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Enantioselective alkylation of carbonyl compounds. From stoichiometric to catalytic asymmetric induction

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Abstract– Multinuclear organometallic species play a significant role in alkylation of carbonyl compounds. Enantioselective alkylation of aldehydes using a 1:1 reagent/substrate stoichiometry is achievable by chirally modified lithium/magnesium binary organometallic reagents. For example, diethylmagnesium treated with di-*O*-lithio-(*S*)-2,2'-dihydroxy-1,1'-binaphthyl reacts with benzaldehyde in a THF–dimethoxyethane mixture at –100 °C to give (*S*)-1-phenyl-1-propanol in 92% ee. In the presence of a catalytic quantity of (–)-3-*exo*-(dimethylamino)isoborneol (DAIB), reaction of dialkylzincs and aldehydes in nonpolar media is accelerated greatly to lead to the corresponding *S* alcohols in very high enantiomeric excesses (up to 99% ee). The enantioselective catalysis involves fluxional organozinc species and the product-forming dinuclear intermediate possesses DAIB auxiliary, an aldehyde ligand, and three alkyl groups, where it is the bridging alkyl group, rather than the terminal alkyls, that migrates from zinc to the carbonyl carbon.

Reaction of organometallic compounds with carbonyl substrates is one of the most fundamental operations in synthetic organic chemistry. There are two major ways to provide a chiral, nonracemic environment to the organometallic reagents, leading to enantiomeric alcoholic products (ref. 1 and 2). The first is coordination of chiral solvents or neutral complexing agent(s) to the metallic center (ref. 3 and 4), and the other method is the modification of the organometallics by protic chiral auxiliaries such as alcohols or amines, giving organometallic alkoxides or amides respectively (ref. 5 and 6). Although

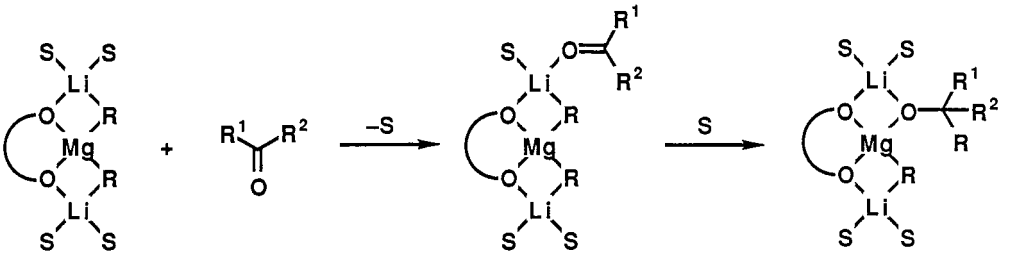
several successful results along these lines have been reported, high enantioselectivities have been obtained only by a careful combination of carbonyl compounds and organic groups (alkyl, aryl, etc.), and a general method is still elusive. In addition, most stereoselctive reactions of organolithium or -magnesium compounds so far recorded suffer from the necessity of using excess amounts (usually 4 equivalents or more) of chiral source to carbonyl substrates, which may be associated with aggregation of the chirally modified organometallic reagents. We aimed to attain a high level of enantioselective reaction with a stoichiometric, or hopefully catalytic, amount of chiral auxiliary per organometallic or carbonyl compound.

LITHIUM/MAGNESIUM BINARY ORGANOMETALLIC REAGENTS MODIFIED BY BINAPHTHOL

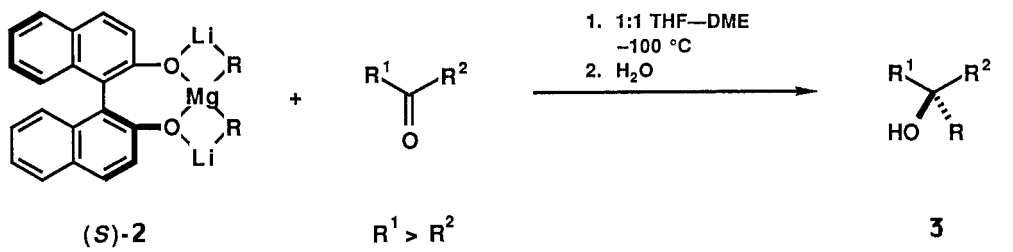
We planned to create lithium/magnesium binary organometallic agents having the empirical formula **1**, because (1) the requisite organometallic reagents are readily accessible, (2) such well-shaped, coordinatively saturated reagents consisting of tetrahedral lithium and magnesium metal centers could avoid the formation of complicated polymers or aggregates in ethereal solvents, and (3) the two kinds of metals

might play specific roles as the alkyl donor and carbonyl activator. The chemical and optical yields of organometallic alkylations are often variable. This can be a result of competing alkylating agents present in the reaction system, leading to products of opposite configuration at different rates. As such, the achievement of singularity of reactive species is significant for obtaining a high level of enantioselection in the reaction of Scheme 1, and bifunctional chiral modifiers with C_2 axis are particularly advantageous. We have been interested in the use of chiral 2,2'-dihydroxy-1,1'-binaphthyl (binaphthol) as an organometallic modifier in view of the excellent chiral recognition ability of the binaphthol-modified lithium aluminum hydride reagent (BINAL-H) (ref. 7) and aryltitanium reagents (ref. 6b) in reactions with carbonyl compounds.

