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ENANTIOSE
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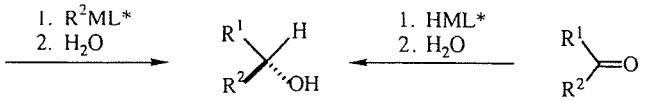
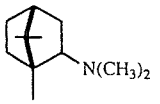
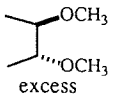
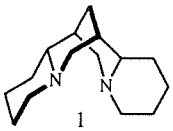
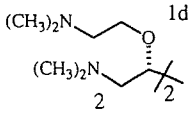
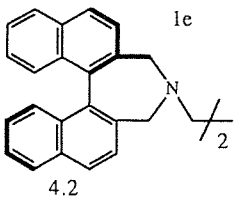
ORGANOMETALLIC REACTIONS

Enantioselective alkylation of aldehydes by chiral
metallic reagents is a very simple and fundamental
This asymmetric reaction, together with enantiose
prochiral ketones, provides a general method for
active secondary alcohols (Scheme 1). Because of
nificance, a number of highly stereoselective react
modification of organolithium, -magnesium, -titar
ganometallic reagents by optically active organic s
described. Both aprotic and protic organic compo
chiral modifiers. Schemes 2 (*1*) and 3 (*2*) show th
velopment in this area (*3*). Appropriate combinati
strates and organometallic reagents modified by

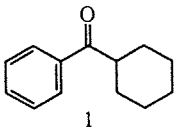
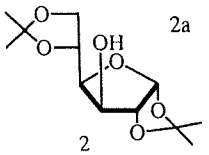
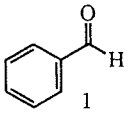
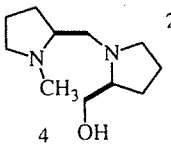
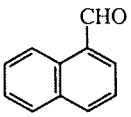
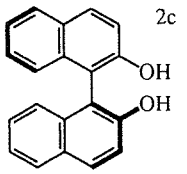
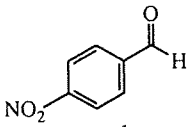
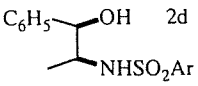
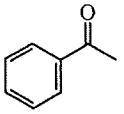
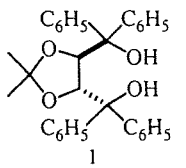


HEME 1. Asymmetric synthesis of chiral alcohols.

hols allows synthesis of alcohols in acceptable optical ganometallic reagents formulated as RLi or RMgX lose ition of chiral alcohols. But organometallics present in asymmetric induction in the nucleophilic addition reac- the formation of mixed aggregates containing the alkyl al anionic ligands (*5*). For example, dialkylmagnesium d with an equimolar amount of the dilithio salt of opti- phthol cleanly alkylate aromatic aldehydes to give, after

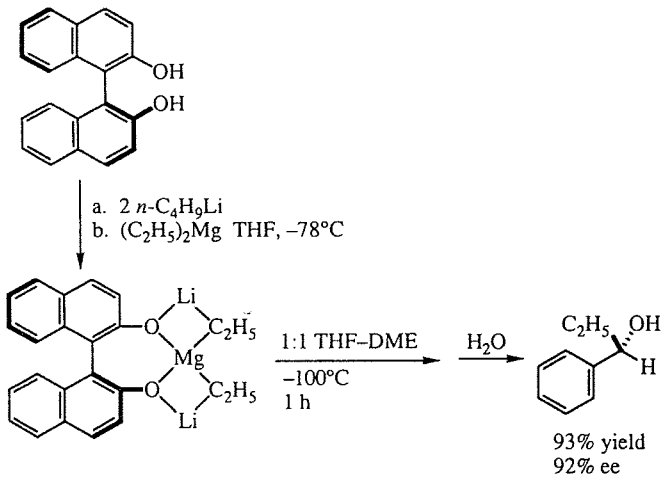
te	reagent equiv	chiral ligand equiv	product confign, optical yield
	CH_3MgI	 1a	—, 0.7% (?)
OC_2H_5	C_2H_5MgCl 1	 1b excess	—, 5%
	C_2H_5MgBr 1	 1c	*R*, 22%
	n-C_4H_9Li 1.1	 1d	*S*, 52%
	n-C_4H_9Li 3.7	 1e	*R*, 95%

2. Enantioselective alkylation using aprotic chiral ligands.

substrate equiv	reagent equiv	auxiliary equiv
 1	CH_3MgBr 3.5	 2a 2
 1	n-C_4H_9Li 6.7	 2b 4
 1	C_6H_5MgBr 1.3	 2c + $TiCl[OCH(CH_3)_2]_3$ 1.3
 1	$(CH_3)_4Ti$ 1.1	 2d + $(CH_3)_2CHOH$ 1.1 Ar = mesityl
 1	C_2H_5MgBr 3	 2e 1

SCHEME 3. Enantioselective reaction using protic chi

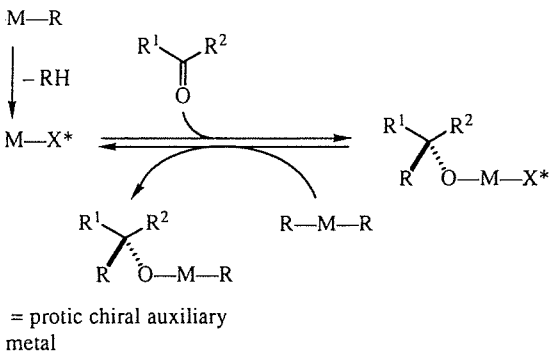
aqueous workup, the secondary alcohols in greater th 4) (*6*). Because of the C_2 symmetry of the chiral mo groups in the Li–Mg binary organometallic reagent react equally toward alkylation. Many organomagn methyl- diethyl- dibutyl-, and diphenylmagnesium ca for this asymmetric synthesis. In all of these cases, tion requires use of one or several equivalents of c which is, of course, not ideal.



EME 4. Enantioselective ethylation of benzaldehyde.

tioselective Alkylation

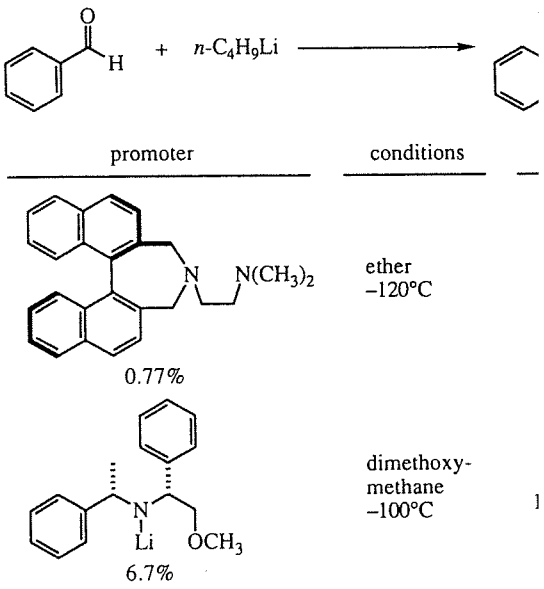
w shall we proceed toward catalytic asymmetric induc- illustrates a possible way to achieve enantioselective ing a small amount of chiral source. Under certain consence of a protic chiral auxiliary HX* can catalyze the anometallic reagent, R_2M, to a prochiral carbonyl sub- f RMX*. To obtain sufficient chiral efficiency, the an- must have a three-dimensional structure that allows difween the diastereomeric transition states of the alkyl addition, unlike in stoichiometric reactions, the rate of



EME 5. Principle of catalytic asymmetric alkylation.

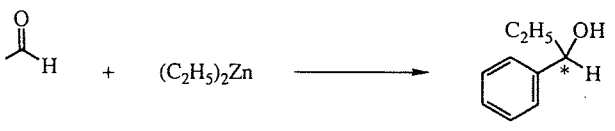
the reaction of the chirally modified reagent and carbo substantially exceed that of the reaction of unmodifi R_2M. Furthermore, X* must readily detach from th alkylation product, a metal alkoxide, by the action o substrate in order to establish the catalytic cycle. coordination number, and bond polarity of the or pound is significantly affected by the steric and elect the ligand (*5a*, *8*, *9*). Moreover, the actual structu simple as expected and the compounds perhaps exis in forms associated with other molecules. In any ev celeration (*10*) satisfying such kinetic requirements high turnover efficiency. These considerations also metallic reactions using aprotic modifiers.

