Rational Designing of Efficient Chiral Reducing Agents. Highly Enantioselective Reduction of Aromatic Ketones by Binaphthol-Modified Lithium Aluminum Hydride Reagents[1]

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Abstract: A new chiral hydride reagent, BINAL-H, has been devised by the modification of lithium aluminum hydride with equimolar amounts of (*R*)- or (*S*)-2,2′-dihydroxy-1,1′-binaphthyl and a simple alcohol. This reducing agent exhibits exceptionally high enantioface-differentiating ability in the reduction of prochiral alkyl phenyl ketones in tetrahydrofuran. The phenyl and alkyl groups attached to the carbonyl function are differentiated primarily by the difference in electronic properties rather than the relative bulkiness. A six-membered-ring transition-state model is proposed to account for the stereochemical consequences. This mechanism is consistent with the phenomena observed with other unsaturated carbonyl substrates.

Among a wide variety of asymmetric reactions, enantioselective reduction of prochiral carbonyl compounds is one of the most extensively studied chiral transformations.[2] The standard method to this end stems from the utilization of complex metal hydride reagents bearing chiral alkoxyl or amino ligands.[3] Since the first attempt by Bothner-By in 1951[4a] and to our knowledge the first successful experiment by Landor in 1964,[4b] a number of reagents have been elaborated by the modification of lithium aluminum hydride ($LiAlH_4$) with alkaloids,[5] sugars,[6] amino alcohols,[7] and other derivatives of readily accessible naturally occurring substances,[8] but these systems are not always satisfactorily employable.[9] The objective of this study is rational designing of a new chiral reagent which permits a high level of enantioselective reduction of a wide range of prochiral carbonyl substrates.[10]

We interpret the general difficulty in obtaining a high level of stereoselectivity with modified $LiAlH_4$ reagents as mainly due to the presence of plural reactive species which are placed in different chemical and chiral environments. Under such circumstances, one can obtain only overall or average selectivity which relies on the concentration, reactivity, and chiral recognition ability of each species. The present approach originates from the consideration that minimization of the number of reactive species or, if possible, creation of a single, highly reactive hydride which possesses excellent chiral recognition ability is crucial for obtaining a high degree of enantioselection. Here we thought that the use of axially dissymmetric 1,1′-biaryl derivatives as chiral modifying agents is the most suitable for this purpose.[11]

In order to create a system exhibiting a high level of chirality recognition, a number of problems must be solved. For instance, reaction of $LiAlH_4$ with 2 equiv of chiral alcohol, R*OH, introduces a chiral environment to the hydride reagent by forming a compound symbolized as $LiAlH_2(OR^*)_2$.[3] Actually, however, this aluminum hydride tends to undergo disproportionation,[12] producing a mixture of $LiAl(OR^*)_4$, $LiAlH_n(OR^*)_{4-n}$ (n = 1–3), and achiral $LiAlH_4$.[4b] In addition, each species, depending on the solvent and concentration, may exist in a variety of aggregation states.[13] Further, a number of conformations are possible for the chiral ligands. In order to minimize the possibility of the disproportionation of the aluminum hydrides and at the same time fix the conformation, bifunctional compounds such as diols, diamines, and amino alcohols are commonly utilized as the modifying agents. Here, however, another problem arises, as is easily understood by considering the chelating structures A–D ($R^1 \neq R^2$). H_a and H_b in such reagents derived from naturally occurring chiral compounds are, in most cases, diastereotopic and behave differently in the enantioselective reaction. Only reagents of type D ($R^1 = R^2$), which possess a modifying ligand with a C_2 axis,

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(3) For a review on the reduction with alkoxyaluminum hydrides see: Málek, J.; Černý, M. *Synthesis* **1972**, 217.

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(10) For an attempt to systematic manuplation using synthetic modifiers, see: Morrison, J. D.; Grandbois, E. R.; Howard, S. I.; Weisman, G. R. *Tetrahedron Lett.* **1981**, *22*, 2619.

(11) For highly enantioselective catalytic reactions based on this concept, see: (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245. (c) Tani, K.; Yamagata, T.; Otsuka, S.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1982**, 600.

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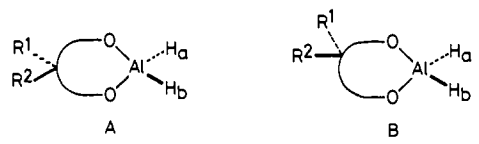

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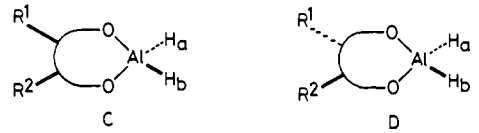


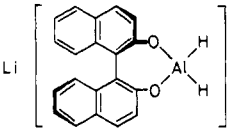
C D

(R)-(+)-1 (S)-(-)-1

bear homotopic H_a and H_b and thereby can halve the kinds of active hydrogens attached to Al. 2,2′-Dihydroxy-1,1′-binaphthyl (binaphthol, **1**),[14] an axially dissymmetric bifunctional molecule, should be one of the ideal auxiliary chiral ligands in this respect. This free ligand is conformationally mobile and can accommodate an aluminum atom through proper rotation about the C(1)–C(1′) pivot and the C–O bonds to produce a stable chelate structure without introducing significant strain. The seven-membered ring thus formed contains only sp^2-hybridized carbon atoms and is conformationally unambiguous. Further, we anticipated that employment of such simple system would provide an opportunity to shed light on the mechanism of the asymmetric induction.

Results

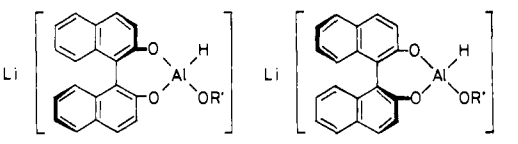
Asymmetric Reduction of Alkyl Phenyl Ketones with BINAL-H Reagents. To test the validity of the above-described concept, the reducing agent (*R*)-**2** (empirical formula) was prepared by mixing



(R)-2

$LiAlH_4$ and an equimolar amount of optically pure (*R*)-(+)-binaphthol [(*R*)-**1**] in tetrahydrofuran (THF). However, the initial attempt failed to reduce prochiral acetophenone (**4a**) in a high optical yield. Thus exposure of **4a** to this solution (**4a**/(*R*)-**2** = 0.3) at 30 °C resulted in the formation of (*R*)-(+)-1-phenylethyl alcohol (**5a**) in only 2% ee (85% chemical yield).[15,16]

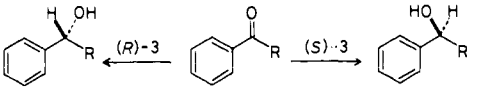
This disappointingly low level of asymmetric induction prompted us to examine further modification of the reagent by a second simple alcohol (R′OH) leading to (*R*)–**3**.[17] Notably, since the remaining two hydrogens in (*R*)–**2** are homotopic, replacement of either hydrogen by an R′O moiety produces an identical, single



(R)-3 (S)-3

aluminum hydride reagent. Thus addition of equimolar amounts of R′OH and (*R*)–**1** as THF solution to $LiAlH_4$ dissolved in THF evolved the theoretical amount of hydrogen gas, affording a milk-white, nearly homogeneous mixture. This contained little suspension[18] and is contrasted with most conventionally used reagents which are heterogeneous in ethereal media. Fortunately, use of this binaphthol-modified aluminum hydride reagent **3** (empirical formula, hereafter abbreviated to BINAL-H) resulted in a remarkable increase in optical yield in the reduction of **4a**.[19] Table I summarizes the results of the asymmetric reduction with 2 equiv of (*R*)-BINAL-H [(*R*)-**3**] possessing various R′O groups. The sense and extent of the asymmetric induction are highly dependent on the nature of the R′O group. Interestingly, reversal in the sense of differentiation occurred by changing the R′O group from simple alkoxyls to β,β,β-trifluoroethoxyl or 2,6-di-*tert*-butylphenoxyl (entry 10, 11, and 13). Apparently the nature of the R′O group affects not only the structure of **3** but also the ease with which disproportionation takes place, the degree of aggregation, etc., all of which influence the overall enantioselectivity of the reduction. As usual, modification with simple alcohols such as methanol or ethanol afforded high enantioselectivity. The optical yield was generally enhanced by lowering the reaction temperature. Thus the highest value, up to 95%, was recorded by carrying out the reduction with **3** (R′O = C_2H_5O) at −100 to −78 °C (entry 7). Usually for the completion of the reaction at reasonable rate and with high enantioselectivity, use of 2–3 equiv of the reducing agent was required. Attempted improvement of optical yield by addition of a 0.5 equiv of ethanol to (*R*)–**2** failed; reaction of **4a** with such a reagent (2 equiv, −100 °C for 1 h and then −78 °C for 2 h) gave (*R*)-**5a** in only 5% ee. The reagent prepared from equimolar amounts of AlH_3 and (*R*)-**1** reduced **4a** at 30 °C to afford (*R*)-**5a** in 11% ee. This result, coupled with the observed R′O dependency of the enantioselectivity, dismisses the possibility of the participation of binaphthoxyaluminum hydride, a trivalent aluminum compound, in the asymmetric reduction.