Scheme 1



First, diethylmagnesium was chirally modified by the dilithio salt of binaphthol. Thus the ethylating agent, (*S*)-**2** (R = ethyl, empirical formula), possessing two homotopic ethyl groups, was prepared by treatment of enantiomerically pure (*S*)-binaphthol dissolved in THF with 2 equiv of *n*-butyllithium, and then 1 equiv of diethylmagnesium (ref. 8) at –78 °C. When benzaldehyde was reacted with this reagent (~0.07 M solution, 1:1 mole ratio and not excess) at –100 °C for 1 h, (*S*)-1-phenyl-1-propanol (**3**, R = ethyl, R^1 = phenyl, R^2 = H) was obtained after aqueous workup in 85% ee and 90% yield. The optical yield was improved by addition of dimethoxyethane (DME) and reached 92% when the reaction was carried out in a 1:1 mixture of THF and DME. The reaction mixture was a golden yellow solution, and apparent homogeneity persisted throughout the alkylation reaction. The degree of enantioselection was little affected by the extent of conversion of the starting materials. The ethylation of benzaldehyde using 4 equiv of (*S*)-**2** (R = ethyl) afforded the same enantioselectivity (*S*/*R* = 96:4), while the reaction with a half equiv of the reagent resulted in decrease in the selectivity, *S*/*R* = 91:9 (90% yield).



The level of stereoselectivity is highly dependent on the manner of preparation of the reagents. For example, the alkylating agent **2** (R = *n*-butyl), prepared by the standard procedure using (*S*)-binaphthol, 2 equiv of *n*-butyllithium, and 1 equiv of di-*n*-butylmagnesium (ref. 8), reacted with benzaldehyde at –100 °C in a 1:1 THF–DME mixture to give (*S*)-**3** (R = *n*-butyl) in 88% ee in 98% yield, whereas the reagent having the same empirical formula which was generated by treatment of (*S*)-binaphthol by 1 equiv of di-*n*-butylmagnesium and then 2 equiv of *n*-butyllithium led to (*S*)-**3** (R = *n*-butyl) in only 18% ee in 95% yield. The actual structures of **2** in these cases were different each other.

As shown in Table 1, a variety of aromatic aldehydes were alkylated in an enantioselective manner (>90:10) with the alkyl or phenyl reagents using a 1:1 stoichiometry, but satisfactory selectivity was not obtained by the allyl, vinyl, or acetylenic reagents. The enantioselective alkylation could be extended to aliphatic aldehyde substrates giving

TABLE 1. Enantioselective reaction of the lithium/magnesium reagent, (*S*)-**2**, and carbonyl compounds.[a]

Organometallic, (*S*)-**2**	Substrate, $R^1R^2C{=}O$		Solvent	Product		
R	R^1	R^2	(additive, equiv)	% yield [b]	% ee [c]	Confign[d]
CH_3	C_6H_5	H	1:1 THF–DME	75	82	*S*
C_2H_5	C_6H_5	H	ether [e]	82 [f]	64	*S*
C_2H_5	C_6H_5	H	THF	90 [f]	85	*S*
C_2H_5	C_6H_5	H	THF (DME, 2)	96 [f]	88	*S*
C_2H_5	C_6H_5	H	1:1 THF–DME	93	92	*S*
C_2H_5	C_6H_5	H	DME [e]	94 [f]	73 [g]	*S*
C_2H_5	C_6H_5	H	1:1 DME–hexane [g]	80	84	*S*
C_2H_5	C_6H_5	H	1:1 DME–toluene [g]	95 [f]	81	*S*
C_2H_5	C_6H_5	H	THF (HMPA,[h] 4)	60 [f]	6	*S*
C_2H_5	C_6H_5	H	THF (DMI,[h] 4)	90 [f]	75	*S*
C_2H_5	C_6H_5	H	THF (TMEDA,[h] 2)	92 [f]	85	*S*
C_2H_5	*p*-$CH_3OC_6H_4$	H	1:1 THF–DME	98	83	*S*
C_2H_5	*p*-ClC_6H_4	H	1:1 THF–DME	88	68	*S*
C_2H_5	(*E*)-$C_6H_5CH{=}CH$	H	1:1 THF–DME	97	37	*S*
C_2H_5	$C_6H_5CH_2CH_2$	H	1:1 THF–DME	40	85 [i]	*S*
C_2H_5	*n*-C_6H_{13}	H	1:1 THF–DME	86	85 [j]	*S*
C_2H_5	$(CH_3)_2CH$	H	1:1 THF–DME	99 [k]	37 [l]	*m*
C_2H_5	*c*-C_6H_{11}	H	1:1 THF–DME	68	84 [l]	*m*
C_2H_5	*n*-$C_5H_{11}C{\equiv}C$	H	1:1 THF–DME	97	55 [l]	*m*
C_2H_5	C_6H_5	CH_3	1:1 THF–DME	57	45 [n]	*m*
n-C_4H_9	C_6H_5	H	1:1 THF–DME	98	88	*S*
t-C_4H_9	C_6H_5	H	1:1 THF–DME	76 [f]	4	*m*
$CH_2{=}CHCH_2$	C_6H_5	H	1:1 THF–DME	70	17	*m*
C_6H_5	1-naphthyl	H	1:1 THF–DME	89 [f]	82	*m*
$CH_2{=}CH$	C_6H_5	H	1:1 THF–DME	75	12	*m*
$(CH_3)_3SiC{\equiv}C$	C_6H_5	H	1:1 THF–DME	47	14 [o]	*m*