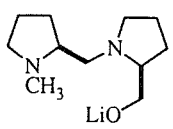
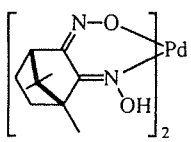
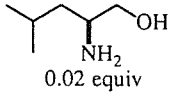
Although a wide array of well-shaped chiral auxi cessible from nature or by synthesis, kinetic condit required are not easily obtained with conventional o ganomagnesium compounds (*11*). Although there a of catalytic asymmetric alkylation with organoli (Scheme 6), the turnover numbers are not large er thetically meaningful ee values (*1e*, *12*), primarily b *n*-butyllithium is highly reactive toward benzaldehyc



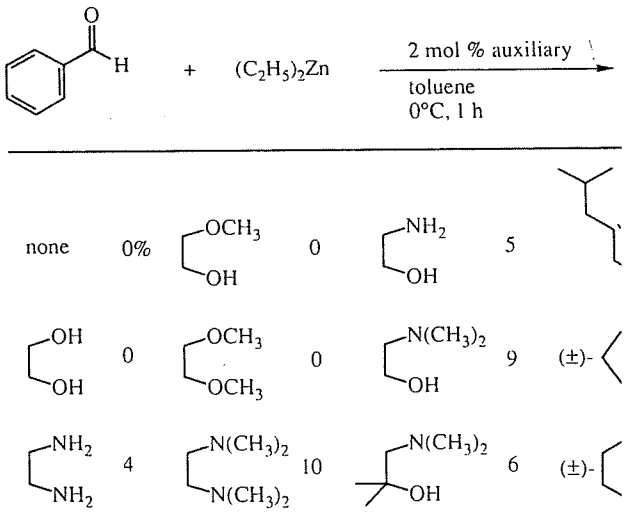
SCHEME 6. Attempt on catalytic asymmetric al

hemistry. Organozinc chemistry provides an opportu- the catalytic asymmetric alkylation of benzaldehyde (*3*, hough dialkylzincs are inert to ordinary carbonyl sub- ıcarbon or ethereal solvents, their reactivity may be en- tives, like those shown in Scheme 7 (*2b*, *17*, *18*). Par- ɔrthy is the finding by Oguni (*18*) that a small amount of talyzes the reaction of diethylzinç and benzaldehyde to ɜous workup, (*R*)-1-pheny-1-propanol in 49% ee. In view nce of "ligand acceleration" in the scenario of Scheme laboratory at Nagoya University screened a variety of ls and auxiliaries for activation of dialkylzincs. Scheme ıical yields of the addition product formed by reaction of ınd diethylzinc in toluene at 0°C for 1 h assisted with 2 tives, and indicates that not only protic compounds but es such as *N,N,N′,N′*-tetramethylethylenediamine en- ivity of diethylzincs. Simple β-amino alcohols derived mino acids are not very effective activators; however, creases the reactivity. In addition, impressive rate en- bserved with some sterically constrained β-dialkylamino



promoter	conditions	product
 4 equiv	ether –78–0°C 3 h	76% yield 0% ee
 0.01 equiv	toluene 30°C 48 h	98% yield *S*, 58% ee
 0.02 equiv	toluene 24°C 43 h	96% yield *R*, 49% ee

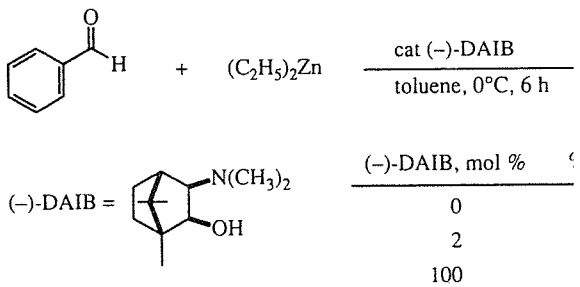
EME 7. Alkylation of benzaldehyde with diethylzinc.



none	0%		0		5		
	0		0		9	(±)-	
	4		10		6	(±)-	

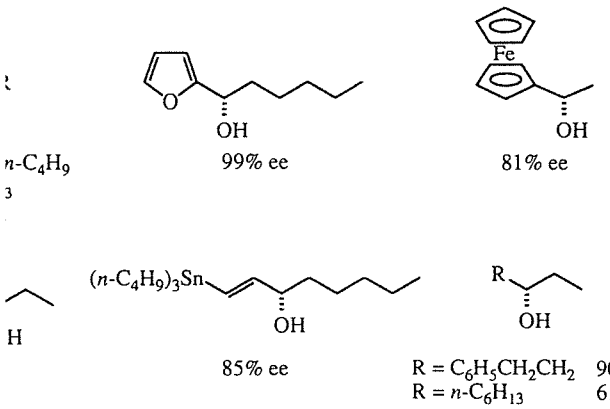
SCHEME 8. Effect of auxiliaries on reactivity of diethylzinc:

Amino Alcohol Catalyzed Alkylation. (−)-3-*exc* isoborneol [(−)-DAIB] is a sterically restrained β-di that has proven to be an extremely efficient catalyst in the presence of 2 mol % of (−)-DAIB, the reacti and diethylzinc proceeds smoothly to give, after (*S*)-1-phenyl-1-propanol in 98% ee and in 97% yiel amount of benzyl alcohol (Scheme 9). Nonpolar s uene, hexane, ether, or their mixtures produce satis optical yield in toluene is affected by temperature 98% at −20°C to less than 95% at 50°C. The catal reaction has been extended to a range of alkylating substrates, which are summarized in Scheme 10 (*15*)



(−)-DAIB, mol %
0
2
100

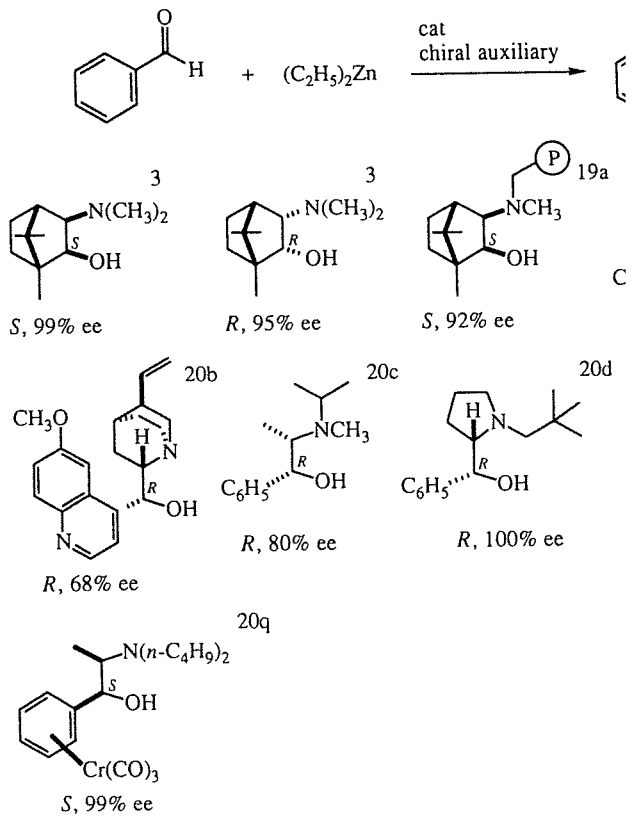
SCHEME 9. Catalytic enantioselective ethyl



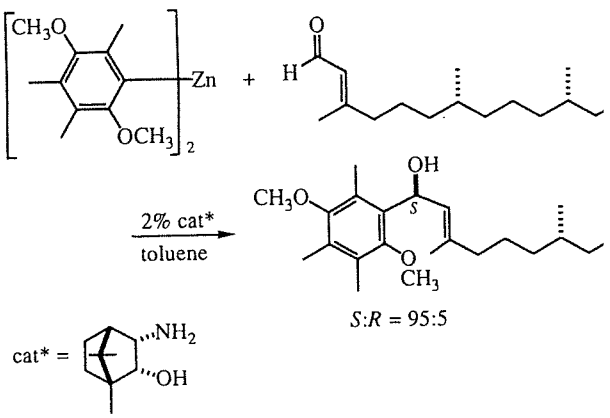
ntioselective synthesis of secondary alcohols by (−)-DAIB-cata-

certain α,β-unsaturated or aliphatic aldehydes can also th a high degree of enantioselectivity. Dimethyl-, di--butylzinc may be used as alkylating agents; however, ceeds about 20 times more slowly than ethylation but ırable stereoselectivity. Acetophenone and *n*-butyl ace- ert to these alkylation conditions. Propyl pyruvate is l (even in the absence of DAIB), but, unfortunately, the ıic.

chiral β-dialkylamino alcohols other than DAIB can be selective alkylation; Scheme 11 shows examples of some ions (*3*, *15*, *19*, *20a–e*, *q*, *21*). Good correlation be- and enantioselectivity is observed—High enantioselec- l by a fast reaction. Polymer-supported DAIB or ephed- ıtes the reaction (*19*, *20a*). In addition to dialkylzincs, and dialkynylzincs as well as cyanomethylzinc bromide ed. Extension of the reaction to a diarylzinc reagents hesis of an α-tocopherol intermediate (Scheme 12) (*24*). he enhanced β-hydrogen reactivity, diisobutylzinc re- ıyde to produce benzyl alcohol (*19a*). The reaction of ylpropanal and diethylzinc in the presence of (2*R*)-1- o-3,3-dimethyl-2-butanol proceeds with 5.4 : 1 enan- ıation (*25a*, *b*). Appropriate choice of the chiral auxil- ective conversion of (3*R*)-benzyloxybutanal to protected ?,4*R*)-hexane-2,4-diol with good diastereoselectivities lbenzaldehyde is ethylated chemoselectively only at the (*20f*).



