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ASYMMETRIC SYNTHESIS VIA AXIALLY DISSYMMETRIC MOLECULES. A BINAPHTHOL-MODIFIED COMPLEX ALUMINUM HYDRIDE REAGENT POSSESSING EXTREMELY HIGH ABILITY OF CHIRAL RECOGNITION

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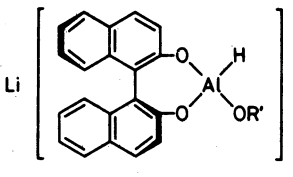
Abstract—A new chiral hydride reagent, BINAL-H, has been devised by the modification of lithium aluminum hydride with axially dissymmetric (S)- or (R)-binaphthol and a simple alcohol. This reducing agent possesses exceptionally high enantioface-differentiating ability and reduces a wide variety of structurally diverse unsaturated (but not saturated) carbonyl substrates in high optical yields and in a predictable manner. A six-membered ring transition state model is proposed to explain the stereochemical consequences. The unsaturated moiety and alkyl group attached to the carbonyl function is differentiated primarily by the difference in the electronic properties rather than the bulkiness. The utility of the asymmetric reduction is exemplified by the efficiently stereocontrolled synthesis of prostaglandin intermediates, some insect pheromones, chiral primary terpenic alcohols, etc.

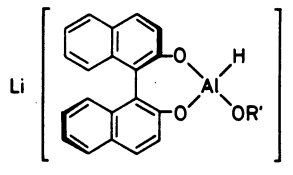
Enantioselective reduction of prochiral carbonyl compounds is one of the most fundamental chiral transformations (1). The standard method involves the utilization of complex metal hydride reagents bearing chiral auxiliary ligands. Our approach originates from the considerations that, firstly, minimization of the number of the reactive hydride species is crucial for obtaining a high level of the enantioface differentiation and, secondly, use of axially dissymmetric, bifunctional 1,1'-binaphthyl derivatives is the most effective for this purpose (2). We thus devised new chiral hydride reagents by modification of lithium aluminum hydride (LAH) with 2,2'-dihydroxy-1,1'-binaphthyl (binaphthol) and simple alcohols, which are capable of reducing a wide range of carbonyl substrates in high optical yields.

Reduction of aromatic ketones

The binaphthol modified aluminum hydride reagents (hereafter abbreviated to BINAL-H reagents) of type 1 can be made in situ by mixing LAH with equimolar amounts of optically pure (S)-(-)- or (R)-(+)-binaphthol and a second hydroxylic component, R'OH (3). The



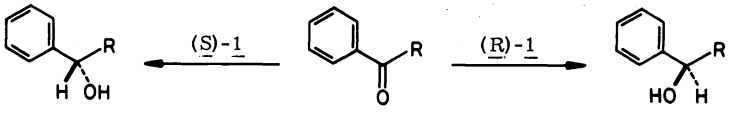
(S)-BINAL-H, (S)-(1)



(R)-BINAL-H, (R)-(1)

sense and extent of the asymmetric induction in the acetophenone reduction is profoundly influenced by the nature of R'O groups and, as usual, the reagents with a simple alkoxyl group such as CH_3O or C_2H_5O exhibit high enantioselectivity. The optical yield was

generally enhanced by lowering the reaction temperature. Thus the value as high as 95% has been obtained by carrying out the reaction with 1 (R'O = C_2H_5O) at -100 to -78 °C. For the completion of the reaction at reasonable rate and with high enantioselectivity, use of 2—3 equiv of the reducing agent 1 is required. Results of the reduction of a series of alkyl phenyl ketones (2) leading to the carbinols (3) are summarized in Table 1. The optical purities of the carbinols were assayed by measurement of the rotation value and analysis by ^1H NMR and high pressure liquid chromatography of the (S)-β,β,β-trifluoro-α-methoxy-α-phenylpropionate derivatives. The asymmetric reduction exhibits exceptionally high selectivity and, in some cases, the enantioface differentiation is virtually complete. Although the degree of the stereoselectivity depends on the kind of the alkyl groups attached to the carbonyl function, in general, the reduction by (R)-1 gives the R carbinol preferentially, and (S)-1 produces the S enantiomer predominantly.