[a] Reaction was carried out at –100 °C unless otherwise specified. [b] Yield after isolation by usual workup followed by silica-gel column chromatography. [c] Determined by HPLC analysis (Bakerbond DNBPG covalent column, 0.25–1% 2-propanol in hexane). [d] Based on sign of rotation. [e] Reaction at –78 °C. [f] ^{1}H-NMR analysis. [g] Reaction at –95 °C. [h] HMPA: *N,N,N',N',N'',N''*-hexamethylphosphoric triamide. DMI: 1,3-dimethyl-2-imidazolidinone. TMEDA: *N,N,N',N'*-tetramethylethylenediamine. [i] Determined by comparison of rotation value. [j] HPLC analysis of the (*R*)-1-(1-naphthyl)ethyl carbamate (Develosil 100-5 column, 1:100 ether-hexane). [k] GLC analysis. [l] HPLC analysis of the (*R*)-α-methoxy-α-[(trifluoromethyl)phenyl]acetate (Develosil 100-5 column, 1:20–100 ether-hexane). [m] Not determined. [n] ^{1}H-NMR analysis in the presence of Eu(hfc)$_3$. [o] ^{1}H-NMR analysis of the (*R*)-α-methoxy-α-[(trifluoromethyl)phenyl]acetate.

nonracemic secondary alcohols in >80% ee, which are difficult to obtain by enantioselective reduction of ketones. The alkylation of acetophenone formed a tertiary alcohol with moderate enantioselectivity. Binaphthol was the best C_2 chiral diol so far examined; use of (*R*)-10,10'-dihydroxy-9,9'-biphenanthryl, (*R,R*)-2,4-pentanediol, and (*R,R*)-2,3-butanediol in the ethylation of benzaldehyde (1:1 THF–DME, –100 °C) resulted in the *R* alcohol only in 40, 4, and 2% ee, respectively. Replacement of one of the ethyls in **2** by heteroatom moieties such as halogen, alkoxyl, diethylamino, etc. failed to improve the stereoselectivity. The enantioselectivity of the reaction of **2** (R = ethyl) was diminished by addition of 4 equiv of HMPA.

A 0.074 M THF-d_8 solution of di-*O*-lithiobinaphthol, prepared by mixing (*S*)-binaphthol and *n*-butyllithium in a 1:2 mol ratio followed by recrystallization from THF–hexane, exhibited a broad ^{7}Li-NMR signal at –0.25 ppm (LiCl in THF-d_8 as external reference, half-width 14 Hz at 20 °C). The aromatic protons also gave broad signals. However, addition of

1 equiv of diethylmagnesium to this solution sharpen the signals to a great extent, as illustrated in Fig. 1. The ^1H spectra of the ethylating agent **2** (R = ethyl) revealed a very sharp, single triplet and quartet due to the methyl and methylene protons at δ 1.32 and –0.92 (THF as internal standard), respectively, at temperatures ranging from 20 to –50 °C. The ^7Li-NMR, measured at 20 °C, showed a single signal (half-width 2.2 Hz) at –0.96 ppm, and this signal was broadened at –50 °C (–0.98 ppm, half-width 7.0 Hz). Obviously some equilibration such as exchange of coordinated THF molecules exists but such a dynamic effect does not affect magnetic environment of the ethyl protons to any great extent. Upon addition of benzaldehyde the spectra became complicated, giving several new broad ^7Li signals at lower field. Notably, however, the original –0.98-ppm signal due to **2** remained, though with decreased intensity, during the alkylation reaction.