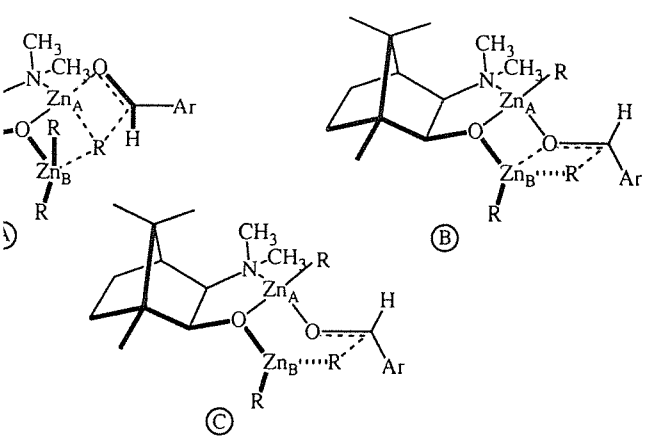
SCHEME 11. Effective chiral auxiliaries: configuration and product in ethylation of benzaldehyde.



SCHEME 12. Synthesis of an intermediate of α-

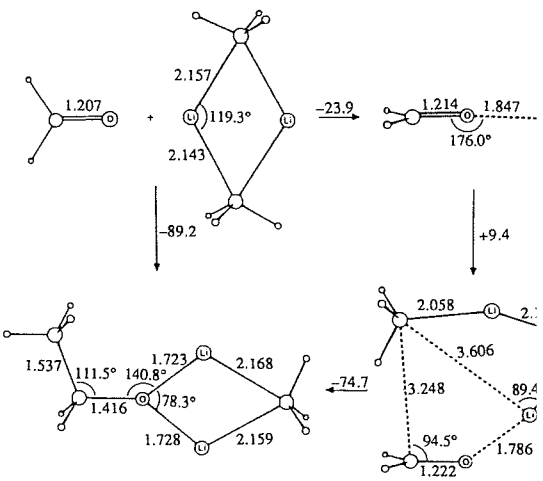
te Models. The stoichiometry of aldehyde, dialkylzinc, auxiliary strongly affects reactivity (Scheme 9) (*3*). Eth-:aldehyde does not occur in toluene at 0°C without added , however, addition of 100 mol % of DAIB to diethylzinc the reaction either. Only the presence of a small amount) of the amino alcohol accelerates the organometallic re-:ly to give the alkylation product in high yield. Dialkyl-ıction with DAIB, eliminate alkanes to generate alkylzinc ch are unable to alkylate aldehydes. Instead, the alkylzinc ıs excellent catalysts or, more correctly, catalyst dimers w) for reaction between dialkylzincs and aldehydes. The ence of the reactivity on the stoichiometry indicates that s per aldehyde are responsible for the alkyl transfer re-

olecular assemblies that have been proposed for the tran-shown in Scheme 13 (*14*, *19a*, *20g*). Bicyclic transition :s transfer of bridging alkyl group (R) to the terminally le, while transition structure **B** involves reaction between bridging aldehyde. The reaction may proceed via mono-:e six-membered transition state **C**. Transition structures l **C** were originally proposed for the reactions of orga-ɔmpounds and carbonyl substrates (*26*, *27*). Ab initio cal-:st that methyllithium dimer reacts with formaldehyde clic transition state related to **A** (*28*). The dinuclear Zn

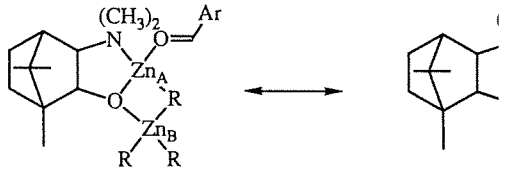


ısition state models. [E. Kaufmann, P. von R. Schleyer, K. N. Houk, *Am. Chem. Soc.*, **107**, 5560 (1985). Reproduced by permission of mical Society.]

■ Ab initio calculation of reaction of methyllithium dimer ar



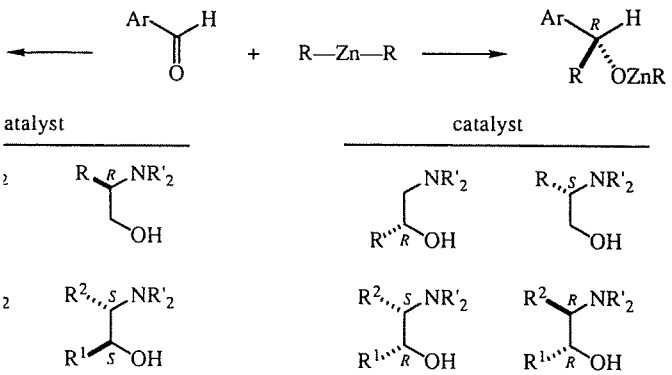
■ Property of the dinuclear Zn complex:



SCHEME 13. (*Continued*)

complex of Scheme 13 may be suitable for activa aldehyde and transferring an R group. The carbon nated to the more Lewis-acidic, DAIB-attached Zn_A Zn_B atom carries a nucleophilic R group as shown b formula. The latter situation is pronounced in trans

A survey of the literature (*3*) has led to the em Scheme 14, which says that the *α-S* or *β-*. *β*-dialkylamino alcohols consistently produces the the *α-R* or *β-S* configuration forms the *R* enantio absolute configuration is determined primarily by t containing *α* asymmetric carbon of the amino alcoh sense is in accord with all the bimetallic assemblies The preference of **A** over the diastereomeric struct enantiomer is interpreted in terms of relative nonb tween the terminal R group and hydrogen or an ar carbonyl substrate. Transition states **B** and **C** are a



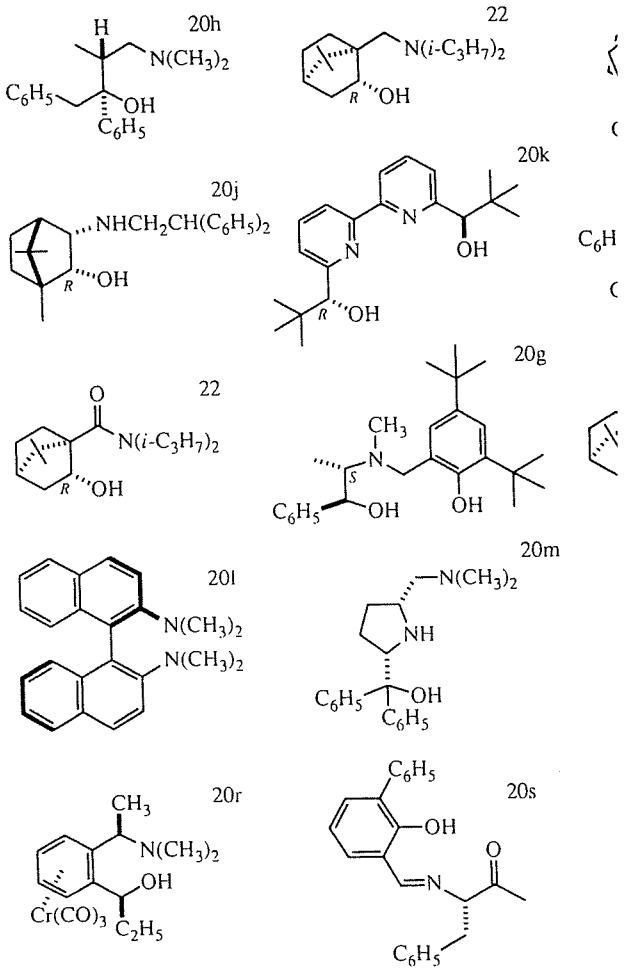
CHEME 14. General sense of asymmetric induction.

