$ +43.6° (*c* 4.18, benzene); (*R*)-*i*-PrCHOHPh[22], $[\alpha]^{20}D$ +47.7° (*c* 6.8, Et_2O); (*R*)-*t*-BuCHOHPh,[23] $[\alpha]^{20}D$ +27.4° (*c* 2.2, benzene); (*R*)-*t*-$BuCHOHCH_3$,[24] $[\alpha]^{20}D$ −3.31° (*c* 10.3, benzene); (*S*)-PhCHDOH,[25] $[\alpha]^{20}D$ +1.70° (*c* 2.2, EtOH), $[\alpha]^{20}D$ +1.52° (*c* 7.1, cyclopentane), $[\alpha]^{24}D$ +1.58° (neat). The optical rotation of methylphenylcarbinol in cyclopentane solvent was found to be significantly dependent upon the concentration of acetophenone present in solution. The following data were determined on solutions with known enantiomeric compositions of methylphenylcarbinol and known amounts of added acetophenone (the enantiomeric composition of samples made by procedure B which contained unreduced acetophenone were calculated based on these data and the known carbinol:ketone ratios determined by glc): $[\alpha]^{20}D$ +43.1° (*c* 7.19, C_5H_{10}, zero $PhCOCH_3$); $[\alpha]^{20}D$ +44.8° (*c* 7.86, $PhCHOHCH_3$, *c* 0.99, $PhCOCH_3$ in C_5H_{10}); $[\alpha]^{20}D$ +50.0° (*c* 6.66, $PhCHOCH_3$, *c* 5.12, $PhCOCH_3$ in C_5H_{10}); $[\alpha]^{20}D$ +52.0° (*c* 5.12, $PhCHOHCH_3$, *c* 5.12, $PhCOCH_3$ in C_5H_{10}); $[\alpha]^{20}D$ +54.0° (*c* 4.86, $PhCHOHCH_3$, *c* 7.28, $PhCOCH_3$ in C_5H_{10}); $[\alpha]^{20}D$ +56.5° (*c* 3.71, $PhCHOHCH_3$, *c* 8.99, $PhCOCH_3$ in C_5H_{10}); $[\alpha]^{20}D$ +58.3° (*c* 2.64, $PhCHOHCH_3$, *c* 10.60, $PhCOCH_3$ in C_5H_{10}).

Determination of Stereoselectivity by Nmr Method.—The carbinol (for instance, 0.10 mmol, 12 mg of $PhCHOHCH_3$) was treated with excess acid chloride from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA-Cl, 37 mg, 0.15 mmol) in pyridine according to the usual procedure.[11,26]

General Procedure A (Insoluble Reagent).—All experiments were carried out under a nitrogen atmosphere; transfers were made *via* syringe through rubber septums. The following is a detailed description of experiment 13, Table I. An ether solution (2.0 ml), containing the chiral amino alcohol **6** (R*OH) [1.02 g, 3.6 mmol, $[\alpha]^{28}D$ +8.09 (*c* 9.6, EtOH], was added at 0° to a magnetically stirred solution of $LiAlH_4$ (1.56 mmol, $LiAlH_4$:R*OH mole ratio 1.0:2.3) in ether (4.0 ml). A white, pasty precipitate began to form when about one half of **6** was added. The transfer was completed by rinsing the original flask and the syringe with 1.0 ml of ether. The reaction flask was shaken thoroughly at 0°; 3 min from the time of initial mixing, acetophenone, **4** (120 mg, 1.0 mmol), in 0.5 ml of ether was added dropwise to the precipitated reagent. The precipitate dissolved and gave a clear, transparent solution. The mixture stood for 12 hr and was then hydrolyzed with 1 drop of water (vigorous evolution of gas) and then excess dilute hydrochloric acid to dissolve the amino alcohol **6**. The ether extracts were washed (H_2O, three times), dried ($MgSO_4$), and concentrated (water aspirator) to give a colorless oil (0.10 g, 82% yield) which contained no unreduced acetophenone as measured by glc (column temperature 170°): $[\alpha]^{20}D$ +29.3° (*c* 8.15, C_5H_{10}), 68.0% e.e. (*R*)-(+)-**5**. Alternate analysis by conversion to the MTPA derivative and measuring the nmr spectrum gave the same % e.e. Neutralization of the acid extract gave recovered chiral amino alcohol **6**, $[\alpha]^{20}D$ +8.18° (*c* 10.2, EtOH).