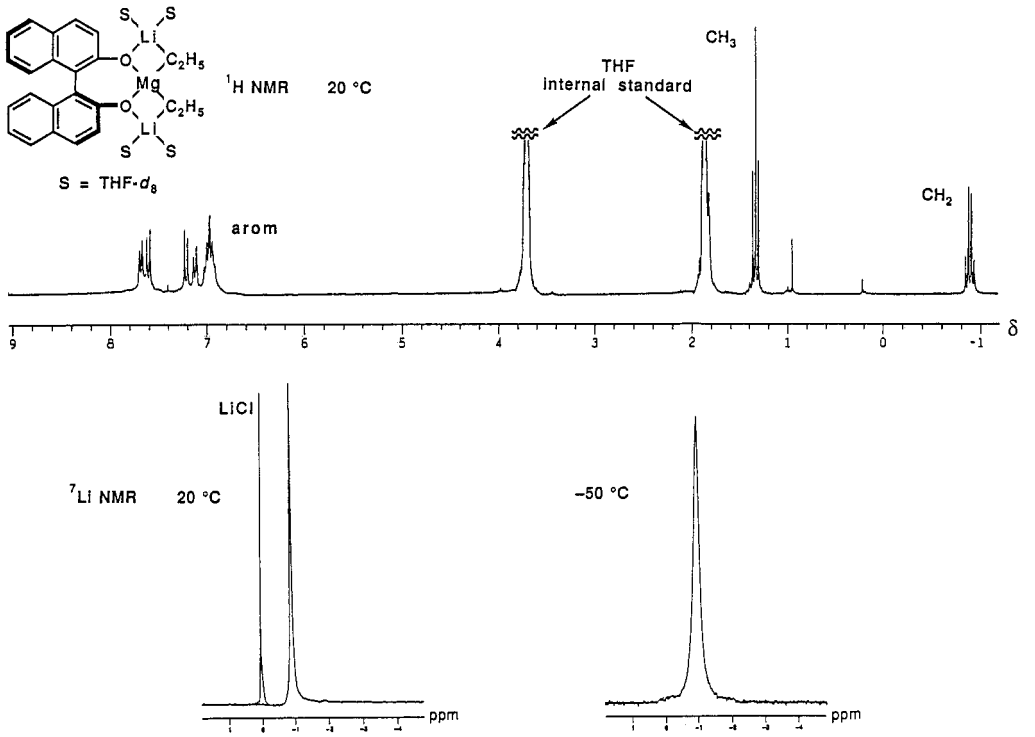


Fig 1. ^1H (top) and ^7Li (bottom) NMR spectra of the lithium/magnesium ethylating agent (a 0.074 M THF-d_8 solution).

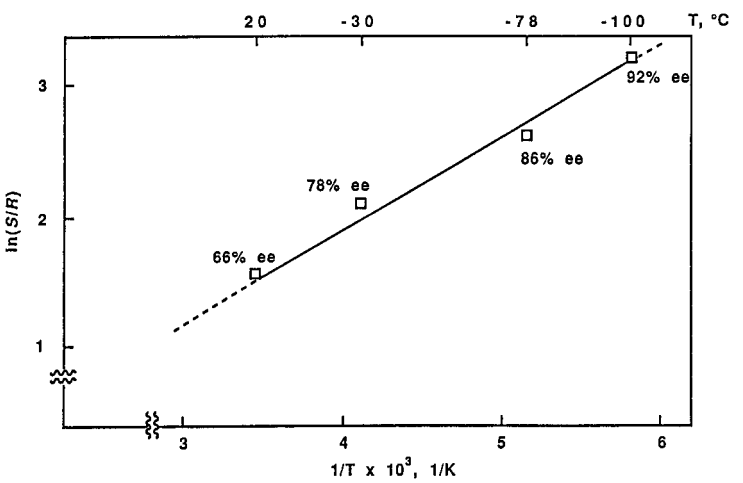
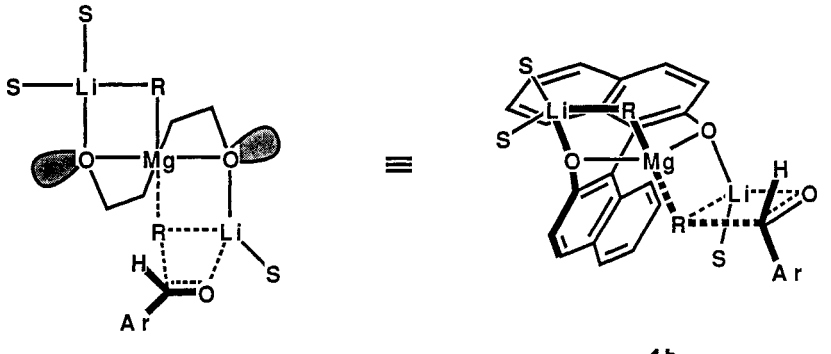


Fig 2. Temperature effects on the enantiomeric excess of the product in the reaction of (S)-**2** (R = ethyl) and benzaldehyde in a 1:1 THF–DME mixture.

The enantioselectivity of the ethylation of benzaldehyde appeared to increase monotonously on lowering the reaction temperature from 20 to -100 °C, as shown in Fig. 2. This tendency suggests the participation of a single organometallic reagent in the enantioselective alkylation over this temperature range and, from the line slope in Fig. 2, the difference in activation energy of the alkylation leading to the *S* and *R* alcohols is calculated to be 1.3 kcal/mol. In summary, although further efforts should be made to achieve generally high enantioselection, the present procedure provides an effective way to allow kinetic generation of single (or nearly so) chiral organometallic species. The possible transition state giving the enantiomeric product is illustrated by the structure **4** (naphthalene rings are omitted in **4a**).



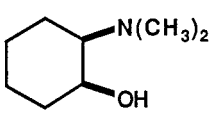
4a **4b**

ORGANOZINC REAGENTS MODIFIED BY CHIRAL AMINO ALCOHOLS

Since the discovery in 1966 of asymmetric cyclopropanation of olefins with diazoalkanes catalyzed by a chiral Schiff base/Cu(II) complex (ref. 9), a variety of homogeneous asymmetric reactions by metal complex catalysts have been developed. Most of them rely on transition metal chemistry but the chiral multiplication can also be achieved by main group elements. Monomeric dialkylzincs possessing an sp-hybridized linear geometry are inert to carbonyl compounds, because the alkyl-metal bond is rather nonpolar. However, addition of a ligand or auxiliary, generating a coordinatively unsaturated, bent structure, can accelerate the alkyl transfer reaction. Particularly, replacement of the alkyl groups by an electronegative substituent increases polarity of the alkyl–Zn bond, thereby enhancing the donor property of the alkyl group and the acceptor character of the Zn atom (ref. 10). Indeed, reaction of diethylzinc and benzaldehyde was reported to occur in the presence of a catalytic amount of (*S*)-leucinol giving (*R*)-1-phenyl-1-propanol in 48.8% ee (ref. 11).