iastereomers, which suffer serious nonbonded interaction n_A–R and Ar groups. The configuration of the β-carbon-lamino moiety and the bulkiness of the nitrogen substit-ct the degree of enantioselection but do not override the carbon center. For example, in the ethylation of benzal-1*S*,2*R*)- and (1*S*,2*S*)-2-diethylamino-1,2-diphenylethanol duct in 94 and 81% ee, respectively (*15*). A similar ten-with (1*R*,2*S*)-*N*-ethylephedrine and (1*R*,2*R*)-*N*-ethylpseu-77% and 72% ee, respectively) (*29*).

ions Using Other Chiral Auxiliaries or Organometal-

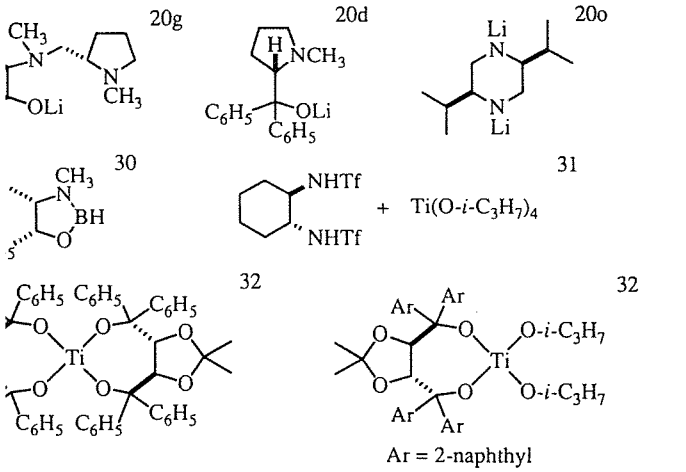
he simple β-dialkylamino alcohols listed in Scheme 11,) alcohols (*20h*, *22*), ferrocenyl amino alcohols (*20i*), bstituted amino alcohols (*20j*), hydroxymethylpyridines) alcohol chromium complexes (*20r*), Schiff bases (*19b*, lcohols (*22*), dialkylamino phenolic alcohols (*20g*), bis-ılcohols (*22*), diamino-binaphthyl (*20l*), and other che-an also be used as promoters (*3*). Examples are given in , proline-derived diamino alcohol acting as a tridentate s with diethylzinc to form a catalytically active mono-c complex (*20m*). β-Dialkylamino alcohols and the cor-disulfonylamino analogues may deliver the opposite ıse (*20t*). Although simple 1,2-diols do not accelerate the)-1,2-diphenylethane-1,2-diol brings about the enantio-ion of diethylzinc to aromatic aldehydes in up to 78% *20n*).

ly modified metallic compounds (or combined systems) ium (*20d*, *g*, *o*, *p*), boron (*30*), or titanium (*31*, *32*) also

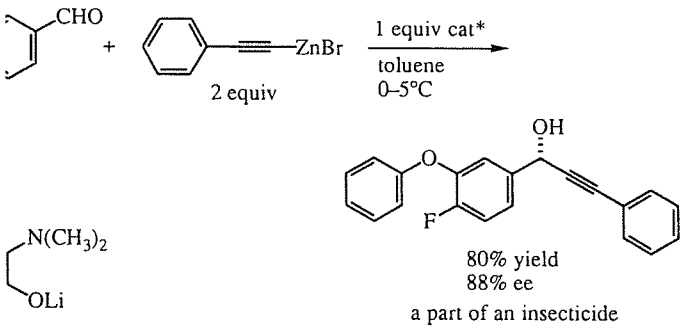


SCHEME 15. Effective chiral auxiliarie

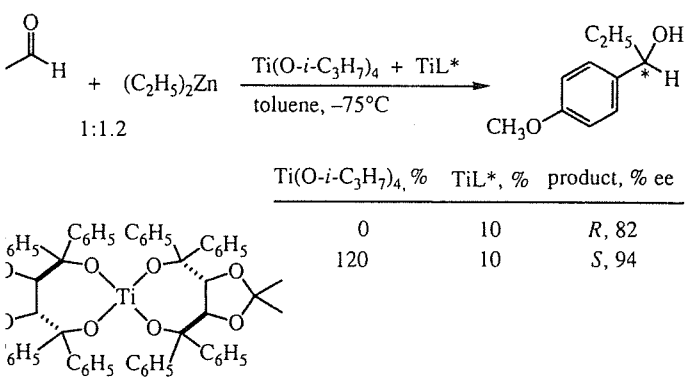
act as catalysts (Scheme 16). Enantioselective alky hyde was used for the synthesis of an alcoholic p (*20p*). Certain titanium complexes are particularly hyde and diethylzinc react with 0.1 equiv of the chir to give the *R* alcohol in 82% ee in 15% yield (Sc the presence of one additional equivalent of Ti(IV) the *S* enantiomer in 94% ee in 86% yield (*32*). The *situ* from Grignard reagent and zinc chloride can b ized dialkylzincs are conveniently prepared by the i reaction between organic iodides and diethylzinc (



oichiometric version):



SCHEME 16. Chiral metal catalysts.



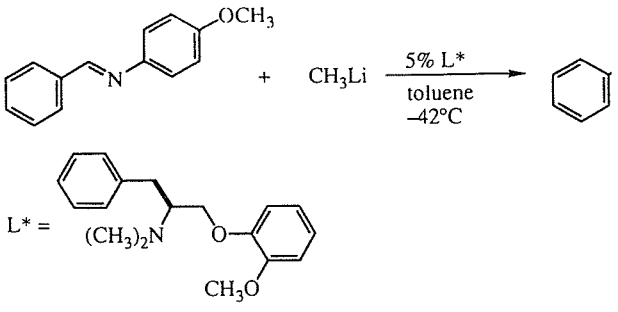
$Ti(O\text{-}i\text{-}C_3H_7)_4$, %	TiL*, %	product, % ee
0	10	*R*, 82
120	10	*S*, 94

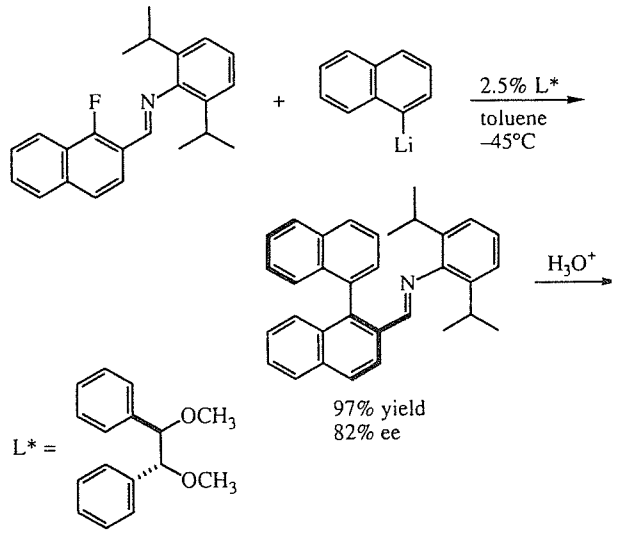
17. Enantioselective alkylation using a chiral titanate catalyst.

are easily converted to the corresponding zinc reage dimethyl- or diethylzinc (*34*). The DAIB-catalyzed hydes affords optically active allylic alcohols in 73-

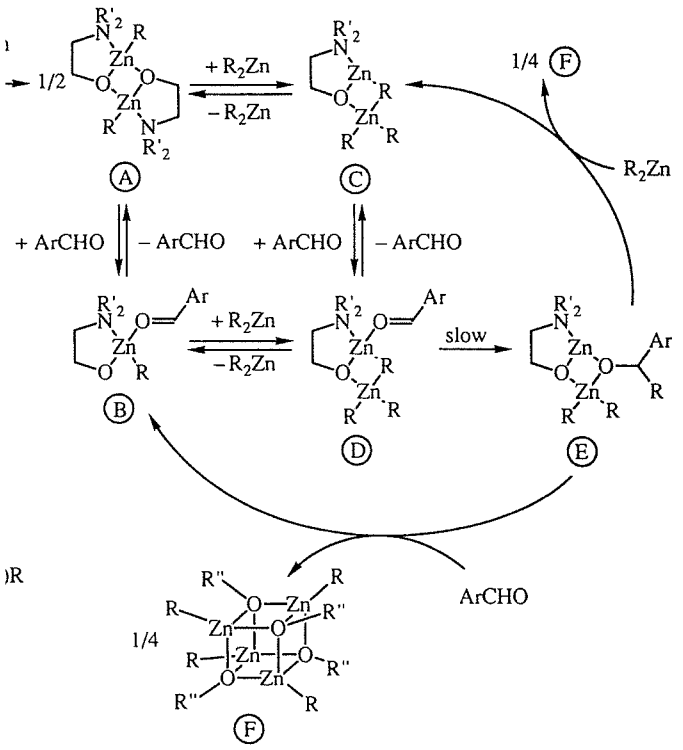
This type of catalytic strategy has recently been e selective addition of alkyllithiums to certain prochi 18) (*35*). Relevantly, in the presence of a small amo ligand, 1-naphthyllithium reacts with a sterically 1-fluoro-2-naphthaldehyde (conjugate addition/elin binaphthyl compound in greater than 80% ee.