(S)-(3) (2) (R)-(3)

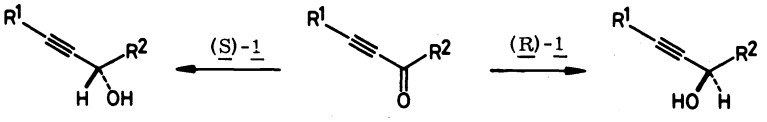
TABLE 1. Enantioselective reduction of aromatic ketones with BINAL-H (R'O = C_2H_5O)[a]

Ketone	Binaphthol confign in BINAL-H	Carbinol product: Chemical yield, %	Carbinol product: Optical purity, % ee	Carbinol product: Confign
$C_6H_5COCH_3$	R	61	95	R
$C_6H_5COC_2H_5$	S	62	98	S
C_6H_5CO-n-C_3H_7	S	78	100	S
C_6H_5CO-n-C_4H_9	S	64	100	S
$C_6H_5COCH(CH_3)_2$	S	68	71	S
$C_6H_5COC(CH_3)_3$	R	80[b]	44	R
α-Tetralone	R	91[c]	62	R

[a] Reaction was carried out in THF with 3 equiv of 1 at -100 °C for 2—3 h and then at -78 °C for 16 h. [b] Reaction at 25 °C for 12 h. [c] Reaction was completed by warming the mixture at -50 °C (6 h) and then at 20 °C (16 h).

Reduction of acetylenic ketones

When an acetylenic ketone of type 4 was reduced by the chiral BINAL-H reagent 1 (R'O = CH_3O or C_2H_5O) in THF, the corresponding alcoholic product 5 was obtained in high chemical and optical yield (4). Some examples are given in Table 2. The ketonic substrates bearing an ethynyl group and a longer alkynyl substituent are equally employable. The S reducing agent tends to produce the S propargylic alcohol as the major product, whereas the R reagent affords the R product predominantly.



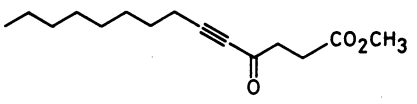
(S)-(5) (4) (R)-(5)

TABLE 2. Enantioselective reduction of acetylenic ketones with BINAL-Hs[a]

Ketone	Binaphthol config in BINAL-H[b]	Carbinol product: Chemical yield, %	Carbinol product: Optical purity, % ee	Carbinol product: Config
CH≡CCO-n-C_5H_{11}	S	87	84	S
CH≡CCO-n-C_5H_{11}	S[b]	71	84	S
CH≡CCO-n-C_8H_{17}	S	80	96	S
CH≡CCO-n-C_8H_{17}	S[b]	74	90	S
CH≡CCO-n-$C_{11}H_{23}$	S	90	92	S
CH≡CCOCH$(CH_3)_2$	S	84	57	S
n-C_4H_9C≡CCOCH_3	R	79	84	R
n-C_4H_9C≡CCO-n-C_5H_{11}	S	85	90	S

[a] Reaction was performed in THF by using 3 equiv of 1 (R'O = CH_3O) at -100 °C for 1 h and then at -78 °C for 2 h. [b] Reaction with 1 (R'O = C_2H_5O).

The chiral propargylic alcohols thus obtained are important synthetic intermediates. This enantioselective reduction is applicable to the asymmetric synthesis of certain insect pheromones. The reduction of the acetylenic ketone 6 with (R)-1 (R'O = CH_3O) produced the optical active alcohol, (R)-7, in 85% ee and 80% yield. Lactonization of (R)-7 by p-toluenesulfonic acid followed by the partial hydrogenation over the Lindlar catalyst led to the Japanese beetle pheromone (R)-8. Exposure of the ynone 9 to (S)-1 (R'O = CH_3O) gave the alcohol (S)-10 in 87% ee (80% yield). Diimide reduction of this product followed by acid catalyzed lactonization afforded the levorotatory rove beetle pheromone, (S)-11.