A series of prochiral alkyl phenyl ketones were then subjected to the reduction with 3 equiv of (*R*)- or (*S*)-BINAL-H [(*R*)- or (*S*)-**3**, R′O = C_2H_5O] at low temperatures (-78 to -100 °C), to give the corresponding carbinols in an optically active form.[19] The reduction of sterically hindered pivalophenone (**4f**) was conducted at elevated temperatures. As listed in Table II, the reduction exhibited exceptionally high optical yields and, in some cases (entry 3 and 4), the enantioface differentiation was virtually complete. The optical purity of the alcoholic product **5c** (entry 3) was



(R)-5 4 (S)-5

a, R = CH_3 d, R = n-C_4H_9
b, R = C_2H_5 e, R = $CH(CH_3)_2$
c, R = n-C_3H_7 f, R = $C(CH_3)_3$

determined by careful comparison of the rotation value and ^1H NMR spectrum and HPLC behavior of the (*S*)-β,β,β-trifluoro-α-methoxy-α-phenylpropionate (MTPA) derivative[20] with those of the authentic optically pure specimen. It is worth pointing out

(14) (a) Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173. (b) Jacques, J.; Fouquey, C.; Viterbo, R. *Tetrahedron Lett.* **1971**, 4617. (c) Akimoto, H.; Shioiri, T.; Iitaka, Y.; Yamada, S. *Ibid.* **1968**, 97.

(15) This poor result is interpretable in various ways. This might be due to the undesired disproportionation of the chiral aluminum dihydride, giving some achiral $LiAlH_4$ and lithium bis(binaphthoxy)aluminum (see footnote 23). Reduction of 4-*tert*-butylcyclohexanone by this reagnet at 30 °C gave a 92:8 mixture of *trans*- and *cis*-4-*tert*-butylcyclohexanol (Table IV). This isomeric ratio is very close to that observed in the $LiAlH_4$ reduction [Winstein, S.; Sonnenberg, J. *J. Am. Chem. Soc.* **1961**, *83*, 3235. Eliel, E. L.; Ro, R. S. *Ibid.* **1957**, *79*, 5992. Lansbury, P. T.; MacLeay, R. E. *J. Org. Chem.* **1963**, *28*, 1940.]. However, (*R*)- or (*S*)-**2** itself may not have any high enantioface-differentiating ability (see Discussion).

(16) For modification of $LiAlH_4$ with other ligands of C_2 chirality, see ref 8i and 8j and Seebach, D.; Daum, H. *Chem. Ber.* **1974**, *107*, 1748. Baggett, N.; Stribblehill, P. *J. Chem. Soc., Perkin Trans. 1.* **1977**, 1123.

(17) Modification of $LiAlH_4$ with ephedrine and **1** failed to produce an effective reagent.[7d]

(18) This is important. In order to obtain a high degree of enantioselectivity, the nearly homogeneous mixture is to be used (see Experimental Section).

(19) Preliminary report: Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129.

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Table I. Enantioselective Reduction of Acetophenone with BINAL-Hs[a]

	BINAL-H (3)			carbinol product **5a**	
entry	R'O	binaphthol confign	reaction conditions T, °C (time, h)	% ee	confign
1	CH_3O	*R*	30 (5)	73	*R*
2	CH_3O	*R*	−78 (5)	87	*R*
3	C_2H_5O	*R*	30 (5)	65	*R*
4	C_2H_5O	*R*	−20 (5)	77	*R*
5	C_2H_5O	*R*	−50 (5)	84	*R*
6	C_2H_5O	*R*	−78 (5)	90	*R*
7	C_2H_5O	*R*	−100 (1) + −78 (2)	95	*R*
8	$(CH_3)_2CHO$	*R*	30 (5)	46	*R*
9	$(CH_3)_3CO$	*R*	30 (5)	38	*R*
10	CF_3CH_2O	*R*	30 (5)	14	*S*
11	CF_3CH_2O	*R*	−100 (2) + −78 (16)	42	*S*
12	C_6H_5O	*R*	30 (5)	17	*R*
13	2,6-(*tert*-$C_4H_9)_2C_6H_3O$	*R*	30 (5)	44	*S*
14	AlO[b]	*R*	30 (5)	33	*R*

[a] Reaction was carried out by using 2 equiv of BINAL-H. Chemical yield of the reaction at 30 °C was 95–100%, whereas the low-temperature reaction afforded carbinols in ca. 60% yield. The remainder was unreacted acetophenone. [b] Water (0.5 equiv) was used for the preparation of the hydride reagent.

Table II. Enantioselective Reduction of Aromatic Ketones with BINAL-H (**3**, R'O = C_2H_5O)[a]

			carbinol product **5**		
entry	ketone **4**	binaphthol confign in **3**	chemical yield, %[b]	% ee	confign
1	$C_6H_5COCH_3$	*R*	61	95	*R*
2	$C_6H_5COC_2H_5$	*S*	62	98	*S*
3	C_6H_5CO-*n*-C_3H_7	*S*	92, 78[c]	~100	*S*
4	C_6H_5CO-*n*-C_4H_9	*S*	64	~100	*S*
5	$C_6H_5COCH(CH_3)_2$	*S*	68	71	*S*
6	$C_6H_5COC(CH_3)_3$[d]	*R*	80[c]	44	*R*
7	α-tetralone	*R*	91[c]	74	*R*

[a] Reaction was carried out by using 3 equiv of BINAL-H at −100 °C for 3 h and at −78 °C for 16 h. [b] Determined by GC analysis. [c] Isolated yield. [d] Reaction was started at −100 °C, and the mixture was gradually warmed to room temperature and stirred for 10 h.

that throughout these experiments reduction by (*R*)-**3** (R'O = C_2H_5O) proceeded with a preference for the production of the corresponding *R* carbinol, and the reaction with the *S* reducing agent afforded the alcohol enriched with the *S* enantiomer. Although several successful asymmetric reductions have already been reported,[7,8] the present results compare favorably with the earlier records.

When propiophenone (**4b**) was treated with 1 equiv of **3** (*R'*O = C_2H_5O) in THF at 30 °C for 3 h and quenched by adding methanol, there were obtained the carbinol **5b** (77% yield) and hydrogen (21%) together with unreacted **4b** (23%). Monitoring of the reaction by analysis of the aliquots (after quenching by dilute HCl) indicated that the **5b**/**4b** ratio reached a constant value, 77:23, at this stage and, even though some aluminum hydride still survived, further reduction did not proceed any more.[21] When this reaction mixture without methanol quenching was further treated by 1 equiv of acetophenone (**4a**) at 30 °C for 4 h and then quenched, **5b** (77%) and hydrogen (14%) were produced. The ketones **4a** and **4b** were recovered in 100 and 23% yields, respectively, and the acetophenone-derived carbinol **5a** was not detected in the mixture. This result indicates that the BINAL-H reduction is irreversible in nature, and therefore, the stereoselectivity is a subject of kinetic control and not of thermodynamic stability of the resulting aluminum or lithium alkoxide products.[22]

The BINAL-H reagents are not capable of reducing prochiral *dialkyl* ketones in a high optical yeild. Reaction of benzyl methyl ketone with (*S*)-**3** (R'O = C_2H_5O) (−100 °C/2 h and −78 °C/16 h) gave (*S*)-1-phenyl-2-propanol in 13% ee. Reduction of 2-octanone with the same reagent under similar conditions produced (*R*)-2-octanol in 24% ee. *tert*-Butyl methyl ketone was inert to the standard BINAL-H reduction. It should be added that BINAL-Hs are not particularly bulky reagents. Attempted diastereoselective reduction of 4-*tert*-butylcyclohexanone with (±)-**3** in THF at 30 °C exhibited only moderate selectivity as shown in Table III.