Reaction Mechanism. The amino alcohol-catalyze by the mechanism illustrated in Scheme 19. First, t molar amounts of (−)-DAIB and dialkylzinc elim





SCHEME 18. Enantioselective reaction of organolithi



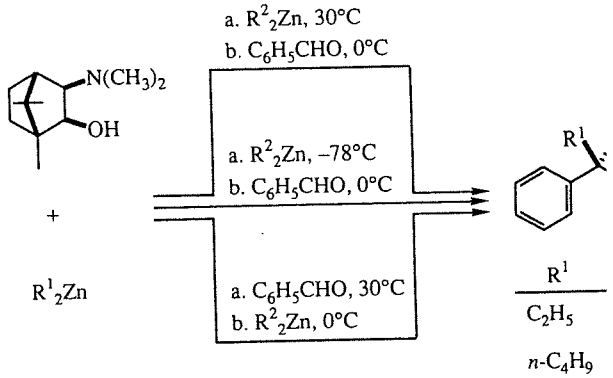
SCHEME 19. Reaction mechanism.

ylzinc alkoxide with a five-membered chelate ring. Mo- measurements indicate that this complex exists in aro- rbons as dimer **A** in equilibrium with a small amount of When **A** and an equivalent amount of benzaldehyde are neric structure of **A** is ruptured, probably via a dissocia- n, to produce an equilibrating mixture of **A** and **B**. The gand complex possesses an aldehyde and alkyl group in dination sphere and is incapable of undergoing intramo- ansfer reaction. Upon standing, this intermediate slowly yl alcohol, after aqueous workup. Further transformation addition of an equimolar amount of dialkylzinc to give nixed-ligand complex **D**. The dimer **A** is also cleaved by equiv of dialkylzinc to reversibly produce **C**. This new plex accepts benzaldehyde at its vacant coordination site tually, species **A**–**D** exist as a rapidly equilibrating mix- cies is also convertible with other possible structural iso- nolecular or intermolecular processes. In fact, the Zn–R

groups in the mixture of **A**–**D** are indistinguishable b copy. **D**, then undergoes intramolecular alkyl transfer state given in Scheme 13 to produce the alkoxide-bric product, **E** (molecular weight unknown). The final p isomer is stable enough to be observed in the NMR s reaction conditions but is kinetically labile. Thus, benzaldehyde or dialkylzinc, **E** instantaneously decon cubic alkylzinc alkoxide **F**, which is free of chiral D regenerates **B** for benzaldehyde or **C** for dialkylzinc. of the tetrameric structures of the alkylzinc alkoxides of these conversions. This mechanism has been supp isolation experiment using polymer-anchored DAIB

In the (−)-DAIB-catalyzed reaction of diethylzinc the rate is first-order in the amino alcohol. The initia influenced by the concentration of diethylzinc and soon becomes unaffected by increased concentratior standard catalytic reaction conditions, the reaction sh netics; the rate is zeroth order with respect to both and aldehyde substrate. These data support the prese rium of **A**–**D**, and alkyl transfer occurs intramolecu nuclear mixed-ligand complex **D**. This is the stere also turnover-limiting step.

The alkyl groups scramble during the reaction (3(of two different dialkylzinc agents, $R^1{}_2Zn$ and $R^2{}_2Z$ tical distribution of the possible alkylation products i

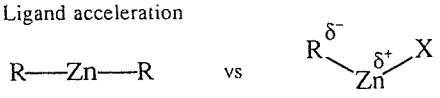


SCHEME 20. Alkyl scrambling.

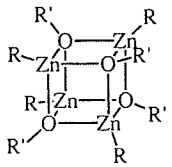
luct distribution is determined by the ratio of the two alkyl
ıd R^2, present in the reaction system and their reactivities,
:ally obtained relative reactivities are methyl : ethyl : *n*-bu-
3. The product ratio is neither influenced by the order of
e conditions, including temperature, of mixing the initially
3-chelated alkylzinc complex with benzaldehyde and the
inc agent.
-DAIB, a chiral amino alcohol auxiliary, efficiently pro-
antioselective addition of dialkylzincs to prochiral alde-
ıusly, the high stereoreguration relies on the appropriate
onal structure of this ancillary. In addition, several kinetic
ıine with this stereochemical effect to accomplish the ideal
atalysis (*3*). The first feature to be noted is the structure/
file of alkylzinc compounds. Monomeric dialkylzincs with
linear geometry at Zn are inert to carbonyl compounds
lkyl–metal bonds are rather nonpolar (*37*). However, the
can be enhanced by creating a bent geometry in which the
:s molecular orbitals (MOs) of a higher p character. In
ɔrdinatively unsaturated bent compounds with an electro-
tituent have the high donor ability of the alkyl group and
acter at the zinc center. Such an auxiliary-induced struc-
tion increases the reactivity toward carbonyl substrates
This activation, in fact, is achieved by modification by
gh the actual reaction proceeds through more complicated
ıpounds. Second, alkylzinc alkoxides tend to form stable
:s in hydrocarbons. Removal of such compounds from the
ıed alkylation products facilitates the catalytic cycle
The final product has virtually no effect on the rate or
ty of the alkylation (*38*). The third essential factor is steric
the auxiliary; DAIB and all other efficient chiral amino
l in Scheme 11 are sterically congested. Reaction of sim-
laminoethanol, which has a similar but uncongested struc-
ethyl- or diethylzinc produces alkanes and, as noted ear-
trimeric alkoxide (Scheme 21) (*39*). By contrast, when
1 dimethylzinc are mixed in a 1 : 1 mole ratio in toluene,
ɔlved and a dimeric methylzinc alkoxide is formed. This
:n proven by X-ray crystallographic analysis and cryo-
ılar weight measurement in benzene. Steric congestion
great rate enhancement (*see also* Scheme 8), because the
ide compounds can readily dissociate into the coordina-
ıted monomers that act as the actual catalysts, whereas

■ Stereodifferentiation by auxiliary

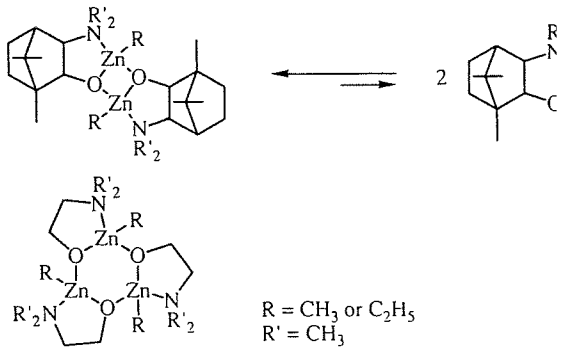
■ Ligand acceleration



■ Product stability



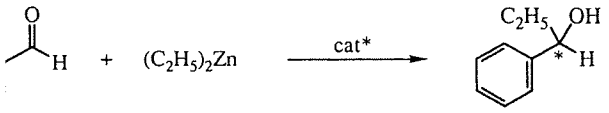
■ Congestion of auxiliary

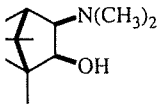
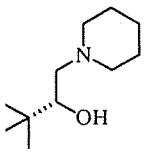


SCHEME 21. Origins of efficiency.