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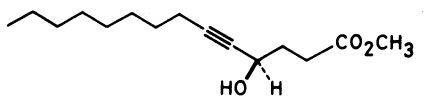
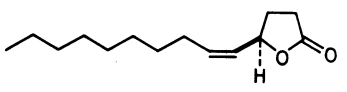
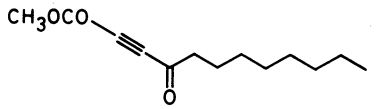


(R)-(7)



(R)-(8)



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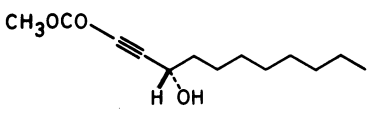
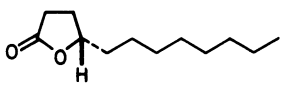


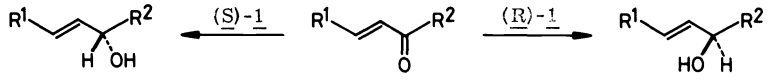
(S)-(10)



(S)-(11)

Reduction of olefinic ketones

Reduction of a simple alkenyl alkyl ketone of type 12 with the chiral BINAL-H in THF proceeded in a stereoselective fashion to give the allylic alcohol 13 in substantially high enantiomeric excess. Table 3 shows some examples. Use of vinyl ketones (12, R^1 = H) resulted in the undesired 1,4-reduction. Reaction of β-ionone, a conjugated dienone, with (S)-1 led to (S)-β-ionol in essentially quantitative optical yield (NMR analysis).



(S)-(13) (12) (S)-(13)

TABLE 3. Enantioselective reduction of olefinic ketones with BINAL-H (R'O = C_2H_5O)[a]

Ketone	Binaphthol confign in BINAL-H	Carbinol product: Chemical yield, %	Carbinol product: Optical purity, % ee	Carbinol product: Confign
(E)-n-C_4H_9CH=CHCOCH$_3$	R	73	79	R
(E)-n-C_4H_9CH=CHCO-n-C_5H_{11}	R	85	91	R
(E)-cyclo-C_5H_9CH=CHCO-n-C_5H_{11}	R	91	92	R
β-Ionone	S	87	100	S

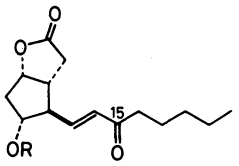
[a] Reaction was performed in THF by using 3 equiv of 1 at -100 °C for 1 h and then at -78 °C for 2—4 h.

The BINAL-H reduction has proved to be extremely useful for prostaglandin (PG) synthesis; this method allows stereoselective generation of the 15S natural configuration from the corresponding ketonic substrates (5). Thus when the α,β-unsaturated ketones 14—16 were treated with (S)-1 (R'O = C_2H_5O) at low temperatures, the allylic alcohols, 17—19, possessing the 15S absolute stereochemistry (PG numbering) were produced with excellent (greater than 99%) stereoselectivity. The general tendency is not affected by the nature of the 11-hydroxyl protective groups or whether the hydroxyl moiety is protected or not (Table 4). The reaction of the 11-unprotected enone 16 gave rise to the desired 15S alcohol 19 exclusively. The reduction of the monocyclic substrate 20 afforded the $PGF_{2\alpha}$ derivative 21 as a single stereoisomer. The model prochiral enone 12 (R^1 = cyclopentyl and R^2 = n-pentyl) was reduced by (S)-1 to give (S)-13 and (R)-13 in 96:4 ratio. Notably, the reduction by (S)-1 of the enone 15 bearing a chiral cyclopentane unit exhibited a substantial increase in the degree of the S stereoselection (S/R = 99.5:0.5), whereas use of the R hydride reagent resulted in a decrease in the enantioselectivity, S/R = 32:68. Thus the stereoselection observed with the chiral PG synthetic intermediates appears to be a result of the "double stereodifferentiation".