In one run according to procedure A, the acetophenone was added just 30 sec after preparation of the reagent. This gave an oil containing no unreduced ketone, $[\alpha]^{21}D$ +29.8° (*c* 9.15, C_5H_{10}), corresponding to 69% e.e. of (*R*)-(+)-**5** as given in Figure 1, point b. In still another experiment, **6** (3.6 mmol, 1.02 g) and **4** (1.0 mmol, 120 mg) were dissolved in ether (3.0 ml) and were added at 0° to $LiAlH_4$ (1.56 mmol, in 2.4 ml of ether). No precipitate formed. The solution yielded carbinol **5**, containing no ketone, $[\alpha]^{21}D$ +14.2° (*c* 2.25, C_5H_{10}), corresponding to 33% e.e. of (*R*)-(+)-**5**. This is represented as the zero time, point a, in Figure 1.

Procedure B (Soluble Reagent).—Under a nitrogen atmosphere, an ether solution of amino alcohol **6** (1.02 g, 3.6 mmol in 2.0 ml of ether) was added to $LiAlH_4$ (1.56 mmol in 4.0 ml of ether, $LiAlH_4$:R*OH ratio 1.0:2.3) at room temperature. The transfer was completed by rinsing the original flask and syringe containing amino alcohol **6** with 1.0 ml of ether. The precipitate which formed initially dissolved after 2–3 min of reflux. After the solution was refluxed for 10 min and had stood for 24 hr at room temperature, acetophenone (**4**, 120 mg, 1.0 mmol) was added and the mixture was processed as in procedure A after standing at room temperature overnight to give 0.11 g of an oil, $[\alpha]^{20}D$ −35.4° (*c* 1.64, C_5H_{10}), which by glc analysis was 40% methylphenylcarbinol (**5**) and 60% acetophenone (**4**). Using $[\alpha]^{20}D$ +54.0° for the rotation of enantiomerically pure methylphenylcarbinol in the presence of 60% acetophenone, this corresponds to 66% e.e. as shown in example 19, Table I. A duplicate run which was refluxed for an additional 2 hr gave a 43:57 ratio of 5:4 with 66% enantiomeric purity of **5** as measured by optical rotation. Upon hydrolysis of these reaction mixtures hydrogen was evolved indicating excess unreacted reducing reagent.

Procedure C (Reduction in Benzene Solution).—Under nitrogen, 1.56 mmol of $LiAlH_4$ in ether was transferred to a 20-ml flask. The ether was removed under high vacuum and the residue of $LiAlH_4$ was treated with benzene solution (6.0 ml) containing 1.02 g (3.6 mmol) of amino alcohol **6**. There was an exothermic reaction which resulted in the formation of a clear solution. Occasionally there was a small amount of a white solid that did not dissolve. After this benzene solution had stood for 1.5 hr, acetophenone (120 mg, 1.0 mmol) in benzene (0.5 ml) was added and the mixture was allowed to stand overnight. Processing as

(18) Aldrich Chemical Co., Milwaukee, Wis. We also acknowledge with gratitude a sample of the free base supplied by Dr. A. Pohland of Eli Lilly and Co.

(19) Spectrograde cyclopentane (C_5H_{10}) was used because of its ready availability in high purity and because the chiral alcohols could be freed readily of this volatile solvent. This value was determined on a sample of enantiometrically pure carbinol which had $[\alpha]^{21}D$ +43.5° (neat). R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