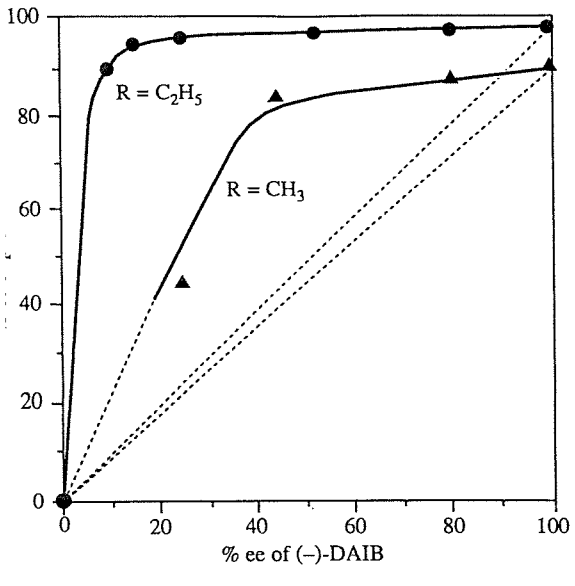
such trigonal monomeric species are difficult to gene
trimers.

Amplification of Chirality. Perhaps the most strik
sical aspects that emerge from the enantioselective a
nomenon illustrated in Scheme 22 (*3*, *14*, *16*, *20k*
nonlinear relation that allows for catalytic chiral am
tween the enantiomeric purity of the chiral auxilia
meric purity of the methylation or ethylation produc
ically, when benzaldehyde and diethylzinc react i
mol % of (−)-DAIB of only 15% ee [(−) : (+) =
ethylation product is obtained in 95% ee. This en
close to that obtained with enantiomerically pure (−
idently, chiral and achiral catalyst systems compet
tion. The extent of the chiral amplification is influen
including the concentration of dialkylzincs, benza



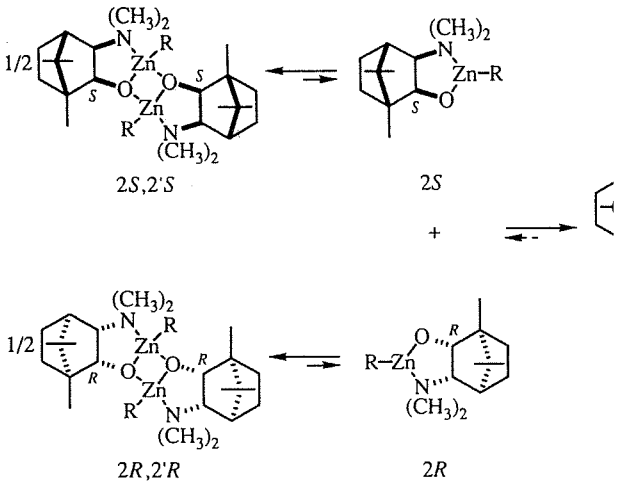
cat*		product	
structure	% ee	% ee	confign
	100	98	*S*
	15	95	*S*
	100	98	*R*
	11	82	*R*

SCHEME 22. Auxiliary ee versus product ee.



.42 M $(C_2H_5)_2Zn$, 0.42 M C_6H_5CHO, 34 mM DAIB, toluene, 0°C
.47 M $(CH_3)_2Zn$, 0.49 M C_6H_5CHO, 47 mM DAIB, toluene, 32°C

onlinear effect in DAIB-catalyzed reaction of R_2Zn and benzaldehyde.

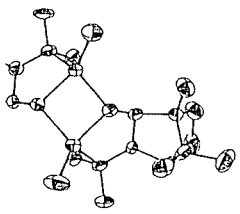


SCHEME 24. Enantiomer recognition of zinc alkoxides: ho
chiral dimerization.

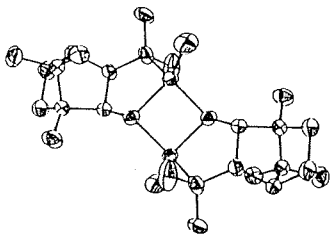
auxiliaries. Under certain conditions, the turnover ef
catalyst may become more than 600 times higher
existing achiral counterpart.

The origin of this chirality amplifying phenom
elucidated at the molecular structure level (*14*). Th
of the curve with respect to an *anticipated* linear cor
strict matching of chirality through mutual enantic
displayed by the thermodynamic relationship of Sc
catalyst that induces reaction of dialkylzinc and al
five-membered zinc alkoxide, which normally exis
dimer. The homochiral dimerization leads to 2*S*,2
with C_2 chirality, but the heterochiral interaction
monomers gives a meso 2*S*,2′*R* dinuclear comple
molar amounts of dimethylzinc and enantiomeric
with a 2*S* configuration affords the 2*S*,2′*S* dimer (
reaction with racemic DAIB affords the meso dime
sively. The molecular structures of these crystalli
termined by X-ray analysis are given in Scheme
meric 2*S*,2′*S* and 2*R*,2′*R* dimers in a 1 : 1 ratio in tol
produces only the meso compound. Thus, the he
of the enantiomeric monomers is overwhelming
homochiral interaction.

The chemical properties of these diastereomeric



2*S*,2'*S* dimer
C_2 chiral
reactive

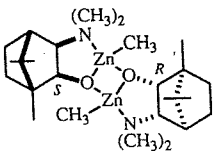


2*S*,2'*R* dimer
C_i meso
less reactive

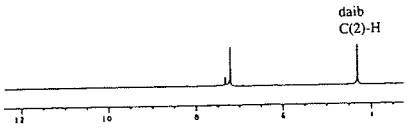
olecular structures of the complexes formed from $(CH_3)_2Zn$ and (−)-
IB.

different. Scheme 26 shows ^{1}H-NMR spectra of the meso
CH_3) and the mixtures with 1 equiv of dimethylzinc
dehyde in toluene-d_8. The structure of the achiral com-
cted by addition of organozinc and produces distinct Zn–
caused by the dimeric complex and dimethylzinc. Other
ing the aldehyde signal, also remain sharp. Thus, the
, dimethylzinc, and benzaldehyde exist as independent
ene. In sharp contrast, a mixture of the homochiral di-
x, dimethylzinc, and benzaldehyde in a 1 : 1 : 1 equivalent
a spectrum with a broad, inseparable singlet due to the
ups and a broad aldehydic proton signal. Obviously, rapid
f **A–D** (Scheme 19) occurs with this homochiral dimer,
ldehyde and coordinated benzaldehyde are not differen-
ergence of a small amount of the alkylation product **E** is
e spectrum. Thus, the thermodynamically favored meso
ctive, while the less stable chiral dimer easily enters the

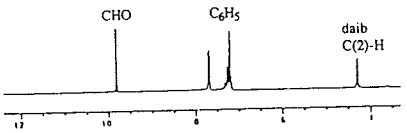
lly resolved (−)-DAIB is used, the two diastereomers are
thermodynamically controlled ratio. All the minor (+)-
converted to the meso dimer by taking an equivalent
)-enantiomer; the meso dimer does not dissociate. The
ier, which is present in excess, forms the less stable chiral
has a higher propensity to dissociate into the catalytic
phenomenon is explained by the X-ray crystallographic
cheme 25. The homochiral 2*S*,2'*S* dimer has a C_2 sym-
ire. The Zn_2O_2 four-membered ring is "endo-fused" to
)AIB–Zn five-membered rings because of the sterically
nane backbone and, notably, the central 5/4/5 tricyclic

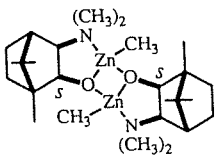


$Zn_2[(-)\text{-daib}][(+)\text{-daib}](CH_3)_2$

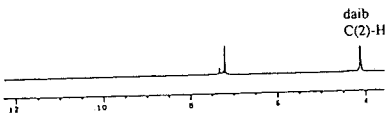


with
1 equiv $(CH_3)_2Zn$
1 equiv C_6H_5CHO

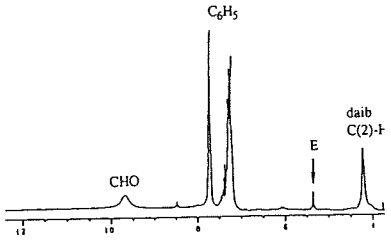




$Zn_2[(-)\text{-daib}]_2(CH_3)_2$



with
1 equiv $(C_2H_5)_2Zn$
1 equiv C_6H_5CHO



SCHEME 26. ^{1}H-NMR spectra in toluene-d_8 at 25°C. [M
Suga, and R. Noyori, *J. Am. Chem. Soc.*, **111**, 4028 (198
sion of the American Chemical Society.]