unreactive reactive

We screened a variety of β-amino alcohols for activation of dialkylzincs and found impressive rate enhancement with some sterically constrained β-dialkylamino alcohols. In the reaction of diethylzinc and benzaldehyde in toluene, for instance, racemic **5** and **6** proved to be 10–100 times as effective as related acyclic dialkylamino alcohols or cyclic amino or monoalkylamino analogues of these compounds. With such information in hand, we selected as a chiral auxiliary 3-*exo*-(dimethylamino)isoborneol (DAIB) (**7**), a camphor-derived amino alcohol possessing the requisite structure (ref. 12). In fact, in the presence of 2 mol % of (-)-DAIB, reaction of diethylzinc and benzaldehyde (1.2:1 molar ratio) proceeded even more rapidly in toluene at 0 °C, and (*S*)-1-phenyl-1-propanol (**8**, R = ethyl, R' = phenyl) was obtained in 98% ee and in 97% yield (ref. 13). Table 2 exemplifies the enantioselective alkylation aided with DAIB. Enantioselectivity of the reaction of *p*-



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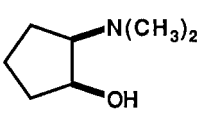

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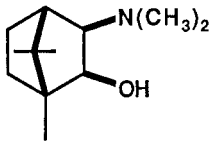

7, (–)-DAIB

substituted benzaldehydes is generally high. Certain α,β-unsaturated or aliphatic aldehydes can also be alkylated with a high degree of enantioselectivity (ref 14). Nonpolar solvents such as hexane, toluene, ether, or their mixtures afforded consistently satisfactory results, but use of THF retarded the reaction and lowered the enantioselectivity to some extent. Acetophenone or *n*-butyl acetoacetate was not alkylated under the standard conditions; propyl pyruvate was readily ethylated (even without DAIB) but the product was racemic. Dimethyl-, diethyl-, and di-*n*-butylzinc could be used as alkylating agents, though the methylation was rather slow. No asymmetric induction was observed in reaction of benzaldehyde and *n*-butyllithium, diethylmagnesium, or triethylaluminum in the presence of 2 mol % of DAIB.

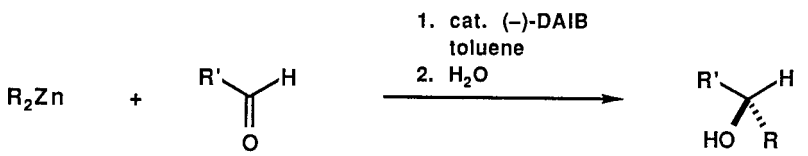

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TABLE 2. DAIB-aided enantioselective addition of dialkylzincs to aldehydes.[a]

Aldehyde	Alkylating agent	Conditions		Alkylated product		
		Solvent	Time, h	% yield [b]	% ee [c]	Config[d]
C_6H_5CHO	$(C_2H_5)_2Zn$	toluene	6	97	98	*S*
C_6H_5CHO	$(C_2H_5)_2Zn$	toluene	6	94	98	*R* [e]
C_6H_5CHO	$(C_2H_5)_2Zn$	hexane–toluene	6	94 [f]	98	*S*
C_6H_5CHO	$(C_2H_5)_2Zn$	ether–toluene	6	98 [f]	99	*S*
C_6H_5CHO	$(C_2H_5)_2Zn$	THF–toluene	64	44 [f]	91	*S*
C_6H_5CHO	$(n\text{-}C_4H_9)_2Zn$	toluene	24	97 [f]	95	*S*
C_6H_5CHO	$(CH_3)_2Zn$	toluene	70	59	91	*S*
p-ClC_6H_4CHO	$(C_2H_5)_2Zn$	toluene	12	86	93	*S*
p-$CH_3OC_6H_4CHO$	$(C_2H_5)_2Zn$	toluene	12	96	93	*S*
(*E*)-$C_6H_5CH{=}CHCHO$	$(C_2H_5)_2Zn$	toluene	6	81	96	*S*
(*E*)-$(n\text{-}C_4H_9)_3SnCH{=}CHCHO$	$(n\text{-}C_5H_{11})_2Zn$	toluene	24	84	85	*S*
$C_6H_5CH_2CH_2CHO$	$(C_2H_5)_2Zn$	toluene	12	80	90 [g]	*S*
$n\text{-}C_6H_{13}CHO$	$(C_2H_5)_2Zn$	toluene	24	81	61 [g]	*S*

[a] Reaction was carried out at 0 °C by using 2 mol % (–)-DAIB and 1.2 equiv of the alkylating agent per aldehyde. [b] Yield after isolation by distillation or silica-gel column chromatography. [c] HPLC analysis (Bakerbond DNBPG covalent column, 0.25–1% 2-propanol in hexane). [d] Based on sign of rotation. [e] (+)-DAIB was used. [f] HPLC analysis. [g] HPLC analysis of the (*R*)-1-(1-naphthyl)ethyl carbamate (Develosil 100-3, 1:2 ether–hexane).