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(26) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **95**, 512 (1973). The signals of both the *O*-methyl and *C*-methyl groups of the *R,R* diastereomer from methylphenylcarbinol appear at higher field than those of the *R,S* diastereomer. The peaks are too close together to be accurately integrated on the T-60 instrument but relative peak heights were shown to give a good approximation of the isomeric composition. The ^{19}F resonances for the α-CF_3 group at 94.1 MHz were clearly separated and readily integrated. The addition of the nmr shift reagent, $Eu(fod)_3$ (0.1 *M*), caused both the *O*-methyl and *C*-methyl resonances of the *R,R* diastereomer to be shifted to lower field more strongly than that of the *R,S* diastereomer, so that quantitative integration of the respective *O*-methyl signals was readily possible.

in procedure A gave a yellowish oil, 0.092 g, $[\alpha]^{20}D$ −22.1° (*c* 3.75, C_5H_{10}), which, as determined by glc, was a 49:51 mixture of 5:4 and thus corresponds to 43% e.e., *S* isomer.

Procedure D.—General procedure A was followed except that 1.2 mmol of $LiAlH_4$ was dissolved in 47 ml of ether maintained at 0° instead of 4 ml of ether. Under these circumstances no precipitate was formed when amino alcohol **6** (1.02 g, 3.6 mmol) was added to the solution. To this homogeneous solution was immediately added acetophenone (120 mg, 1.0 mmol) at 0°. The reaction mixture ws processed after standing overnight at room temperature to give a colorless oil (0.10 g, 82% yield), $[\alpha]^{20}D$ +12.5° (*c* 7.18, C_5H_{10}), 29% e.e., *R* isomer, which by glc analysis contained no unreduced acetophenone.

Sodium Aluminum Hydride Reductions.—To a suspension of sodium aluminum hydride (1.0 mmol) (Alfa Inorganics) in ether (5 ml, 1.0 mmol) was added chiral amino alcohol **6** (2.0 mmol in 3 ml of ether) at room temperature. After stirring overnight sodium aluminum hydride went into solution, leaving a small amount of turbidity. To this solution at room temperature was added acetophenone (1.0 mmol) and the reaction mixture was processed as usual to give an oil which was a 48:52 mixture of **5** and unreacted **4**, $[\alpha]^{20}D$ +2.73° (*c* 6.1, C_5H_{10}), corresponding to a 55% excess of the *R* enantiomer of **5**.

Repetition of this experiment using $NaAlH_4$ (1.2 mmol), amino alcohol **6** (3.6 mmol), and acetophenone (0.5 mmol), followed by processing in the usual way, gave an oil (97% **5** and 3% **4**) containing 17% e.e. of (*R*)-(+)-**5** enantiomer. A repetition of this experiment in benzene solvent gave a 99% yield of (*R*)-(+)-**5**, 12% e.e.

Commercial $NaAlH_2(OCH_2CH_2OMe)_2$ (Eastman Kodak, Vitride) in benzene solution (5.12 ml, containing 1.2 mmol) was mixed at 0° with 20 ml of a benzene solution containing amino alcohol **6** (0.34 g, 1.2 mmol). Hydrogen was evolved but there was no precipitate. Acetophenone (120 mg, in 1 ml of benzene) was added. The usual processing, after standing at room temperature overnight, gave a colorless oil which by glc was 73% carbinol **5** and 27% recovered ketone **4** with $[\alpha]^{20}D$ +0.98 ± 0.12° (*c* 1.63, cyclohexane), corresponding to 2.1 ± 0.3% e.e. of *R*-(+) isomer.