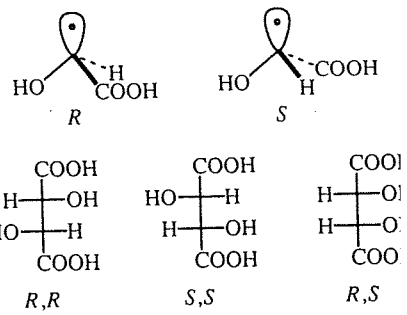
syn geometry. The heterochiral 2*S*,2′*R* dimer has a meso, he Zn_2O_2 part is endo-fused to the DAIB–Zn five-mem- in the homochiral compound, but the central 5/4/5 tri- ıas an anti arrangement. Evidently, the syn 5/4/5 fused ch more congested than the anti ring structure. The crys- ndicate that the angle between the five- and four-mem- he syn isomer is about 20° larger than the angle between anti stereoisomer. Consequently, in solution, the chiral ends to dissociate into its monomer to a greater extent neso dimer, and so exhibits a much greater turnover ef-

IB does, indeed, catalyze the reaction in the presence of of diethylzinc and aldehyde, although its reactivity is ın that of the the enantiomerically pure compound. This bly involves bimolecular reaction of the meso 2*S*,2′*R* di- lzinc or benzaldehyde. The possibility of reaction with s indicated by the dependence of the rate on the reagent oncentration. This dependence of reaction rate is unlike -catalyzed reaction, which shows saturation kinetics. for a given concentration of organozinc and aldehyde, e chiral amplification is greatly influenced by concentra- Greater amplification is obtained by using a higher DAIB

, the origin of the chiral amplification is basically the ability of the homochiral and heterochiral dinuclear Zn ese complexes act as catalyst precursors, but differences behavior also affect the degree of the nonlinear effect. on is probably the first example of elucidation of a mo- ism of catalytic chiral amplification (*41*) and may pro- l model of one means of propagation of chirality in na-

ERIC INTERACTION OF ENANTIOMERS

ognition is a general principle in chemistry. Molecular chieved by numerous electronic and steric factors in- . This is also the case among molecules with the same ion and connectivity. As illustrated in Scheme 27, chiral tartaric acid may be seen as a homochiral dimer of the lal radicals, respectively; meso tartaric acid is a result



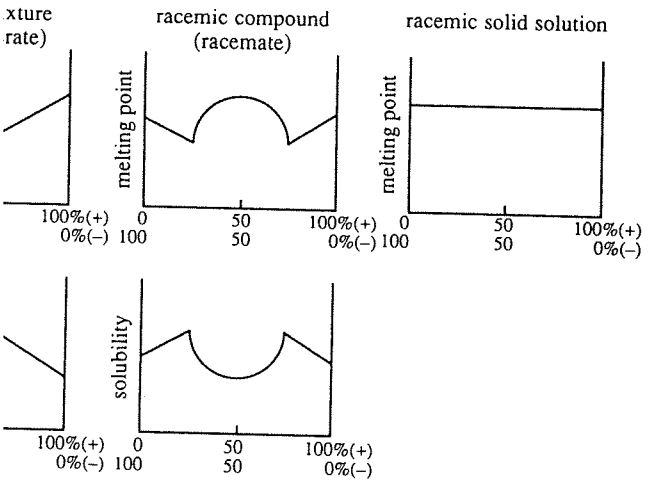
SCHEME 27. Mutual recognition of enantio

of heterochiral coupling of the enantiomeric radica meric interactions that form covalent bonds eviden Such enantiomer interactions, which are based on sembly, are also significant in various solid- and nomena related to physical, spectroscopic, and chı erties of chiral organic substances. Some examples effects are described below (*3*, *42*).

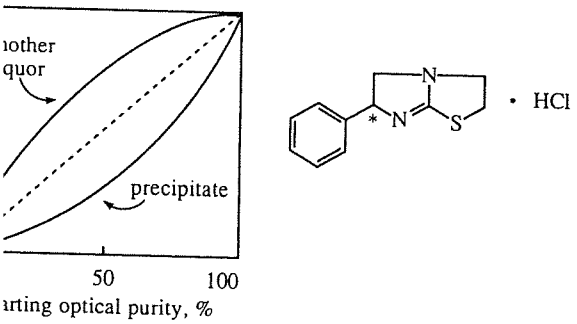
Effects on Solid-State Properties

Solubility and Melting Point. The strength of th tion generally decreases in the following order: cry tals > liquid phase > concentrated solution > d phase. Homochiral and heterochiral interaction of damental in crystal lattice formation, and results in erates, or multi-stage interactions. Recrystallizatioı pure compounds is simply based on the homochiral depending on the conditions, a mixture of enant either conglomerate, a 1 : 1 mixture of two enantioı compound arising from repeated heterochiral inter points and solubility are known to be affected by th enantiomers (Scheme 28). In some cases, a racem form. Resolution of conglomerates is often facili enantiomerically pure substance (*43*), whereas, in growth of one enantiomorph is retarded by additi of a foreign optically active compound (*44*).

Scheme 29 shows the results of titration of a ch chloride with aqueous sodium hydroxide in which the precipitate is lower than that of the original con



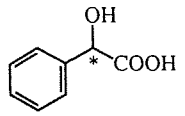
IEME 28. Solubility and melting point diagrams.



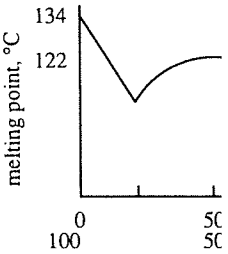
:omparison of optical purity during titration with aq NaOH.

ıtion may be caused by the presence of a specially
: with a eutectic point.

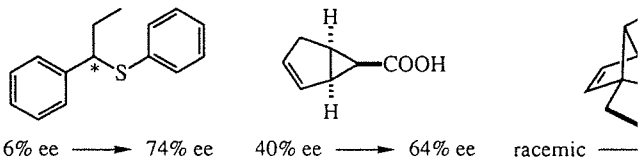
:h effects can also be seen in solid-gas interphase.
; the consequences of fractional sublimation of par-
nandelic acid (*47*). The optical purity could be en-
l, depending on the optical purity of the starting ma-
utectic point of mandelic acid is obtained with about
:r ratio, such a mixture is more readily sublimed than
ınglomerate. Scheme 30 gives other examples of op-
ıy sublimation. Phenyl 1-phenyl-1-propyl sulfide in
sublimed compound in 74% ee, but the residue is



sample	enantiomeric purity	% of L isomer
stg material	20.7	60.3
fraction 1	37.2	68.6
fraction 2	31.5	65.7
fraction 3	25.2	62.6
fraction 4	16.0	58.0
fraction 5	4.7	52.3
stg material	60.2	80.1
fraction 1	52.5	76.3
fraction 2	62.0	81.0
fraction 3	64.1	82.1
fraction 4	74.3	87.1



Related examples:

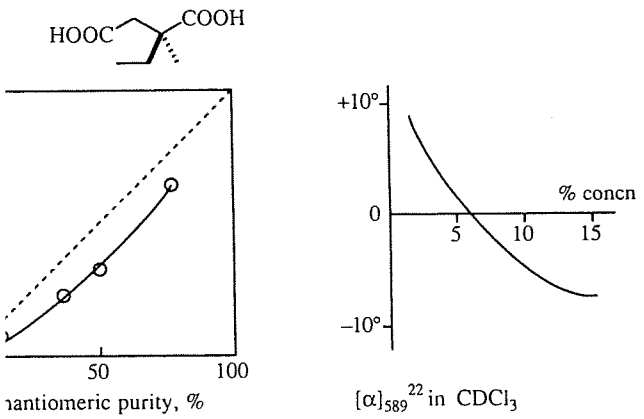


SCHEME 30. Fractional sublimation of L-mandeli

racemate (*48*). A similar trend has been seen with the
ylic acid given in the scheme (*47*). These results are c
tially resolved nonracemic chiral materials. On the oth
(*49*) found spontaneous resolution by sublimation o
pound (Scheme 30). Evacuation of the tetracyclic alc
20°C for several days gave a crystal of the sublimed
proven enantiomerically pure by X-ray analysis. Beca
needles were clustered and never very large, several
together for optical rotation measurements. As a resul
mixing of the two mirror-image forms. Nevertheless, t
tals were optically active, either dextrorotatory or levo
the residue was not.

