Enantioselective Addition of Organozinc Reagents to Aldehydes

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Contents

Kenso Soai was born in 1950 in Hiroshima, Japan. He received his B.S. in 1974 and his Ph.D. in 1979 with Prof. Teruaki Mukaiyama from the University of Tokyo. He then moved to the United States and spent 17 months as a postdoctoral associate with Prof. Ernest L. Eliel at the University of North Carolina at Chapel Hill. He returned to Japan in 1981 and joined the faculty of Science University of Tokyo, where he is currently a full professor. At the age of 30, he began independent research, which is rare among Japanese universities. He received Progress Award in Synthetic Organic Chemistry, Japan, in 1988 and Chisso Award in Synthetic Organic Chemistry, Japan, in 1990. His research interests include the methodology of organic synthesis, especially enantioselective and diastereoselective synthesis and chemoselective reduction, and the design of chiral catalysts. In the long term, he plans to apply these methodologies to the synthesis of the compounds of biological interest and new materials.

Seiji Niwa was born in 1962 in Sendai, Japan. He received B.S. in 1986 and his Ph.D. in 1991 with Kenso Soai from Science University of Tokyo for his work entitled *Study on the Asymmetric Synthesis of Optically Active Alcohols Using Organozinc Reagents*. He is a coauthor of 16 scientific papers with K. Soai. He joined Ajinomoto Co., Inc. in 1991, where he continues research at Central Research Labs.

I. Introduction

Enantioselective addition of organometallic reagents to aldehydes affords optically active secondary alco-

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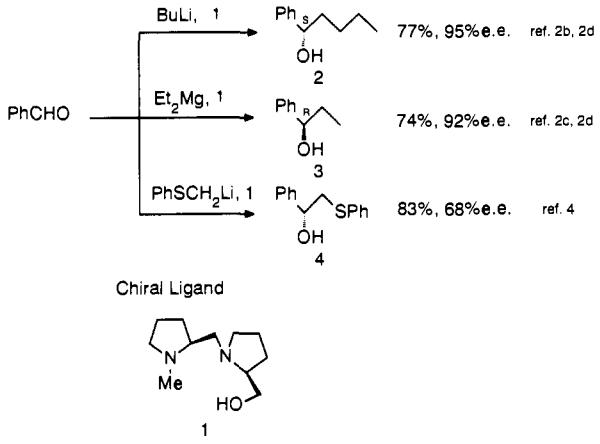
Scheme 1



hols. The reaction is one of the most important and fundamental asymmetric reactions. The optically active secondary alcohols are components of many naturally occurring compounds, biologically active compounds, and materials such as liquid crystals. They are also important as synthetic intermediates of various functionalities such as halide, amine, ester, ether, etc.

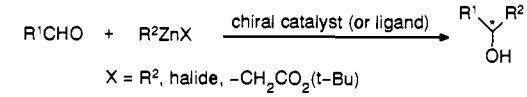
Two major methods for the enantioselective synthesis of optically active secondary alcohols are the enantioselective alkylation of aldehydes (i.e., addition of organometallic reagents to aldehydes)[1] and the enantioselective reduction of ketones. The former reaction can achieve at the same time the formation of optically active alcohols and the construction of the carbon skeleton of the alcohol (carbon–carbon bond formation). Despite the advantage of the reaction, the enantioselectivity of the addition of organometallic reagents to aldehydes has been only low to moderate.

It was not long ago that an enantioselectivity of over 90% was first achieved in this reaction. Mukaiyama et al. reported the highly enantioselective addition of alkyllithium and dialkylmagnesium to aldehydes in the presence of a lithium salt of the chiral diamino alcohol 1 derived from (*S*)-proline (Scheme 1).[2] (*S*)-1-Phenylpentanol (**2**) with 95% ee and (*R*)-1-phenylpropanol (**3**) with 92% ee were obtained from the enantioselective addition of butyllithium and diethylmagnesium, respectively, to benzaldehyde.

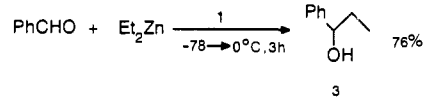
Several other highly enantioselective chiral ligands have been reported for the addition of alkyllithium, Grignard reagents, and alkyltitanium to aldehydes.[3] In many cases, the chiral ligands can be recovered and used repeatedly. These methods require at least a stoichiometric amount of chiral ligands for the high enantioselection because these organometallic reagents, even without the influence of chiral ligands, react with aldehydes to afford racemic alcohols. Therefore, catalytic enantioselective addition of organometallic reagents to aldehydes is a challenging problem.