Notably, a catalytic quantity of DAIB accelerates the alkylation reaction. As illustrated in Table 3, the stoichiometry of aldehyde substrate, alkylzinc, and DAIB auxiliary has marked effects on the reaction rate and course. Diethylzinc does not react with benzaldehyde at 0 °C in toluene. A complex formed by mixing equimolar amounts of diethylzinc and DAIB (evolution of ethane was observed) did not alkylate the aldehyde either; instead benzyl alcohol was formed slowly. Ethylation of benzaldehyde thus occurred only when diethylzinc/DAIB ratio was greater than 2. These results clearly indicate that two Zn species per aldehyde are responsible for the alkylation reaction (ref. 13 and 14c).

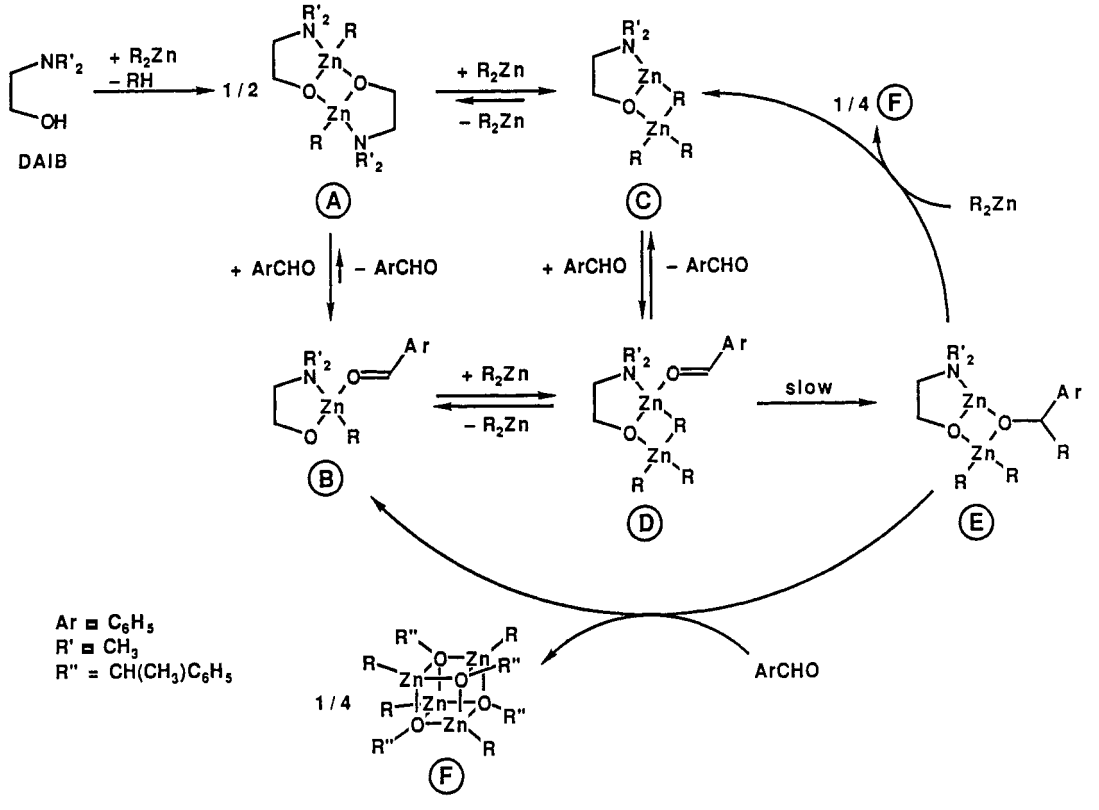
TABLE 3. Effect of the ratio of benzaldehyde/diethylzinc/DAIB on the reactivity.[a]

Molar ratio			(S)-1-Phenyl-1-propanol		Benzyl alcohol
C_6H_5CHO	$(C_2H_5)_2Zn$	(-)-DAIB	% yield [b]	% ee [c]	% yield [b]
1	1	0	0	–	1 [d]
1	1	1	1	0	29
1	2	2	0	–	64 [e]
1	2	1	88	98	1
1	1	0.5	49	96	13
1	1	0.02	97	98	1
1	0.5	0.01	48	98	12 [f]

[a] Reaction was carried out in toluene at 0 °C for 170 h. [b] HPLC analysis. [c] HPLC analysis (Bakerbond DNBPG covalent column, 0.25–1% 2-propanol in hexane). [d] Reaction for 1 h. [e] Reaction for 1500 h. [f] Propiophenone was obtained in about 10% yield.

We propose the alkylation mechanism of Scheme 2. First, reaction of DAIB and a dialkylzinc produces the dinuclear Zn complex A, which is unable to alkylate aldehydes but acts as catalyst precursor. The dimeric structure is cleaved by addition of either aldehyde substrate or another dialkylzinc molecule, leading to B or C, respectively. The mononuclear complex B reacts with dialkylzinc to generate the dinuclear complex D, which undergoes an alkyl transfer reaction. Coordination of an aldehyde to the dinuclear species C also leads to the product forming complex D. Finally, resulting E upon interaction with aldehyde produces the Zn alkoxide tetramer F and the key species B, completing the catalytic cycle. Reaction of E and dialkylzinc produces F and C (ref.15).