Effects in Solution

Optical Rotation. Homochiral or heterochiral associa
usually labile. Enantiomeric excess of chiral compoun
affected to any noticeable extent by distillation (*50*, :

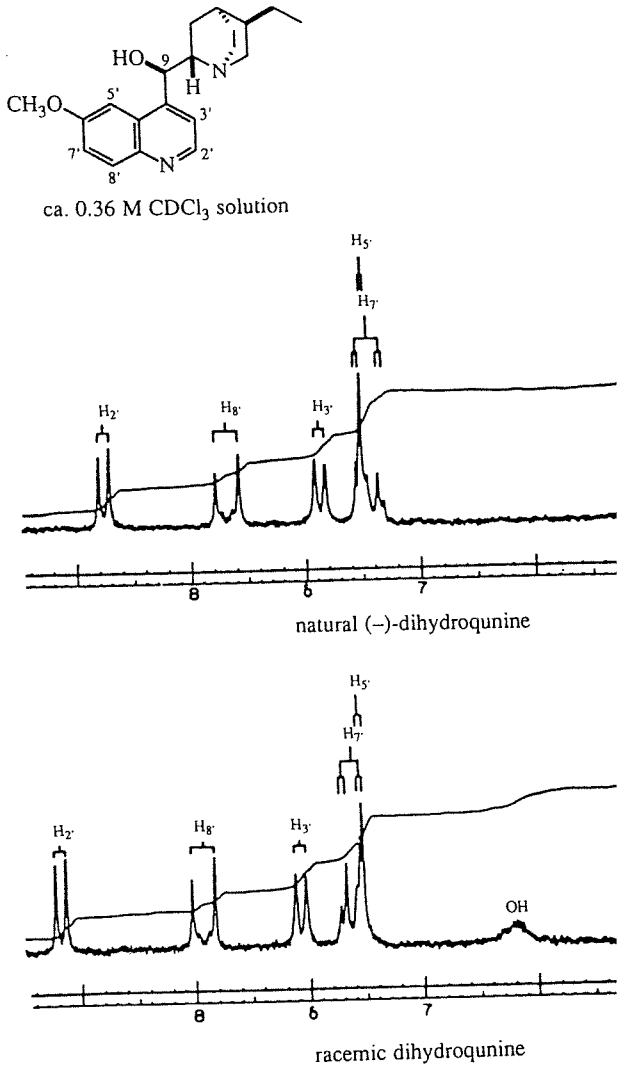


EME 31. Optical rotation versus enantiomeric purity.

of enantiomerically pure 2-octanol and the racemic com- / 2°C, indicating the diastereomeric nature of the inter- ılcohol enantiomers (*52*). Existence of such molecular solution was clearly shown by Horeau, who found that cal purity determined by rotation value, in general, need related (Scheme 31) (*50*, *51*). In some cases, the sign of ı opposite depending on the concentration of the solute, he molecular association.

Uskoković was probably the first to report the difference ? spectra of an optically pure compound and its racemate rated in Scheme 32, the spectra of optically pure dihy- the racemate differ significantly when taken at the same n chloroform-*d*. The spectrum of the partially resolved rds two sets of peaks whose areas are proportional to the t of each enantiomer. These observations can be under- lering the presence of the solute-solute interactions of the hus, to the extent that there is some solute aggregation, ay exhibit different spectra.

H-NMR spectra of nonracemic, but not enantiomerically of methylphenylphosphinic amide exhibit distinct ɔ signals (Scheme 33) that may be ascribed to dimer for- h hydrogen bonding (*54*). The enantiomerically pure luces the *P*-methyl proton signals at δ 1.74 ppm, whereas ives the corresponding signal at δ 1.685 ppm. The par- sample displays two sets of the signals. The hydrogen- hiral dimer is more stable than the heterochiral dimer. the enantiomeric *N*-acetylvaline *tert*-butyl ester exhibits

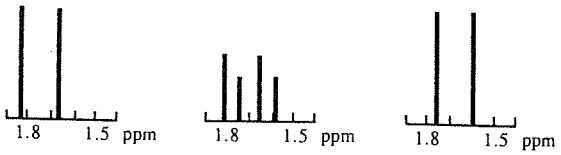


SCHEME 32. ^{1}H-NMR spectra of dihydroquinine. [T. Will Bommer, J. Gutzwiller, and M. Uskoković, *J. Am. Chem.* Reproduced by permission of the American Chemical Societ

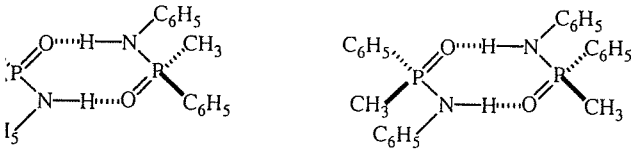
self-induced NMR nonequivalence through the d diastereomeric dimers interlinked via NH···O= (Scheme 33) (*55*). A similar self-induced anisoch with chiral 1,5-benzothiazepins and related compou groups of chiral compounds also cause NMR r Stannoxane compounds derived from partially res and dibutyltin oxide have been shown by ^{1}H NM

de dimers:

IC$_6$H$_5$



100% *S* 60% *S*, 40% *R* 50% *S*, 50% *R*



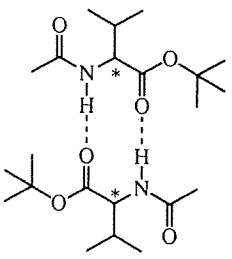
heterochiral homochiral

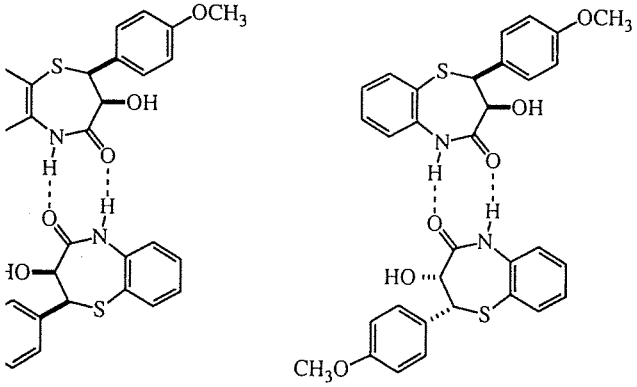
s:

J = 8.30 Hz

5 6.566 ppm

ıe NH proton of a 9:1
and D-*N*-acetylvaline
r, 0.1 M CCl_4 solution,





homodimer heterodimer

imers:

chiral meso

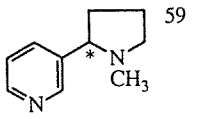
R = *n*-C_4H_9

: 33. ^{1}H-NMR difference of chiral dimeric compounds.

composed of the chiral and meso dimers (Scheme 3
tereomeric relationship may be used for analysis of
and the optical enrichment of such chiral diols. Recr
stannoxane in 75% ee from benzene gives crystals
leaves the sample in 37% ee in solution.

Chromatography. Under certain conditions, even h
erochiral self-assemblies can be separated by achir
chromatography of partially resolved enantiomers c
or enrichment of enantiomers on achiral stationary ph
mobile phase. ^{14}C-Labeled nicotine was first resolv
mers by high-performance liquid chromatography (H
stationary phase (Partisil-ODS or -SCX) through co
cally active nicotine (*59*). This observation was foll
of a number of chiral compounds by chromatograph
34). When a chiral diamide in 74% ee was separate

■ Partisil-ODS or -SCX



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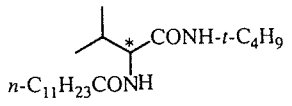
■ Silica gel



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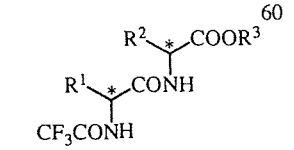
74% ee ⟶ 46% ee, 90% ee



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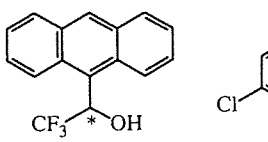
R^1 = $(CH_3)_2CH$ R^1 = CH_3
R^2 = $(CH_3)_2CH$ R^2 = H
R^3 = cyclohexyl R^3 = $(CH_3)_2CH$

■ Aminopropyl silica gel



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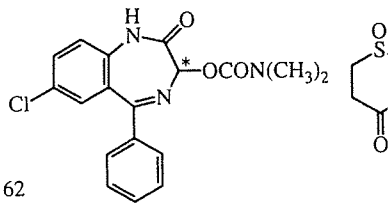

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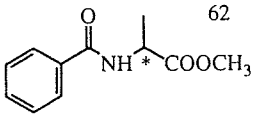

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SCHEME 34 Chromatographic separation of partially re