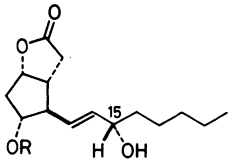
TABLE 4. Stereoselective generation of the 15S configuration in the prostaglandin intermediates[a]

Ketone	Binaphthol confign in BINAL-H	Alcoholic product % yield	Alcoholic product 15S/15R ratio
14	S	95	99.4:0.6
15	S	96	99.5:0.5
15	R	93	32:68
16	S	97[b]	100:0
20	S	76	100:0
22	S	95	98.5:1.5
23	S	96	98:2

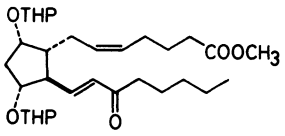
[a] Reaction was carried out in THF by using 3 equiv of 1 (R'O = C_2H_5O) at -100 °C for 1—2 h and then at -78 °C for 1—2 h. [b] Conversion was 41%. [c] This value is based on consumed 16.



(14) R = $COCH_3$
(15) R = THP
(16) R = H



(17) R = $COCH_3$
(18) R = THP
(19) R = H



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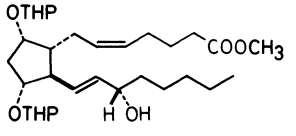

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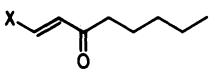
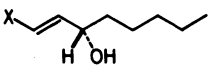
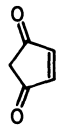
This procedure also permits the facile preparation of the building blocks which are useful for the conjugate addition approaches. The enantioselective reduction of the halovinyl ketones, 22 and 23, with (S)-1 (R'O = C_2H_5O), under the standard conditions formed the corresponding S alcohols, 24 and 25, respectively, in high optical purities (Table 4). Further, the requisite chiral cyclopentenone unit is also obtainable by this method. When cyclopentenedione 26 was mixed with 1.5 equiv of (S)-1 (R'O = C_2H_5O) at -100 °C, rapid reaction took place to give (R)-27 in 94% ee (ca. 60% yield). Thus the combination of these chiral moieties would lead to the PG derivatives having the correct 11R, 15S stereochemistries (6).



(22) X = I
(23) X = Br



(24) X = I
(25) X = Br



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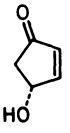
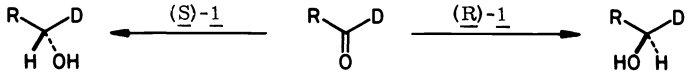


(R)-(27)

Reduction of 1-deuterio aldehydes

When geranial-1-d (28, R = (E)-$(CH_3)_2C$=$CHCH_2CH_2C(CH_3)$=CH) was reduced by 3 equiv of (S)-1 (R'O = C_2H_5O) in THF at -100 °C, (S)-(+)-geraniol-1-d of 91 (rotation) or 84% (NMR) optical purity was obtained in 91% yield (7). Similarly the asymmetric reduction was successfully applied to the synthesis of optically active, deuterium labeled primary alcohols (29) such as nerol, farnesols, and benzyl alcohol. The results are summarized in Table 5.



(S)-(29) (28) (R)-(29)

TABLE 5. Enantioselective reduction of deuterium labeled aldehydes with BINAL-H (R'O = C_2H_5O)[a]

Aldehyde	Binaphthol confign in BINAL-H	Primary alcohol: Chemical yield, %	Primary alcohol: Optical purity, % ee	Primary alcohol: Confign
Geranial-1-d	S	91	91 or 84	S
Neral-1-d	S	90	72	S
(E,E)-Farnesal-1-d	R	91	88	R
(Z,E)-Farnesal-1-d	R	93	82	R
Benzaldehyde-α-d	R	75	82	R

[a] Reaction was carried out in THF by using 3 equiv of 1 at -100 °C for 2—3 h.