Table III. Diastereoselective Reduction of 4-*tert*-Butylcyclohexanone[a]

reducing agent[b]	cis/trans ratio in 4-*tert*-butylcyclohexanol[c]
2	8:92
3 (R'O = CH_3O)	80:20
3 (R'O = C_2H_5O)	73:27
3 (R'O = *tert*-C_4H_9O)	32:68
3 (R'O = 2,6-(*tert*-$C_4H_9)_2C_6H_3O$)	34:66
3 (R'O = AlO)[d]	70:30
3 (R'O = $AlOCH_2CH_2O$)[e]	81:19

[a] Reduction was carried out in THF at 30 °C using 2 equiv of the reducing agent. Yield was almost quantitative. [b] Racemic. [c] Determined by GC analysis. [d] Half-equiv of water was used for the modification. [e] Half-equiv of ethylene glycol was employed.

Effects of Aging of the Reagent and Reaction Temperature on the Enantioselectivity. Although there is no doubt that the reaction system contains various hydride species,[23] we have obtained several

(21) A similar phenomenon has been observed. See ref 8a.

(22) In some cases, $LiAlH_4$ reduction of ketones is reversible. For example, see: Beckett, A. H.; Harper, N. J.; Balon, A. D. J.; Watts, T. H. E. *Tetrahedron* **1959**, *6*, 319.

(23) $LiAlH_4$ and its alkoxy derivatives exhibit the characteristic Al–H stretching band in the infrared region.[24] Parent $LiAlH_4$ is known to show the band in the 1655–1698-cm^{-1} region (1690 cm^{-1} for the 0.61 M THF solution).[25] A 0.28 M THF solution of the $LiAlH_4$/binaphthol 1:1 reagent, empirically formulated as (*R*)-**2**, gave two strong bands at 1755 and 1790 cm^{-1} together with a weak absorption at 1690 cm^{-1} which may be ascribed to $LiAlH_4$ produced by disproportionation. When the spectrum of the BINAL-H reagent depicted as (*R*)-**3** (R'O = CH_3O or C_2H_5O) was taken in 0.30 M THF solution, two bands were observed at 1765 (strong) and 1715 cm^{-1} (weak).

(24) (a) Haubenstock, H.; Mester, T. A., Jr.; Zieger, H. *J. Org. Chem.* **1980**, *45*, 3443. (b) Gorin, P.; Marchon, J.-C.; Tranchant, J.; Kovacevic, S.; Marsault, J.-P. *Bull. Soc. Chim.* Fr. **1970**, 3790. (c) Lippincott, E. R. *J. Chem. Phys.* **1949**, *17*, 1351.

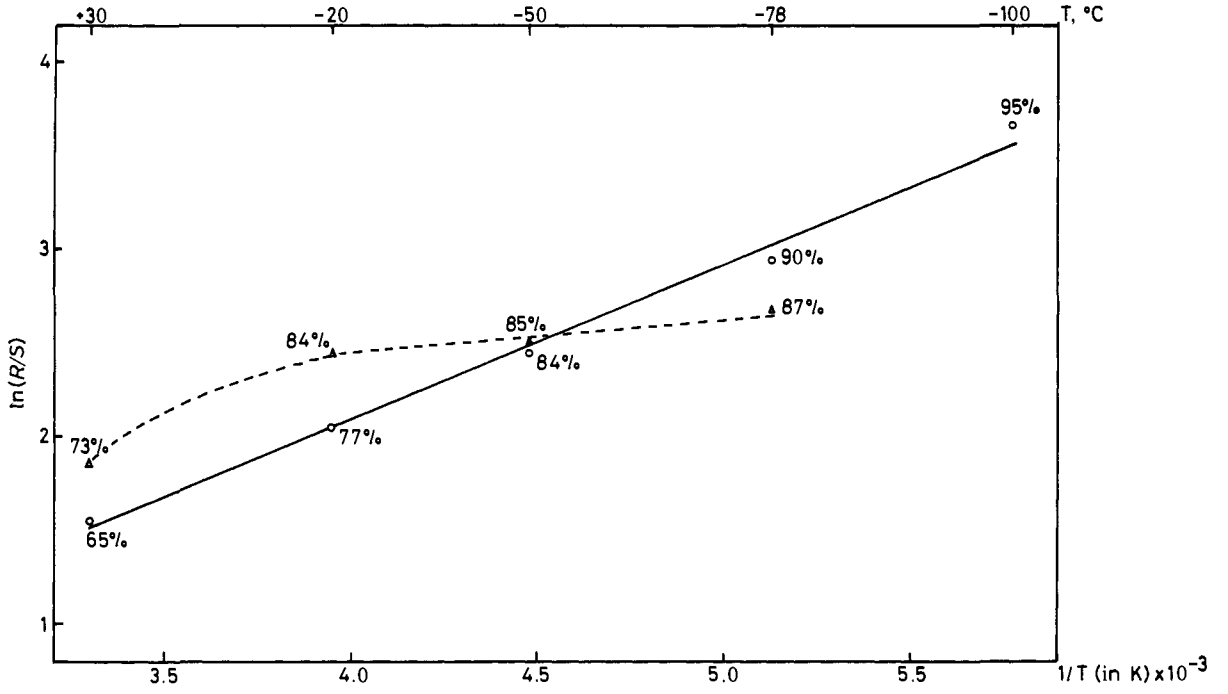


Figure 1. Temperature effects on the optical yield of the enantioselective reduction of acetophenone: solid line, reaction with (*R*)-**3** (R'O = C_2H_5O); broken line; reaction with (*R*)-**3** (R'O = CH_3O).

lines of evidence which indicate the involvement of a single *reacting* species, at least with the system displaying the highest level of enantioselectivity.

The first is the lack of aging effect on the stereoselectivity. It is well known that the sense and degree of the asymmetric reduction with conventional chirally modified $LiAlH_4$ reagents (heterogeneous) are highly dependent on the way and extent of aging of the reducing agents after the preparation,[7a,b,d] which is attributable to the presence of interconvertible plural reactive species. However, the enantioselectivity of the reduction with BINAL-H (nearly homogeneous) is aging time independent. Reduction of acetophenone (**4a**) conducted at 30 °C with (*R*)-**3** (R'O = C_2H_5O) of various aging states (10 min to 10 h at 30 °C) gave the *R* carbinol, (*R*)-**5a**, in virtually constant optical yield, 65%.

The temperature effect on the enantioselectivity is quite enlightening. The optical yield of the acetophenone reduction with (*R*)-**3** (R'O = C_2H_5O) appeared to increase monotonously by lowering the reaction temperature. This is not always the case in the conventional asymmetric reductions.[7b-d] When the observed enantioselectivity, ln *R*/*S*, is plotted against reciprocal of the temperature, $1/T$ (in K), a straight line is obtained at temperatures ranging from 30 to −100 °C (Figure 1). Thus, it is clear that *a single hydride species is responsible for the asymmetric reduction*, at least in this particular case. Entropy factor seems unimportant in this temperature range. From the line slope, the difference in activation energy of the reactions leading to the *S* and *R* carbinols is estimated to be 1.66 kcal/mol. In the case of the methoxyl-containing reagent, (*R*)-**3** (R'O = CH_3O), some deviation from the linear relationship has been observed (Figure 1). Thus, depending on the reaction system, several different hydride species may participate in the reduction.

Discussion

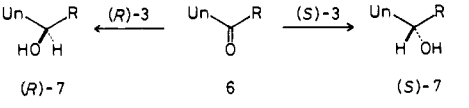
A highly enantioselective reduction of aromatic ketones has been accomplished by the newly designed chiral reducing agent (*R*)- or (*S*)-**3**. As described in the accompanying paper,[26] this hydride reagent is efficiently employed for the asymmetric reduction of a wide variety of unsaturated (but not saturated) carbonyl compounds such as alkenyl and alkynyl ketones. Realization of such uniformly high enantioselection prompted us to rationalize the asymmetric induction.

Table IV. Steric Effects on the Degree of the Enantioselectivity[a]

UnCOR		optical yield[b]	
Un	R	−100 to −78 °C	30 °C
C_6H_5	CH_3	95	65 (73)
C_6H_5	*n*-alkyl	98–100[c]	72[d] (79–85)[e]
C_6H_5	$(CH_3)_2CH$	71	56 (39)
C_6H_5	$(CH_3)_3C$	*f*	20
CH≡C	n-C_5H_{11}	(84)	
CH≡C	$(CH_3)_2CH$	(57)	

[a] The regular *R*/*R* or *S*/*S* binaphthol/product configurational correlation was preserved. [b] Result obtained with **3** (R'O = C_2H_5O). Value in parentheses is optical yield obtained with **3** (R'O = CH_3O). [c] R = ethyl to butyl. [d] R = ethyl. [e] R = ethyl and propyl. [f] No reaction at this temperature.