Scheme 2



When (-)-DAIB and dimethylzinc were mixed in 1:1 mol ratio in toluene-d_8, methane was evolved and a single dimeric compound A (R = methyl), among three possible stereoisomers, was formed (MW obsd. 530, calcd. 553). The ^{1}H-NMR exhibited a sharp singlet due to Zn–methyl at 25 (δ -0.20) to -80 °C (δ 0.10). The molecular structure

determined by single-crystal X-ray analysis is given in Fig. 3. The central Zn_2O_2 four-membered ring has a syn geometry and is "endo-fused" to the adjacent five-membered rings. The dinuclear framework of A is readily broken under the reaction conditions. First, reaction of A (R = methyl) and benzaldehyde formed the mononuclear complex B. This process is reversible, giving a broad aldehydic proton signal in the ^{1}H-NMR spectrum at 0 °C, and the position of the equilibration depends on the A/aldehyde mol ratio as revealed by cryoscopic molecular-weight (MW) determination (MW obsd. 338 (A/benzaldehyde = 1:2), calcd. 383) (ref. 16). The alkyl group in B did not migrate to the aldehyde ligand. Dialkylzincs also cleaved the dimeric structure of A. Upon mixing A (R = methyl or ethyl) and dialkylzinc, a new, unsymmetrical dinuclear complex C emerged (MW obsd. 377 (A/diethylzinc = 1:2), calcd. 414). The formation of C was also reversible. With the ethyl complex no sign of occurrence of higher aggregates was observed in a 0.052–0.17 M concentration range; addition of large excess of diethylzinc did not affect the MW either. The methyl complex, unsaturated at Zn, is fluxional and three different Zn–methyl groups undergo rapid exchange (ref. 17), exhibiting a ^{1}H-NMR signal at δ −0.27 as a very sharp singlet at 25 °C, and as a somewhat broad singlet at −50 °C. When 1 equiv of benzaldehyde was introduced to a toluene solution of C (R = methyl) at 0 °C, a new dynamic system containing D was produced. The same equilibrating mixture was obtained by mixing B and dialkylzinc in 1:1 ratio. The ^{1}H-NMR spectrum, giving very broad signals (C_6H_5CHO, δ 9.7, and Zn–methyl, δ −0.25), indicated the presence of an equlibrium, B⇄D⇄C. Then the methyl transfer occurred in D slowly below room temperature to give an alkoxide assignable to E (R = methyl). In the ^{1}H-NMR spectrum, methyl and methine protons due to the Zn alkoxide afforded a doublet at δ 1.93 and a quartet at δ 5.36, respectively, whereas the Zn–methyl signal appeared as a broad singlet at δ −0.17. This complex was rather stable under such conditions but, upon exposure to benzaldehyde or dimethylzinc, underwent rapid decomposition to form the cubic Zn alkoxide tetramer F (R = methyl) [MW obsd. 759, calcd. 806. ^{1}H-NMR δ −0.44 (singlet, Zn–methyl), 1.72 (doublet, alkoxide methyl), and 5.13 (quartet, alkoxide methine)].

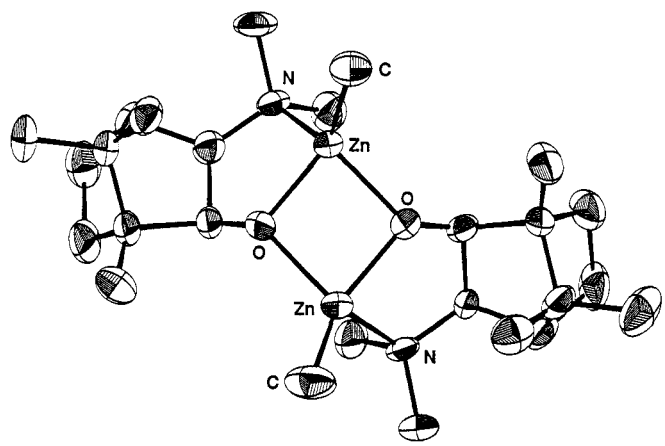


Fig 3. Molecular structure of A (R = methyl) formed from (−)-DAIB and dimethylzinc.

In accord with the fluxional nature of the intermediates, when two different alkylzinc agents were employed, a statistical distribution of the possible products was observed. The results are summarized in Table 4. The product ratio was determined only by a statistical ratio of the two alkyl groups and their relative reactivities (methyl:ethyl:*n*-butyl = 1:20:8) and not influenced by the order, or conditions including temperature (−78 to 30 °C), of mixing the aldehyde and the second dialkylzinc to the initially formed dimeric Zn chelate complex A (ref. 18). The preliminary kinetic measurement using diethylzinc, benzaldehyde, and DAIB in toluene at 0 °C indicated that the reaction is first order in DAIB auxiliary (and then A) and zero order in the dialkylzinc and aldehyde substrate. The degree of enantioselectivity was lowered considerably by raising reaction temperature from −20 °C (*S*/*R* = 99:1) to 50 °C (94.5:5.5). These facts, coupled with the ^{1}H-NMR observation, suggests that the alkyl transfer step, D→E, is the turnover-limiting as well as the stereodetermining step.