Donor atoms such as nitrogen and oxygen of the chiral ligands coordinate the metal atoms of the organometallic reagents to form chiral complexes which differentiate the enantioface of the aldehydes. The nucleophilicity and basicity of organometallic reagents coordinated by chiral ligands are sometimes stronger than those of the original organometallic reagents. For an example of the enhancement of nucleophilicity, Cram described the catalytic effect of chiral diamine in the

Scheme 2



Scheme 3



reaction of alkyllithium with aldehydes although the catalytic efficiency was not enough.[3a] For an example of the enhancement of nucleophilicity, *n*-butyllithium coordinated with chiral amino alcohol abstracts a proton from methyl phenyl sulfide to form [(phenylthio)methyl]lithium. The subsequent reaction with benzaldehyde afforded the corresponding sulfide–alcohol with 68% ee in 83% yield (Scheme 1).[4]

In contrast, organozinc reagents have been known for many years. In fact, Frankland discovered the first organometallic compound, diethylzinc.[5] The preparative method of dialkylzincs and alkylzinc halides has been well documented.[6] The main utilization of organozinc reagents in organic synthesis includes the Simmons–Smith reaction, the Reformatsky reaction, and the polymerization of oxirane.[7] On the other hand, the addition reaction of dialkylzinc to aldehydes is much slower than the corresponding reactions of alkyllithium and Grignard reagents.[8] Thus, in modern organic synthesis, dialkylzinc is not often utilized for the addition reaction to aldehydes.

Recently some methods for the enhancement of the nucleophilicity of dialkylzinc and related organozinc reagents have appeared. Many important optically active compounds have been synthesized using various kinds of chiral compounds as chiral catalysts for the enantioselective addition of organozinc reagents to aldehydes (Scheme 2).

Our purpose in collecting the papers published up to the first half of 1991 in this rapidly growing field was to classify the chiral catalysts and to describe the characteristic features of each chiral catalyst.[9]

II. Chiral Catalysts for the Enantioselective Addition of Dialkylzincs to Aldehydes

A. Homogeneous Chiral Catalysts

1. Chiral Amino Alcohol

The addition of dialkylzincs to aldehydes has rarely been utilized in organic synthesis, because the reaction is extremely sluggish and because a side reaction such as reduction usually occurs.[8] The clean nucleophilic addition of diethylzinc to benzaldehyde was reported by Mukaiyama et al. in the presence of β-amino alcohol 1 derived from (*S*)-proline.[2c,d] β-Amino alcohol 1 accelerates (catalyzes) the carbon–carbon-bond-forming reaction to afford 1-phenylpropanol (**3**) in 76% yield (Scheme 3). Although no asymmetric induction was observed in this reaction, the formation of a carbon–carbon bond from dialkylzinc and aldehyde using a β-amino alcohol suggests the possibility of asymmetric induction using the appropriate chiral β-amino alcohol. Indeed, Oguni and Omi used (*S*)-leucinol (a primary β-amino alcohol) as a chiral catalyst and first obtained

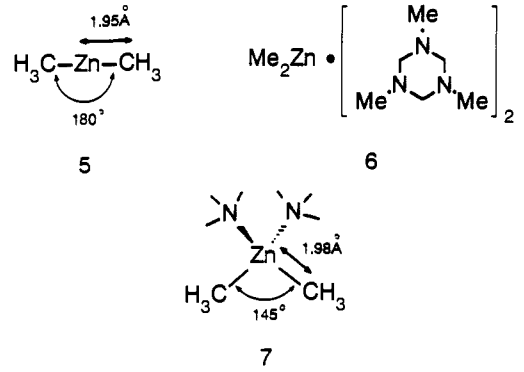


Figure 1. Structures of dimethylzinc and its adduct with 1,3,5-trimethylhexahydro-1,3,5-triazine.

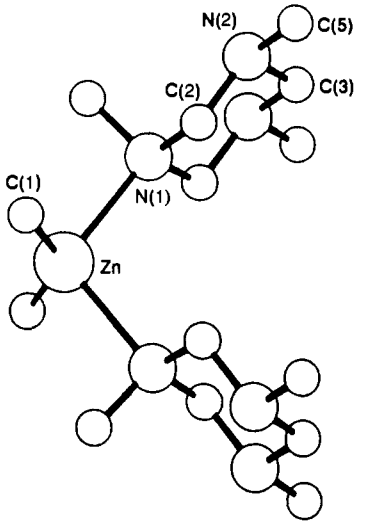


Figure 2. Molecular structure of the adduct of dimethylzinc with 1,3,5-trimethylhexahydro-1,3,5-triazine. Selected bond lengths (Å) and angles (deg) for $Me_2Zn(C_6H_{15}N_3)_2$: Zn(1)–C(1) 1.981 (7), Zn(1)–N(1) 2.410 (5), C(1)–Zn(1)–C(1′) 145.1 (2), N(1)–Zn(1)–N(1′) 105.6 (2), C(1)–Zn(1)–N(1) 100.4 (2) (reprinted from ref 11; copyright 1991 Royal Society of Chemistry).

optically active **3** with moderate optical purity (49% ee).[10]