As to the origin of enantioselection, steric approach control has customarily been considered to play a decisive role, but this view is questionable in the BINAL-H reduction. Among a number of observations which deserve comments, the most important is the empirical rule for the orientation observed in the asymmetric reduction of simple prochiral carbonyl substances of type **6**; the reagent containing *R* binaphthoxyl ligand affords the carbinol **7**

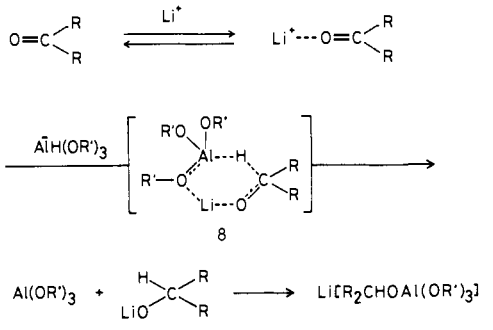


in which the *R* enantiomer predominates, whereas the *S* reducing agent gives the *S* antipode preferentially. The aryl, alkenyl, and alkynyl groups exert qualitatively the same directing influence in the creation of the absolute stereochemistries. This configurational correlation between the binaphthol ligand and carbinol products is quite general through UnCOR having a small R group and that bearing a very bulky substituent (for example, Table II), indicating that the unsaturated and saturated groups attached to the carbonyl function are differentiated *primarily* by the difference

(25) Ashby, E. C.; Dobbs, F. R.; Hopkins, H. P., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 2823. Ashby, E. C.; Prasad, H. S. *Inorg. Chem.* **1976**, *15*, 993. Ashby, E. C.; Sevenair, J. P.; Dobbs, F. R. *J. Org. Chem.* **1971**, *36*, 197. Ashby, E. C.; Lin, J. J. *Tetrahedron Lett.* **1976**, 3865.

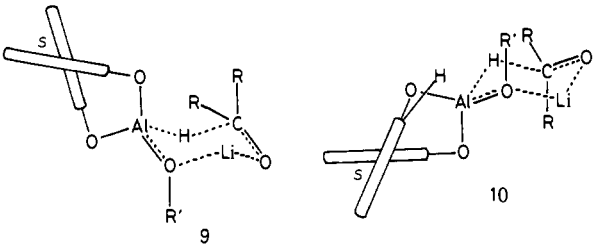
(26) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.*, following paper in this issue.

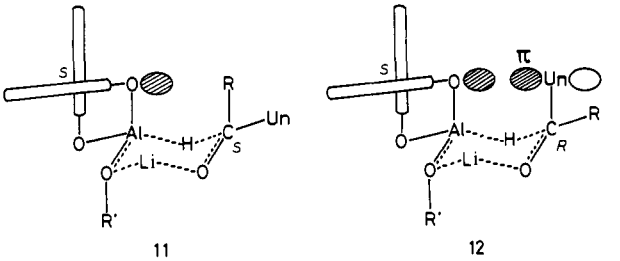
Scheme I



of the electronic properties. The degree of the enantioselection in the reaction of UnCOR varies with R groups but not in a very straightforward fashion.[27] With C_6H_5COR, the optical yield enhances gradually in going from acetophenone to the ketones bearing a long primary alkyl group and then decreases sharply as the bulkiness of R increases (Table IV). In a like manner, enantioselectivity in the reduction of CH≡CCOR drops considerably from the primary alkyl ketones to the isopropyl analogue.[26] A similar trend was also noted with alkenyl ketones.[28] Thus steric effect is obviously important, but we would emphasize that, in view of the generality of the binaphthol/carbinol configurational relationship, it cannot overbalance the electronic bias.

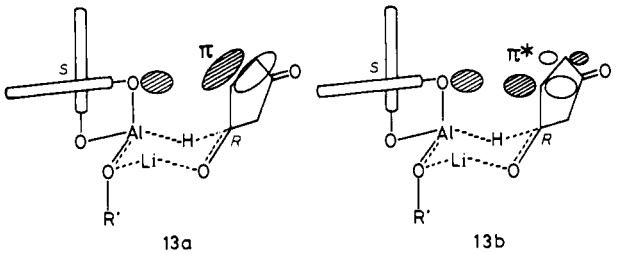
Reactivity of the carbonyl substrates toward the BINAL-H reduction is influenced greatly by steric effects, various electronic factors including LUMO level and electron density at the carbonyl carbon, flexibility of the molecule, etc.[27] Thus the position of the transition state on reaction coordinate and transition state structures (shape, tightness, atomic distances, etc.) vary subtly from reaction to reaction. Therefore it is not easy to present a unifying view of the mechanism by figuring a single transition state picture. Nevertheless, the simple hypothesis outlined below can explain consistently the stereochemical consequences. We consider that reduction of a carbonyl function with $LiAlH(OR')_3$-type reagents proceeds via pathway of Scheme I.[29] The reaction is initiated by the complexation of the Lewis acidic Li^+ ion to the oxygen atom,[30] which activates the C=O group. The product-determining hydride transfer then occurs from Al to the carbonyl carbon by way of the quasi-aromatic, six-membered ring transition state **8**.[31] When this mechanism is applied to the BINAL-H reduction, the oxygen atom of the simple alkoxyl group, rather than the binaphthol-derived oxygens, acts as the bridging atom because of its highest basicity among the three oxygens attached to Al. The two binaphthoxy oxygens in (*S*)-BINAL-H are diastereotopic, and, therefore, two types of chair-like transition states, **9** and **10**, are conceivable. Structure **10**, however, is highly





unfavorable, because it suffers severe steric repulsion between the binaphthyl and R′ moieties, as is easily understood by model inspection.[32] Here when a prochiral unsaturated ketone, UnCOR, is put into **9**, there emerge two diastereomeric transition states **11** and **12**. A series of (*S*)-BINAL-H reductions, giving *S* products selectively, indicates that the transition state **11** is generally favored over the *R*-generating transition state **12**. This **11** vs. **12** relative stability would be controlled primarily by interactions between the axially located groups. The steric interaction is generally repulsive, whereas the electronic effects can be either repulsive or attractive, depending on the situation. The transition state **12** possessing axial-Un and equatorial-R groups, we postulate, is destabilized by the substantial n/π type electronic repulsion between the axially oriented binaphthoxyl oxygen and the unsaturated moiety. Such electronic repulsion is absent in **11**. The 1,3-diaxial type steric repulsion becomes significant by increasing the bulkiness of R group but cannot overcome the overwhelming electronic influence (Table IV).[33]

This mechanism is equally consistent with the unusual behavior displayed by 4-cyclopentene-1,3-dione;[26] its reduction with (*S*)-BINAL-H (R′O = C_2H_5O) proceeds very rapidly and, unlike with ordinary unsaturated ketones, produces 4-hydroxy-2-cyclopentenone *enriched by the R enantiomer* (94% ee). In the transition state **13**, leading to the *R* alcohol, there exists n/π repulsion (see **13a**), but in this particular case the undesired



interaction is surmounted by the newly introduced n/π^* attractive

(27) Aldehydes react much faster than ketones do. *tert*-Butyl ketones are less reactive than primary or secondary alkyl ketones. Acetophenone reacted smoothly with **3** at temperatures as low as −100 °C, but *p*-methoxyacetophenone failed to react under mild conditions. The reaction of 4-cyclopentene-1,3-dione was extremely rapid at −100 °C.[26] In contrast, 2-cyclohexenone, 3-methyl-2-cyclohexenone, and 2-isopropylidenecyclohexanone resisted reduction. The reaction of α-tetralone, an aromatic cyclic ketone, was slower than that of simple primary alkyl phenyl ketones. Reaction of a mixture of cyclohexanone and 2-cyclohexenone at 25 °C gave only cyclohexanol. However, competition experiments revealed that 2-octanone and (*E*)-3-octen-2-one were reduced with almost equal ease (−70 to 20 °C).

(28) Anderson, N. H.; Liu, D. J.-J.; Lin, B. "Abstracts of Papers", 185th National Meeting of the American Chemical Society: Seattle, Wash., March 20–25, 1983; American Chemical Society: Washington, D.C., 1983; ORGN 107.

(29) An analogous mechanism has been advanced by Ashby for the $LiAlH_4$ reduction. See: Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890. Ashby, E. C.; Boone, J. R. *J. Am. Chem. Soc.* **1976**, *98*, 5524.

(30) Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53. Handel, H.; Pierre, J. L. *Tetrahedron* **1975**, *31*, 997. See also ref 13.