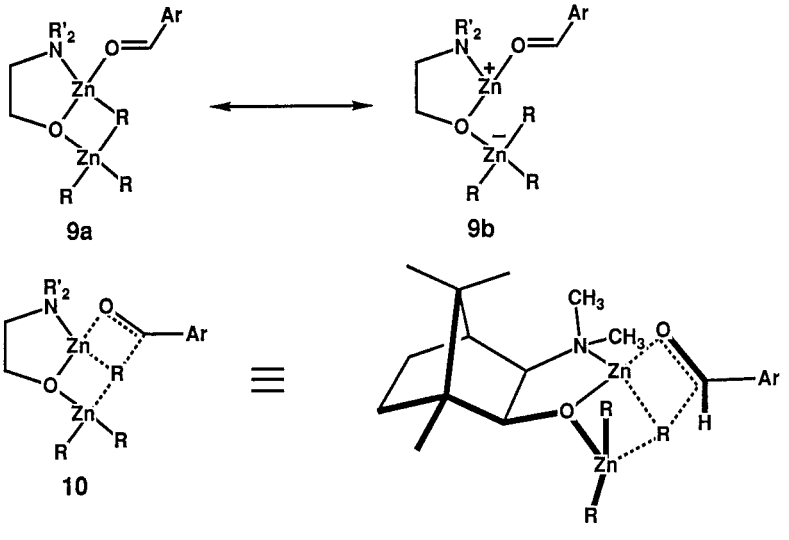
TABLE 4. Scrambling experiments using DAIB, $R^1{}_2Zn$, $R^2{}_2Zn$, and benzaldehyde in 1:1:1:1 ratio [a]

Dialkylzincs		Product ratio [b]			Rel. reactivity
$R^1{}_2Zn$	$R^2{}_2Zn$	$C_6H_5CH(OH)R^1$	$C_6H_5CH(OH)R^2$	$C_6H_5CH_2OH$	R^1/R^2
CH_3	C_2H_5	2	93	3	1/21
C_2H_5	CH_3	76	8	3	19/1
C_2H_5	*n*-C_4H_9	44	35	14	2.5/1
C_2H_5 [c]	*n*-C_4H_9	41	35	14	2.3/1
C_2H_5 [d]	*n*-C_4H_9	41	32	13	2.6/1
C_2H_5 [e]	*n*-C_4H_9	38	32	14	2.4/1
C_2H_5 [f]	*n*-C_4H_9	39	32	12	2.4/1
n-C_4H_9	C_2H_5	14	68	7	1/2.4
n-C_4H_9 [c]	C_2H_5	14	68	7	1/2.4
n-C_4H_9 [d]	C_2H_5	13	66	7	1/2.5
n-C_4H_9 [e]	C_2H_5	14	67	7	1/2.4
n-C_4H_9 [f]	C_2H_5	13	70	7	1/2.7

[a] $R^1{}_2Zn$ was first added to a toluene solution of (-)-DAIB at 30 °C and, after 15-min, $R^2{}_2Zn$ was added. After the mixture was stirred for 10 min and cooling down to 0 °C, benzaldehyde was added. The mixture was stirred at 0 °C for 6 h and quenched with water. [b] Ratio was determined by HPLC analysis (Develosil 100-5, 1:2 ether–hexane). [c] After addition of $R^2{}_2Zn$, the mixture was stirred for 24 h at 30 °C, and then benzaldehyde was added at -78 °C. [d] $R^2{}_2Zn$ was added to the initially formed complex and the mixture was stirred at -78 °C prior to addition of benzaldehyde. [e] Benzaldehyde was added prior to addition of $R^2{}_2Zn$. [f] Benzaldehyde was added at -78 °C prior to addition of $R^2{}_2Zn$, and the mixture was stirred at 0 °C for 6 h.

Interestingly, the degree of the enantioselection does not linearly correlate to enantiomeric purity of the chiral auxiliary. For example, reaction of diethylzinc and benzaldehyde catalyzed by 2 mol % of (-)-DAIB in 35% ee (toluene, 0°C, 24 h) afforded the S ethylation product in 92% ee (90% yield) (ref. 18). NMR analysis indicated that reaction of (±)-DAIB and dimethylzinc in a 1:1 ratio did not form racemate of A (R = methyl), and the newly generated dimeric complex (MW of the ethyl complex, obsd. 537, calcd. 581) was not affected by addition of benzaldehyde or dimethyzinc.

The sterically demanding DAIB auxiliary plays a significant role in the efficient and selective creation of the chiral Zn chelate complexes. All the dinuclear Zn complexes, C–E, would have a single four-membered ring geometry, viz., "endo fusion" to the DAIB five-membered chelate, as has been observed in the complex A. In the product-forming complex D containing two Zn atoms, the more Lewis-acidic DAIB-chelated Zn atom accommodates the aldehyde substrate. Here the bridging R, rather than the terminal R, acts as the migrating group, because the Zn–R(bridging) linkage is more polarizable than the Zn–R(terminal) bond. In going from the ground state to transition state, electrophilicity of the aldehyde and nucleophilicity of the alkyl group must be enhanced.



As easily seen from the polar structure **9b**, the transition state is most stabilized by such ligand arrangement. Thus the bridging R in **9** migrates to the electron-deficient carbonyl carbon via the transition state **10.** Molecular model inspection suggests that the kinetic bias leading to the *S*-configurated alkoxide derives primarily from a nonbonded repulsion between the carbonyl substituents (Ar and H) and a terminal R group attached to Zn. The transition state structure **10** features a tricoordinate structure for the migrating R. Such a nonclassical mechanism has been advanced theoretically for the addition of dimeric methyllithium to formaldehyde (ref. 19).

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