Reduction of dialkyl ketones

The BINAL-H reagents are not effective for the enantioselective reduction of dialkyl ketones. For instance, reaction of benzyl methyl ketone and 3 equiv of (S)-1 (R'O = C_2H_5O) (THF, -100 °C for 2 h and -78 °C for 16 h) gave (S)-1-phenyl-2-propanol in only 13% ee (71% yield); reaction of 2-octanone with (R)-1 produced (S)-2-octanol in 24% ee (67% yield).

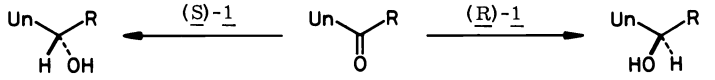
Advantages of the BINAL-H reduction

This asymmetric reduction is operationally quite simple and applicable to a wide variety of unsaturated (but not saturated) carbonyl substrates. The reaction proceeds in satisfactory chemical and optical yields. Although several successful asymmetric reductions have already been reported (1), the present results are compared favorably with the earlier records. In addition, since both enantiomers of binaphthol are available in optically pure form, this method allows the synthesis of either the S or R carbinols from the corresponding carbonyl compounds by choosing handedness of the chiral ligand. The chiral auxiliary ligand can be recovered from the reaction mixture in high yield in reusable form without any racemization. Thus the newly developed method fully satisfies the conditions of being a useful asymmetric reduction.

Mechanistic aspects

It is known that the sense and degree of asymmetric reduction by some chirally modified LAH reagents are highly dependent on the way and extent of aging of the reagents (8). However, the extent of the enantioselection of the BINAL-H reduction is time-independent; the reduction of acetophenone at 30 °C with (R)-1 (R'O = C_2H_5O) of various aging state proceeded in virtually constant optical yield, 65%. The optical yield of the same reduction system increased monotonously by lowering the reaction temperature (30 to -100 °C). When the observed enantioselectivity, ln R/S, was plotted against the reciprocal of the temperature, 1/T (in K), a straight line was obtained. Thus it is clear that a single hydride species is responsible for the asymmetric reduction.

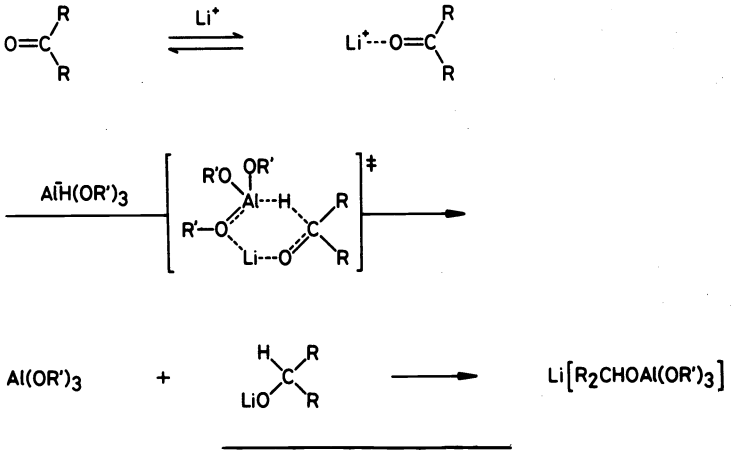
The BINAL-H reduction is irreversible and the stereoselectivity is a subject of kinetic control. Since the relative reactivities of the carbonyl substrates are related to, in addition to some steric factors, the energy level of the LUMOs, the transition states involved are reactant-like. The most important feature of this asymmetric reduction is the general empirical rule for the orientation observed with simple prochiral carbonyl substrates of type 30 (Un = phenyl, alkenyl, alkynyl; R = alkyl, hydrogen); the S reducing agent (S)-1 (R'O = simple alkoxyl) affords the carbinol 31 in which the S enantiomer predominates, whereas the R reagent forms the R antipode preferentially. The phenyl, alkenyl, and alkynyl groups exert qualitatively the same directing influence in the creation of the new asymmetric centers. It should be noted that the overwhelming kinetic preference is primarily determined by the difference in electronic properties of Un and R attached to the carbonyl group. Steric factors are also of some significance but do not overbalance the electronic bias.