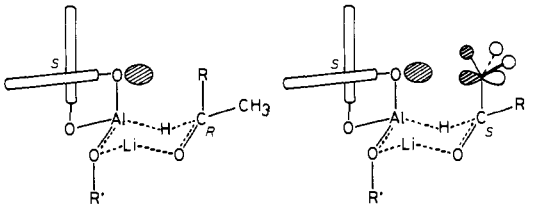
(31) The previously postulated structure[19] is slightly modified. This model is to be distinguished from that claimed by Ashby[29] in some point. The bridging oxygen atom in **8** uses four electrons for bonding with metals (two for a covalent bond with Al and two for the cyclic electron array), whereas bridging hydrides in the Ashby's transition state utilize only two electrons to form a two-electron, three-center bond. In **8**, some solvent THF (up to two molecules) may coordinate to Li^+, which is omitted for the sake of clarity. Although aluminum and lithium compounds may have cluster structures, we are inclined to use this simple, monomeric six-membered-ring transition-state model until more definitive proof for the significance of such cluster structure is obtained. The reaction with lithium trialkoxyaluminum hydrides may or may not involve an electron-transfer process. Here, in any event, the hydride-transfer step via **8** is considered as the stereocontrolling step.

(32) Alternative structures having an R′ group in the equatorial position are even less favored.

(33) Since atomic arrangement in transition states is rather loose, steric effects are generally to be reduced as compared with the case of ground-state molecules [Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199]. The importance of unsaturated substituents seems not specific to the BINAL-H reduction. Similar observations were previously found with reagents of ref 7.

orbital interaction between the oxygen non-bonding orbital and the LUMO of the enone moiety, depicted in **13b**, which results in the anomalous *S*/*R* configurational orientation.

Unique behavior displayed by methyl ketones also reinforces the importance of the electronic factor. Reduction of 2-octanone with (*S*)-**3** (R'O = C_2H_5O) gave (*R*)-2-octanol in 24% ee. The intramolecular competition of the methyl and hexyl groups resulted in the reversal of the general ligand/product configurational correlation (*S* to *R* orientation). Consistent with this phenomenon, throughout the asymmetric reduction of aromatic ketones, olefinic ketones,[26] and acetylenic ketones,[26] the *methyl ketones* have the propensity to give slightly lower optical yields as compared with the corresponding ketones possessing a longer primary alkyl group. Methyl is evidently the least bulky alkyl group but, nevertheless, competes with the unsaturated groups to a greater extent than long primary alkyls do. Such a notable effect, observed in both intra- and intermolecular comparisons, must be electronic in nature and is best interpreted in terms of the pseudo-π character of methyl group.[34] The *S*/*R* direction observed with 2-octanone is accounted



14 15

for by comparing the transition states **14** and **15**. The *S* transition state **15** suffering the oxygen/methyl electronic repulsion is less favorable than the *R* transition state **14**.[35]

Now we would conclude that the direction and extent of the enantioselective reduction with the BINAL-H reagent are determined by the relative stabilities of the six-membered-ring transition states of types **11** and **12**. The reaction occurs in such a way as to minimize repulsion between the axially oriented binaphthol oxygen and carbonyl substituents. Relative magnitudes of the dominant electronic repulsion decrease in the order of phenyl, alkenyl, alkynyl > alkyl (hydrogen) > β-acylalkenyl; methyl > long alkyls. Steric factors, diminishing in the order of *tert*-alkyl > *sec*-alkyl > *n*-alkyl, are also responsible for the enantioface differentiation to some extent.[36] This view is in accord with the fact that a high level of enantioselection can be made only with prochiral carbonyl compounds containing sp- or sp^2-hybridized carbon substituents. The reaction of dialkyl ketones does not proceed with high optical yields. We do not claim that this empirical generalization is applicable to the reduction of all kinds of carbonyl substrates. Such mechanistic arguments are to be limited to the reaction of *simple* unsaturated ketones of type **6**, because the steric course would be affected by various structural and functional parameters. Heteroatoms present near the carbonyl function, for example, may coordinate to Li or Al atom and thereby affect the transition-state structures or even alter the reaction mechanism.

Conclusion

Modification of $LiAlH_4$ with axially dissymmetric binaphthol and a simple alcohol generates a new complex aluminum hydride reagent, BINAL-H, which exhibits an excellent chiral recognition ability in carbonyl group reduction.[37,38] In order to accomplish a high level of asymmetric transformation, minimization of the reactive species is crucially important. As to the origin of the efficiency of the enantioface differentiation, arguments based on the simple steric approach control are implausible. Rather electronic difference of the substituents attached to carbonyl function is of prime significance in determining the steric course of the reaction.

Experimental Section

General. Infrared (IR) spectra were recorded on a JASCO IRA-1 grating infrared spectrophotometer, ^1H nuclear magnetic resonance (NMR) spectra on a JEOLCO JNM-PMX-60 (60 MHz), Varian NV-21 (90 MHz), or Varian HA-100 (100 MHz) spectrometer, and the mass spectra on a JEOLCO JMS-D10 mass spectrometer at 70 eV. The optical rotation was recorded on a JASCO DIP-4 digital polarimeter as neat liquid (0.01-dm cell) or on a precise solution in the indicated solvent and concentration (1-dm cell). For TLC analysis precoated silica gel plates (E. Merck 60 F_{254}, 0.25 mm) were used. Gas chromatography (GC) analyses were conducted on a Hitachi 063 instrument with a column of 5% FFAP on Chromosorb WAW, 2.5 × 2000 mm, by using helium as carrier gas. The products were isolated by bulb-to-bulb distillation on a Büchi Kugelrohr and purified by preparative GC on a Varian 1700 instrument with a column of 5% FFAP on Chromosorb WAW (0.5 × 2000 mm) by using helium as carrier gas and/or preparative column chromatography on silica gel [E. Merck Art 7734 (70–230 mesh) or Fuji-Devison BW-80 (80–200 mesh)]. The high-performance liquid chromatography (HPLC) analyses were carried out on a Waters 6000A apparatus with a JASCO UVIDEC-100 UV detector and a JASCOSIL SS-05 column.

Tetrahydrofuran (THF) was freshly distilled from sodium metal using benzophenone ketyl as indicator. Lithium aluminum hydride ($LiAlH_4$, Metallgesellschaft) was used as a clear THF solution, and the concentration was assayed by determining the volume of hydrogen gas evolved by dropwise addition to water. Methanol and ethanol were distilled from magnesium, and other alcohols employed for the modification of $LiAlH_4$ were distilled from sodium metal. Optically pure (*S*)-(−)-2,2'-dihydroxy-1,1'-binaphthyl [(*S*)-binaphthol, (*S*)-**1**], mp 207–208 °C, $[\alpha]^{21}_D$ -38.0° (*c* 1.00, THF), and its *R* enantiomer [(*R*)-**1**], mp 207–208 °C, $[\alpha]^{21}_D$ +37.1° (*c* 1.00, THF), were prepared according to the Jacques–Cram procedure.[14]

All asymmetric reductions were conducted with magnetic stirring in a long-necked vessel equipped with a rubber septum under an argon atmosphere. Anhydrous reagents were transferred by oven-dried syringes. The progress of the reaction was monitored by GC or TLC. The yields were determined by GC using a Shimadzu chromatopac C-R1 A computer-controlled integrator. Identification of known compounds was done by comparison of the IR and ^1H NMR as well as chromatographic behavior with those of authentic specimen. Optical purity was determined in various ways. Direct comparison of optical rotation, when necessary, was carefully done with the synthetic and authentic resolved materials which had been purified under identical GC conditions; both samples were subjected alternately to the rotation measurement under the entirely *same conditions* (solvent source, concentration, temperature, cell, etc.). The (*S*)-β,β,β-trifluoro-α-methoxy-α-phenylpropionates (MTPA esters) were prepared according to Mosher's procedure[20] using the acid chloride derived from (*S*)-(−)-MTPA supplied from Aldrich (99+%) and subjected to ^1H NMR and HPLC analysis.

Preparation of BINAL-H Reagents. A long-necked flask equipped with a rubber septum was flame-dried and placed under argon atmosphere. To this a 0.66–1.99 M THF solution of $LiAlH_4$ (filtered through dry Celite) was introduced via a syringe, and then at room temperature an alcohol in THF (2.00 M, 1 equiv) was added in a dropwise manner

(34) Hoffmann, R.; Random, L.; Pople, J. A.; Schleyer, P. v. R.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1972**, *94*, 6221. Radom, L.; Pople, J. A.; Schleyer, P. v. R. *Ibid.* **1972**, *94*, 5935. Hehre, W. J.; Pople, J. A.; Devaquet, A. J. P. *Ibid.* **1976**, *98*, 664. Apeloig, Y.; Schleyer, P. v. R.; Pople, J. A. *Ibid.* **1977**, *99*, 5901. DeFrees, D. J.; Bartmess, J. E.; Kim, J. K.; McIver, R. T. Jr.; Hehre, W. J. *Ibid.* **1977**, *99*, 6451. DeFrees, D. J.; Hassner, D. Z.; Hehre, W. J.; Peter, E. A.; Wolfsberg, M. *Ibid.* **1978**, *100*, 641. Pross, A.; Radom, L. *Ibid.* **1978**, *100*, 6572. DeFrees, D. J.; Hehre, W. J.; Sunko, D. E. *Ibid.* **1979**, *101*, 2323. Pross, A.; Radom, L.; Riggs, N. V. *Ibid.* **1980**, *102*, 2253. Lambert, J. B.; Nienhuis, R. J. *Ibid.* **1980**, *102*, 6659. Schlosser, M.; Hartmann, J. *Ibid.* **1976**, *98*, 4674. See also: Jorgensen, W. L.; Salem, L. "The Organic Chemist's Book of Orbitals"; Academic Press: New York, 1973.