Reductions of Benzaldehyde with $LiAlD_4$–R*OH.—Amino alcohol **6** (3.6 mmol, 1.02 g in 1.1 ml of ether) was added to $LiAlD_4$ (1.56 mmol, in 5.84 ml of ether) at 0°. To the resulting reagent containing a precipitate was added benzaldehyde (1.0 mmol, 106 mg in 0.3 ml of ether) at 0° within 3 min of mixing the reagent. The precipitate did not dissolve immediately but went into solution after stirring for 25 min at 0°. The reduction mixture was processed as in procedure A after standing overnight at 0° to give an oil which showed only very small amounts of impurities by glc analysis (170°, retention time of PhCHO, 1.8 min, of PhCHDOH, 4.7 min). This was purified by preparative glc followed by distillation to give 0.07 g, $[\alpha]^{20}D$ +0.68 ± 0.02° (*c* 6.7, C_5H_{10}), which showed 0.988 ± 0.005 deuterium atoms per molecule based upon the relative areas of the benzylic and aromatic nmr proton signals. This corresponds to a stereoselectivity of 43 ± 2% of *S*-(+) enantiomer based upon the known maximum rotation, $[\alpha]^{20}D$ 1.58 ± 0.04° (*c* 7.07, C_5H_{10}), and configuration for benzyl-α-*d* alcohol.[25,27] A 22-mg sample of this product was converted to the (*R*)-MTPA derivative (55 mg). Although the nmr signals of neither the benzylic nor OCH_3 protons of the resulting diastereomers were appreciably separated at 100 MHz in $CDCl_3$ solvent, in the presence of 0.4 *M* Eu(fod)$_3$ shift reagent the benzylic signals appeared respectively at 6.35 and 6.45 ppm (100 MHz) with relative areas 70:30 corresponding to a 40 ± 2% e.e. of the *S* enantiomer.

According to procedure B (duplicating experiment 26, Table I), 212 mg of benzaldehyde was treated with a solution prepared by adding amino alcohol **6** (2.04 g, 7.2 mmol in 6 ml of ether) to $LiAlD_4$ (2.4 mmol in 8 ml of ether). After the indicated processing, an oil, 0.76 g, which was 72% benzyl alcohol and 28% benzaldehyde, was purified by glc and distillation to give benzyl-α-*d* alcohol, 0.98 ± 0.01% deuterium atoms per molecule (by nmr), $[\alpha]^{20}D$ +0.33 ± 0.04° (*c* 5.54, EtOH), corresponding to 19.5 ± 3% e.e. of the *S*-(+) enantiomer based on $[\alpha]^{20}D$ +1.70° (*c* 2, EtOH) for the pure *S* enantiomer.

Reduction of Acetophenone with $LiAlD_4$·R*OH.—At 0° according to procedure A, duplicating experiment 13, Table I but substituting $LiAlD_4$ for $LiAlH_4$ there was obtained an almost quantitative yield of 1-phenylethanol-1-*d*, $[\alpha]^{20}D$ +38.9° (*c* 6.13, C_5H_{10}), 0.99 deuterium atoms per molecule. Assuming that the rotation of the deuterio and isotopically normal compounds are the same, an assumption which could easily introduce a ±3% error, the stereoselectivity of the reaction to give the *R* enantiomer was 90%. A sample of this carbinol was converted to the MTPA derivative and the nmr spectrum was taken in the presence of 0.2 *M* Eu(fod)$_3$ shift reagent. Integration of the OCH_3 signals indicated an 81.4% excess of the *R* enantiomer. Another run using 1:1.54 molar ratio of $LiAlD_4$:**6** gave $[\alpha]^{20}D$ +34.5° (*c* 6.72, C_5H_{10}), $[\alpha]^{20}D$ +34.9° (*c* 5.94, C_5H_{10}), corresponding to 80% e.e. on the assumption that the presence of deuterium does not appreciably alter the optical rotation. Conversion of this derivative to the MTPA derivative followed by integration of the OCH_3 nmr signals in the presence of 0.2 *M* Eu(fod)$_3$ gave a value of 79.5% e.e. We discount the high rotation obtained in the initial experiment and conclude that the reaction goes with a stereoselectivity of approximately 80%.

Registry No.—**6**, 38345-66-3; lithium aluminum hydride, 16853-85-3.

(27) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher[25] have reported the maximum neat rotation of benzyl-α-*d* alcohol as $\alpha^{24}D$ +1.66 ± 0.01° (neat, *l* 1). A sample of benzyl-α-*d* alcohol from fermentation of benzaldehyde-α-*d* with 89 ± 2% deuterium had $\alpha^{24}D$ +1.43 ± 0.02° (neat, *l* 1) and $[\alpha]^{20}D$ +0.100 ± 0.001° (*c* 7.07, C_5H_{10}). On this basis $[\alpha]^{20}D$ +1.58 ± 0.04° (*c* 7, C_5H_{10}) is the maximum specific rotation in this solvent.