(S)-(31) (30) (R)-(31)

We consider that the reduction of a carbonyl function with $LiAlH(OR')_3$ type reagents proceeds via pathway outlined in Scheme I. When this mechanism is applied to the BINAL-H reduction, the oxygen atom of the simple R'O group having the highest basicity acts as the bridging atom in the quasi-aromatic, six-membered ring transition state. In the reduction of 30 by (S)-1, the two chair-like transition states, 32 and 33, are suggested as the candidates by model inspection. Here the structure 32, leading to the S carbinol, is favored over the diastereomeric 33 which gives the R enantiomer, because the latter structure with axial-Un and equatorial-R group is destabilized by the substantial n/π electronic repulsion between the axially oriented binaphthoxy oxygen and the unsaturated moiety. The 1,3-diaxial type steric repulsion, which becomes important by increasing the bulkiness of R, cannot overcome the electronic influence. This mechanism is consistent with the very unusual enantioselection observed in the reaction of cyclopentenedione 26 and (S)-1. In this case, the undesired n/π interaction, 34a, is surmounted by the newly introduced n/π^* attractive orbital interaction between the oxygen nonbonding orbital and the LUMO of the enone moiety, as depicted in 34b, which results in the anomalous S/R ligand/product configurational correlation.

Scheme I



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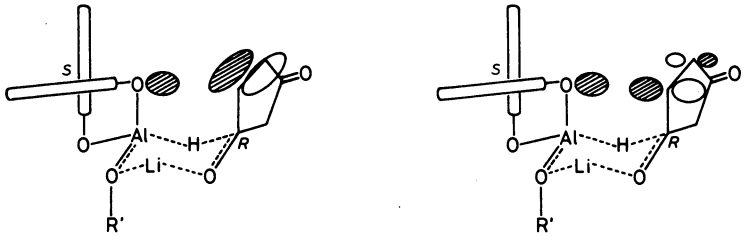

(34a) (34b)

References

1. Reviews: J. D. Morrison and H. S. Mosher, Asymmetric Organic Reactions, p. 160, Prentice-Hall, Englewood Cliffs, NJ (1971); D. Valentine and J. W. Scott, Synthesis 329-356 (1978) ; H. Kagan and J. C. Fiaud, Top. Stereochem. 10, 175-285 (1978); J. W. ApSimon and R. P. Seguin, Tetrahedron 35, 2797-2842 (1979).
2. A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi and R. Noyori, J. Am. Chem. Soc. 102, 7932-7934 (1980).
3. R. Noyori, I. Tomino and Y. Tanimoto, J. Am. Chem. Soc. 101, 3129-3131 (1979).
4. M. Nishizawa, M. Yamada and R. Noyori, Tetrahedron Lett. 22, 247-250 (1981).
5. R. Noyori, I. Tomino and M. Nishizawa, J. Am. Chem. Soc. 101, 5843-5844 (1979).
6. R. Noyori, Organic Synthesis—Today and Tomorrow, p. 273, Pergamon Press, London (1981).
7. M. Nishizawa and R. Noyori, Tetrahedron Lett. 21, 2821-2824 (1980).
8. For example, see S. Yamaguchi, H. S. Mosher and A. Pohland, J. Am. Chem. Soc. 94, 9254-9255 (1972).