(35) The hyperconjugative effect, which makes the methyl group slightly electron-deficient, does not necessarily produce attractive interaction with the oxygen atom. Repulsive interaction between acetyl methyl and a nucleophile is well known [Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438].

(36) The reduction of benzaldehyde-α-*d* was extremely fast.[26] The rather low optical yield, 87%, might result from a very early, loose transition state.

(37) For asymmetric syntheses via biaryl-derived catalyst or reagenst, see ref 8j and 11, and Tamao, K.; Yamamoto, H.; Matsumoto, H.; Miyake, N.; Hayashi, T.; Kumada, M. *Tetrahedron Lett.* **1977**, 1389. Grubbs, R. H.; DeVries, R. A. *Ibid.* **1977**, 1879. Miyano, S.; Nawa, M.; Hashimoto, H. *Chem. Lett.* **1980**, 729. Mazaleyrat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585. Olivero, A. G.; Weidmann, B.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 2485.

(38) We recently observed that a methylmagnesium compound, generated from dimethylmagnesium and (*R*)-2-hydroxy-2'-methoxy-1,1'-binaphthyl, reacted with benzaldehyde to give (*R*)-1-phenylethyl alcohol in 69% ee in 81% yield; Yamada, M.; Noyori, R., unpublished.

over a period of ca. 10 min with stirring. Subsequently a THF solution of optically pure binaphthol [(*R*)- or (*S*)-**1**] (0.6 M, 1 equiv) was added dropwise, and the resulting mixture was stirred usually for an additional 30 min at room temperature and used for the asymmetric reduction. Notably the BINAL-H reagent **3** (R'O = simple alkoxyl) thus formed in THF was cloudy but a near-solution which contained only a very small amount of suspension. *If a large quantity of precipitate separates out for some reason, one should repeat the preparation from the beginning.* Optically active binaphthol may racemize to some extent upon exposure to strong acids or bases in protic media.[14a] Care should be exercised in its recovery in reusable form. Decolorization of optically active binaphthol by charcoal caused serious racemization.

Asymmetric Reduction of Prochiral Ketones. A. Butyrophenone (4c). The BINAL-H reagent, (*S*)-**3** (R'O = C_2H_5O), was prepared from $LiAlH_4$ (1.63 M THF solution, 5.10 mL, 8.31 mmol), ethanol (2.00 M THF solution, 4.20 mL, 8.40 mmol), and (−)-binaphthol [(*S*)-**1**] (2.41 g, 8.43mmol) in THF (13 mL). After stirring for 30 min at room temperature, the reducing agent was cooled to −100 °C in a liquid nitrogen–methanol bath. A solution of butyrophenone (**4c**) (370 mg, 2.5 mmol) in THF (2.5 mL) was added dropwise over a period of 8 min at −100 °C. The mixture was stirred for an additional 3 h at this temperature and at −78 °C (dry-ice bath) for 16 h. After addition of methanol (1 mL) at −78 °C, the mixture was warmed to room temperature. To this was added 2 N HCl (20 mL) and the mixture was extracted with ether. The organic extract was dried and concentrated. Bulb-to-bulb distillation [150–170 °C (19 mmHg)] gave a mixture of unreacted **4c** and (*S*)-1-phenylbutanol [(*S*)-**5c**] (375 mg) as a colorless oil (92% yield by GC analysis). Crystalline binaphthol remained in the distillation flask; recovered (*S*)-**1** showed after recrystallization from benzene $[\alpha]^{25}_D$ −34.5° (*c* 1.80, THF). Preparative GC (160 °C) afforded (*S*)-**5c** (291 mg) as a crystalline solid: mp 46–47 °C; $[\alpha]^{22}_D$ −45.2° (*c* 4.81, benzene), 100% ee.

Authentic optically pure (*S*)-**5c** was prepared by resolution. A mixture of (±)-**5c** (100 g, 0.67 mol), phthalic anhydride (110 g, 0.74 mol), and pyridine (53 g, 0.67 mol) was stirred at 100 °C for 4 h. The mixture was dissolved in benzene (200 mL) and washed with 2 N HCl (50 mL). The organic layer was dried and concentrated to give solid 1-phenylbutyl hydrogen phthalate (190 g). This product (10 g, 33.6 mmol) was dissolved in acetone (100 mL), mixed with brucine dihydrate (14.5 g, 33.7 mmol), and allowed to stand at 5 °C for 2 days. The precipitate was collected and recrystallized repeatedly from hexane–acetone to afford a crystalline salt showing a constant rotation value (1.5 g), $[\alpha]^{22}_D$ −10.4° (*c* 1.08, ethanol). This salt was dissolved in a mixture of methanol (10 mL) and 2 N HCl (50 mL), and extracted with ether. The extracts were dried and concentrated. To the residual syrup was added 2 N NaOH solution (50 mL), and the mixture was heated at reflux for 4 h. The ether extracts were dried and concentrated. Preparative GC (160 °C) gave (*S*)-**5c** (150 mg): mp 46–47 °C, $[\alpha]^{22}_D$ −45.2° (*c* 4.81, benzene).

The (*S*)-MTPA ester of (*S*)-**5c** was prepared as follows. A mixture of (*R*)-MTPA chloride (35 mg, 0.14 mmol), **5c** (resolved, 15 mg, 0.10 mmol), pyridine (0.3 mL), and CCl_4 (0.3 mL) was stirred at room temperature for 18 h. To this was added *N,N*-dimethylethylenediamine (19 mg, 0.22 mmol), and the mixture was stirred for an additional 5 min and diluted with ether (2 mL). The organic solution was washed with 1 N HCl (2 mL), sodium carbonate solution (2 mL), and brine (2 mL) and concentrated. The residue was analyzed directly by ^1H NMR as a CCl_4 solution. In a similar manner, the synthetic (*S*)-**5c** was converted to the MTPA ester. Both samples exhibited identical ^1H NMR signals in CCl_4: δ 0.86 (t, *J* = 7 Hz, CH_2CH_3), 1.17 (m, CH_2CH_3), 1.83 (m, $CHOCH_2$), 3.41 (s, OCH_3), 5.91 (t, *J* = 7 Hz, *CHO*), 7.3 (br, C_6H_5). MTPA esters derived from (±)-**5c** displayed two sets of signals due to the methoxyl (s, δ 3.40 and 3.49) and benzylic methine protons (t-like dd, δ 5.83 and 5.91). In the spectrum of the esters obtained from synthetic or resolved **5c**, only single sets of these signals were observed, and thus these were diastereomerically pure within limits of the NMR accuracy. HPLC analysis of these samples (99.5:0.5 mixture of petroleum ether and acetonitrile, flow rate 2 mL/min) afforded sharp, symmetrical peaks (t_R 8.21 min) and showed no evidence of shoulders, whereas MTPA esters prepared from (±)-**5c** gave separated two peaks (t_R 8.21 and 7.83 min) overlapped only slightly around the base.

B. Acetophenone (4a). Acetophenone (**4a**) (300 mg, 2.5 mmol) in THF (2.5 mL) was treated at −100 °C for 3 h and −78 °C for 14.5 h with BINAL-H reagent, (*R*)-**3** (R'O = C_2H_5O), prepared by mixing $LiAlH_4$ (1.63 M THF solution, 5.10 mL, 8.31 mmol), ethanol (2.00 M THF solution, 4.20 mL, 8.40 mmol), and (*R*)-**1** (2.42 g, 8.46 mmol) in THF (10 mL). Quenching with methanol (1 mL) at −78 °C was followed by aqueous workup and ether extraction. Bulb-to-bulb distillation [120–140 °C (15 mmHg)] gave a mixture of ketone **4a** and alcohol (*R*)-**5a** (261 mg) as a colorless oil (61% yield by GC). Preparative GC (145 °C) gave (*R*)-**5a** (186 mg): α^{22}_D +0.415° (neat, *l* = 0.01), 95% ee assayed by comparison of the rotation value with that of authentic sample of (*S*)-**5a**, α^{20}_D −0.439° (neat, *l* = 0.01), obtained by optical resolution via the hydrogen phthalate brucine salt followed by GC purification (145 °C).

C. Propiophenone (4b). Propiophenone (**4b**) (335 mg, 2.5 mmol) in THF (2.5 mL) was treated at −100 °C for 3 h and at −78 °C for 16 h with the BINAL-H reagent, (*S*)-**3** (R'O = C_2H_5O), prepared from $LiAlH_4$ (1.63 M THF solution, 5.10 mL, 8.31 mmol), ethanol (2.00 M THF solution, 4.20 mL, 8.40 mmol), and (*S*)-**1** (2.41 g, 8.43 mmol) in THF (13 mL), and quenched with methanol (1 mL). Aqueous workup, ether extraction, and bulb-to-bulb distillation [140–160 °C (19 mmHg)] gave a mixture of **4b** and (*S*)-1-phenylpropanol [(*S*)-**5b**] (340 mg) as an oil (62% yield by GC). Preparative GC (150 °C) afforded (*S*)-**5b** as a colorless oil: α^{27}_D −0.284° (neat, *l* = 0.01, *d* 0.994), 98% ee based on the highest reported value of optical rotation (lit.[39] (*R*)-**5b**, $[\alpha]^{27.2}_D$ +29.1° (neat)).

D. Valerophenone (4d). The title ketone (405 mg, 2.5 mmol) in THF (2.5 mL) was treated at −100 °C for 3 h and at −78 °C for 16 h with the BINAL-H reagent, (*S*)-**3** (R'O = C_2H_5O), prepared from $LiAlH_4$ (1.63 M THF solution, 5.10 mL, 8.31 mmol), ethanol (2.00 M THF solution, 4.20 mL, 8.40 mmol), and (*S*)-1 (2.41 g, 8.43 mmol) in THF (10 mL). Quenching with methanol (1 mL), aqueous workup, ether extraction, and bulb-to-bulb distillation [140–160 °C (17 mmHg)] afforded a mixture of **4d** and (*S*)-1-phenylpentanol [(*S*)-**5d**] (401 mg) as an oil (64% yield by GC). Preparative GC (155 °C) provided (*S*)-**5d** (187 mg) as a colorless oil: α^{22}_D −0.200° (neat, *l* = 0.01), 100% ee. An authentic optically pure sample of (*S*)-**5d** was obtained by optical resolution via the hydrogen phthalate brucine salt followed by GC purification, α^{22}_D −0.200° (neat, *l* = 0.01).

MTPA esters of (*S*)-**5d** (synthetic or resolved) and racemic **5d** were prepared by mixing **5d** (16 mg, 0.1 mmol), (*S*)-MTPA chloride (35 mg, 0.14 mmol), pyridine (0.3 mL), and CCl_4 (0.3 mL). The crude product obtained by aqueous workup was subjected to ^1H NMR analysis. The derivative of racemic **5d** displayed two sets of signals due to the methoxy (s, δ 3.41 and 3.51) and benzylic methine protons (t-like dd, δ 5.78 and 5.84), whereas the (*S*)-**5d** derivatives showed only a single set of signals at δ 3.41 and 5.78. HPLC analysis of these samples (99.5:0.5 mixture of petroleum ether and acetonitrile, flow rate 2 mL/min) afforded a sharp, symmetrical peak (t_R 7.13 min) and showed no evidence of shoulders, whereas MTPA esters prepared from (±)-**5d** gave two separated peaks (t_R 7.13 and 6.72 min) overlapped only slightly around the base.

E. Isobutyrophenone (4e). This ketone (370 mg, 2.5 mmol) was treated at −100 °C for 3 h and at −78 °C for 16 h with (*S*)-**3** (R'O = C_2H_5O) prepared from $LiAlH_4$ (1.63 M THF solution, 5.10 mL, 8.31 mmol), ethanol (2.00 M THF solution, 4.20 mL, 8.40 mmol), and (*S*)-**1** (2.41 g, 8.43 mmol) in THF (10 mL). Quenching with methanol (1 mL) was followed by aqueous workup and ether extraction. Bulb-to-bulb distillation [120–140 °C (10 mmHg)] of the crude product gave a mixture of **4e** and (*S*)-1-phenyl-2-methylpropanol [(*S*)-**5e**] (365 mg) as an oil (68% yield by GC). Preparative GC (155 °C) provided (*S*)-**5e** (194 mg) as a colorless oil: α^{26}_D −0.172° (neat, *l* = 0.01, *d* 0.987), 71% ee based on the known maximum rotation (lit.[40] (*S*)-**5e**, $[\alpha]^{25}_D$ −24.6° (neat)).

F. Pivalophenone (4f). Ketone **4f** (75 mg, 0.46 mmol) was treated at −100 °C for 1 h, −78 °C for 12 h, −30 °C for 1 h, 0 °C for 10 h (small conversion at this stage), and finally at room temperature for 12 h with (*R*)-**3** (R'O = C_2H_5O) prepared from $LiAlH_4$ (0.66 M THF solution, 2.27 mL, 1.50 mmol), ethanol (1.00 M THF solution, 1.50 mL, 1.50 mmol), and (*R*)-**1** (429 mg, 1.50 mmol) in THF (2.5 mL). Quenching with methanol (1 mL) was followed by aqueous workup and ether extraction. Column chromatography on silica gel (10 g, a 10:1 mixture of benzene–ether as eluent) and subsequent bulb-to-bulb distillation [130–140 °C (20 mmHg)] gave optically active (*R*)-1-phenyl-2,2-dimethylpropanol [(*R*)-**5f**] (61 mg, 80%) as a colorless oil: $[\alpha]^{22}_D$ +11.5° (*c* 2.39, benzene), 44% ee based on the highest reported rotation value (lit.[7d] (*R*)-**5c**, $[\alpha^{22}_D$ +25.9° (*c* 2.2, benzene)).

G. α-Tetralone. This ketone (100 mg, 0.68 mmol) in THF (1 mL) was mixed at −100 °C with (*R*)-**3** (R'O = C_2H_5O) prepared from $LiAlH_4$ (1.99 M THF solution, 1.03 mL, 2.05 mmol), ethanol (1.00 M THF solution, 2.05 mL, 2.05 mmol), and (*R*)-**1** (558 mg, 2.05 mmol) in THF (2.5 mL), and the mixture was gradually warmed to room temperature, stirred for 10 h, and quenched with water. Extractive workup with ether followed by column chromatography on silica gel (20 g) using a 20:3 mixture of benzene and ethyl acetate as eluent gave (*R*)-1,2,3,4-tetrahydro-1-naphthol (92 mg, 91%) as a colorless oil: $[\alpha]^{24}_D$ −24.2° (*c*

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3.06, $CHCl_3$), 74% ee based on the known maximum rotation (lit.[41] *S* enantiomer, $[\alpha]^{17}_D$ +32.7° (*c* 4.1, $CHCl_3$)).

H. Benzyl Methyl Ketone. A solution of benzyl methyl ketone (335 mg, 2.5 mmol) in THF (2.5 mL) was treated at −100 °C for 2 h and at −78 °C for 16 h with (*S*)-**3** (R′O = C_2H_5O) which was prepared from $LiAlH_4$ (1.63 M THF solution, 5.10 mL, 8.31 mmol), ethanol (2.00 M THF solution, 4.20 mL, 8.40 mmol), and (*S*)-**1** (2.41 g, 8.43 mmol) in THF (10 mL). Quenching with ethanol (0.5 mL) at −78 °C was followed by aqueous workup, ether extraction, and bulb-to-bulb distillation [120–130 °C (17 mmHg)] to give a mixture of the starting ketone and (*S*)-1-phenyl-2-propanol (315 mg) (74% yield by GC). Preparative GC gave the optically active alcohol (182 mg) as a colorless oil: $[\alpha]^{25}_D$ +5.3° (*c* 5.28, benzene), 13% ee based on the highest reported rotation value of *S* carbinol (lit.[42] $[\alpha]^{20}_D$ +41.8° (*c* 5.26, benzene)).

I. 2-Octanone. A solution of 2-octanone (320 mg, 2.5 mmol) in THF (2.5 mL) was treated at −100 °C for 2 h and at −78 °C for 16 h with (*R*)-**3** (R′O = C_2H_5O) prepared from $LiAlH_4$ (1.63 M THF solution, 5.10 mL, 8.31 mmol), ethanol (2.00 M THF solution, 4.20 mL, 8.40 mmol), and (*R*)-**1** (2.41 g, 8.43 mmol) in THF (10 mL). Quenching with ethanol (0.5 mL) at −78 °C was followed by aqueous workup, ether extraction, and bulb-to-bulb distillation [120–140 °C (100 mmHg) to give a mixture of the starting ketone and (*S*)-2-octanol (343 mg) (67% yield by GC). Preparative GC gave the optically active alcohol (137 mg) as a colorless oil: α^{24}_D +0.019° (neat, *l* = 0.01, *d* 0.822), 24% ee based on the highest reported value of optical rotation for *S* carbinol (lit.[43] $[\alpha]^{25}_D$ +9.57° (neat)).

Reduction of 4-*tert*-Butylcyclohexanone with (±)-BINAL-H. A solution of 4-*tert*-butylcyclohexanone (1 M THF solution, 0.20 mL, 0.20 mmol) was treated at 30 °C for 12.5 h with (±)-**3** prepared from $LiAlH_4$ (0.12 M THF solution, 3.33 mL, 0.40 mmol), an alcohol or other hydroxylic component (1.00 M THF solution, 0.40 mL, 0.40 mmol), and (±)-**1** (114 mg, 0.40 mmol) in THF (3 mL). To the reaction mixture was added 1 N HCl and hexane, and the hexane layer was subjected to GC analysis (135 °C). The results are listed in Table IV.

Examination of Irreversibility of the Reduction. A reaction flask was connected to a gas buret via a bubbler and a $CaCl_2$ drying tube. In the flask was placed a THF solution of $LiAlH_4$ (0.25 M, 4.00 mL, 1.00 mmol) which was cooled to 0 °C. When ethanol (1.00 M THF solution, 1.00 mL, 1.00 mmol) was added to this solution, 22.2 mL (0.99 mmol) of hydrogen gas was evolved. Subsequent addition of (±)-**1** (0.25 M THF solution, 4.00 mL, 1.00 mmol) generated 44.6 mL (1.99 mmol) of hydrogen gas. Finally, when this mixture was treated with an excess amount of ethanol (0.5 mL), evolution of 23.8 mL (1.06 mmol) of hydrogen gas was observed.

To a reagent prepared from $LiAlH_4$ (0.25 M THF solution, 4.00 mL, 1.00 mmol), ethanol (1.00 M THF solution, 1.00 mL, 1.00 mmol), and (±)-**1** (0.25 M THF solution, 4.00 mL, 1.00 mmol) was added propiophenone (**4b**) (1.00 M THF solution, 1.00 mL, 1.00 mmol) at 30 °C. This mixture was stirred at this temperature for 4 h and then cooled to 0 °C. Addition of methanol (1.0 mL) led to evolution of 4.7 mL (0.21 mmol) of hydrogen gas. GC analysis (140 °C) of the crude product indicated that unreacted **4b** (t_R 3.0 min) and carbinol **5b** (t_R 4.2 min) were only volatile compounds and that **4b**/**5b** ratio was 25:75.

In the same manner, **4b** was treated with (±)-**3** (R′O = C_2H_5O) prepared from $LiAlH_4$ (0.25 M THF solution, 4.00 mL, 1.00 mmol), ethanol (1.00 M THF solution, 1.00 mL, 1.00 mmol), and (±)-**1** (0.25 M THF solution, 4.00 mL, 1.00 mmol) at 30 °C for 4 h. Then acetophenone (**4a**) (1.00 M THF solution, 1.00 mL, 1.00 mmol) was added, and the mixture was stirred for an additional 2 h at 30 °C and cooled to 0 °C. Addition of methanol (1 mL) generated 3.2 mL (0.14 mmol) of hydrogen gas. The mixture was worked up in an usual manner and subjected to GC analysis (140 °C), which indicated the presence of **4a** (t_R 1.9 min), **4b** (3.0 min), and **5b** (4.2 min) in 100:23:77 ratio (total 200%).

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Registry No. (±)-**1**, 41024-90-2; (*R*)-(+)-**1**, 18531-94-7; (*S*)-(−)-**1**, 18531-99-2; (±)-**2**, 91491-79-1; (±)-**3** (R′ = CH_3), 91602-26-5; (*R*)-**3** (R′ = CH_3), 70945-92-5; (±)-**3** (R′ = C_2H_5), 91602-27-6; (*R*)-**3** (R′ = C_2H_5), 70945-91-4; (*S*)-**3** (R′ = C_2H_5), 70981-93-0; (*E*)-**3** (R′ = $(CH_3)_2CH$), 70945-93-6; (±)-**3** (R′ = $(CH_3)_3CO$), 91602-28-7; (*R*)-**3** (R′ = $(CH_3)_3CO$), 70945-94-7; (*R*)-**3** (R′ = CF_3CH_2O), 70945-95-8; (*R*)-**3** (R′ = C_6H_5O), 70945-96-9; (±)-**3** (R′ = 2,6-(t-C_4H_9)$_2$$C_6H_3$), 91602-29-8; (*R*)-**3** (R′ = 2,6-(t-C_4H_9)$_2$$C_6H_3$), 70945-97-0; (±)-**3** (R′ = AlO), 91602-30-1; (*R*)-**3** (R′ = AlO), 70945-98-1; (±)-**3** (R′ = $AlOCH_2CH_2O$), 91491-78-0; **4a**, 98-86-2; **4b**, 93-55-0; **4c**, 495-40-9; **4d**, 1009-14-9; **4e**, 611-70-1; **4f**, 938-16-9; (*R*)-**5a**, 1517-69-7; (*S*)-**5a**, 1445-91-6; (*R*)-**5b**, 1565-74-8; (*S*)-**5b**, 613-87-6; (±)-**5c**, 21632-18-8; (*S*)-**5c**, 22135-49-5; (±)-**5c** (hydrogen phthalate), 91491-80-4; (*S*)-**5c** (hydrogen phthalate)-brucine, 91602-32-3; (*S*)-**5c** (MTPA ester), 91491-81-5; (*R*)-**5c** (MTPA ester), 39532-70-2; (*S*)-**5d**, 33652-83-4; (*R*)-**5d** (MTPA ester), 91491-83-7; (*S*)-**5d** (MTPA ester), 91491-82-6; (*R*)-**5e**, 14898-86-3; (*S*)-**5e**, 34857-28-8; (*R*)-**5f**, 23439-91-0; (*S*)-**5f**, 24867-90-1; **6** (Un = CH≡C, R = n-C_5H_{11}), 27593-19-7; **6** (Un = CH≡C, R = i-C_3H_7), 13531-82-3; **6** (Un = $C_6H_5CH_2$R = CH_3), 103-79-7; **6** (Un = n-C_6H_{13}, R = CH_3), 111-13-7; (*R*)-**7** (Un = CH≡C, R = n-C_5H_{11}), 32556-70-0; (*S*)-**7** (Un = CH≡C, R = n-C_5H_{11}), 32556-71-1; (*R*)-**7** (Un = CH≡C, R = i-C_3H_7), 73522-97-1; (*S*)-**7** (Un = CH≡C, R = i-C_3H_7), 77943-78-3; (*R*)-**7** (Un = $C_6H_5CH_2$, R = CH_3), 1572-95-8; (*S*)-**7** (Un = $C_6H_5CH_2$, R = CH_3), 1517-68-6; (*R*)-**7** (Un = n-C_6H_{13}, R = CH_3), 5978-70-1; (*S*)-**7** (Un = n-C_6H_{13}, R = CH_3), 6169-06-8; LAH, 16853-85-3; (*R*)-MTPA-Cl, 39637-99-5; CH_3OH, 67-56-1; C_2H_5OH, 64-17-5; $(CH_3)_2CHOH$, 67-63-0; $(CH_3)_3COH$, 75-65-0; CF_3CH_2OH, 75-98-9; C_6H_5OH, 108-95-2; 2,6-(t-C_4H_9)$_2$$C_6H_3OH$, 128-39-2; C_6H_5CHO, 100-52-7; $(CH_3)_2Mg$, 2999-74-8; α-tetralone, 529-34-0; 4-*tert*-butylcyclohexanone, 98-53-3; (*R*)-α-tetralol, 23357-45-1; (*S*)-α-tetralol, 53732-47-1; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; phthalic anhydride, 85-44-9; *p*-methoxyacetophenone, 100-06-1; 2-cyclohexenone, 930-68-7; 3-methyl-2-cyclohexenone, 1193-18-6; 2-isopropylidenecyclohexanone, 13747-73-4; cyclohexanone, 108-94-1; (*E*)-3-octen-2-one, 18402-82-9; (*R*)-2-hydroxy-2′-methoxy-1,1′-binaphthyl, 79547-82-3; (*R*)-methyl-[(2′-methoxy-1,1′-binaphthyl-2-yl)oxy]magnesium, 91491-84-8.

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