The reason for the addition of dialkylzinc to aldehyde catalyzed by amino alcohol may be explained as follows. Dimethylzinc (**5**), for example, has a linear structure with a 1.95-Å bond length between the zinc and carbon atoms and does not add to aldehydes. But, dimethylzinc forms a complex, **6**, with 2 mol of 1,3,5-trimethylhexahydro-1,3,5-triazine (the donor atom is nitrogen). X-ray analysis of the complex revealed that the coordination chemistry of the zinc atom changes to the tetrahedral[7] with a 145° carbon–zinc–carbon bond angle (Figures 1 and 2).[11] It should be noted that the bond length between the zinc and carbon atoms becomes longer (**7**, 1.98 Å). This means that the bond energy of the zinc and carbon bond decreases and that the nucleophilicity of the methyl group of dimethylzinc increases. In fact, 5 mol % of *N,N,N′,N′*-tetramethylethylenediamine catalyzes the addition of diethylzinc to aldehyde to afford the corresponding alcohol quantitatively.[12]

β-Tertiary Amino Alcohol. *Camphor Derivative.* The first highly enantioselective catalytic addition of dialkylzincs to aromatic aldehydes was reported by Noyori et al.[13] (−)-3-*exo*-(Dimethylamino)isoborneol (**8**)[14] catalyzes the addition of diethylzinc to benzaldehyde to afford (*S*)-1-phenylpropanol with 99% ee in 98% yield (Table 1, entry 1; Scheme 4). The catalyst is also effective for other aromatic aldehydes. However, the enantioselectivity in the addition to an aliphatic aldehyde (heptanal) is moderate (61% ee) (entry 5).

The nonlinear relationship between the enantiomeric purity of the catalyst and that of the product attracts much attention.[15a] The optical purities of the alcohols obtained are higher than those of the chiral catalyst used.[16] The reaction of benzaldehyde and diethylzinc in the presence of 8 mol % of (−)-**8** in 15% ee lead to (*S*)-1-phenylpropanol in 95% ee (entry 7). This dramatic effect is explained in that the minor isomer of the chiral catalyst (+)-**9** forms a dimeric meso-type complex (+,−)-*meso*-**10** with the major isomer (−)-**9** of the catalyst and that the resulting meso complex **10** is relatively stable and does not catalyze the reaction (Scheme 5). On the other hand, the rest of the major isomer of the chiral catalyst (−)-**9** forms a less stable dimeric complex (−,−)-**11** which more easily dissociates to the reactive monomeric major isomer of the catalyst (−)-**9**. These enantiomeric recognition and interactions were originally proposed by Horeau et al.[15b] and Wynberg et al.[15c] The enantioselectivities of the optically pure catalyst are higher than those of the catalyst of lower ee's. Therefore, from the viewpoint of organic synthesis, the use of an optically pure catalyst is more practical. However, the nonlinear relationship between the optical purities of the chiral catalyst and the product provides one of the processes of the concentration of the enantiomers and may have some relation to the beginning formation of optically active naturally occurring compounds.

Proline Derivative. The first nonpreexisting chiral catalysts designed for the enantioselective addition of dialkylzincs to aldehydes have been reported by our group.

A series of chiral pyrrolidinylmethanols is synthesized stereoselectively from (*S*)-proline.[18,19] In the presence of 2 mol % chiral pyrrolidinylmethanols, optically active alcohols of up to 100% ee are obtained from the enantioselective addition of dialkylzincs to aldehydes (Scheme 6, Table 2).[20,21] The sense of the asymmetric induction and the degrees of enantioselectivities are highly dependent on the structure of the catalysts. (*S*)-(+)-(**12**) (2 mol %) catalyzes the addition of diethylzinc to benzaldehyde to afford (*S*)-1-phenylpropanol with 97% ee in 100% yield (Table 2, entry 1). The catalyst is also effective in the enantioselective addition of diethylzinc to aliphatic aldehyde (heptanal), and (*S*)-3-nonanol with 91% ee is obtained.

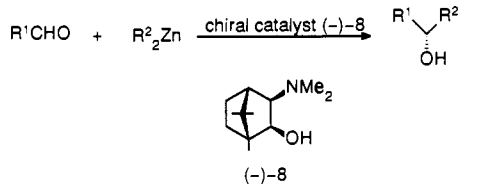
On the other hand, (1*R*,2′*S*)-(−)-phenyl(1-neopentylpyrrolidin-2-yl)methanol (**13**) catalyzes the reaction to afford (*R*) alcohols in high ee (up to 100% ee).[21]

In (*S*)-(+)-diphenyl(*N*-methylpyrrolidin-2-yl)methanol (DPMPM, **12**), the carbon atom bearing the hydroxy group is not a chiral center. Therefore the sense of the enantioselectivity is determined by the configuration of the asymmetric carbon bearing the amino group. In other chiral pyrrolidinylmethanols, the configuration of the carbon atom bearing the hydroxy group determines the sense of the enantioselectivity. *erythro*-(−)-**14** [(*R*) alcohol] afforded (*R*)-1-phenylpropanol, while *threo*-(−)-**15** [(*S*) alcohol] afforded (*S*)-1-phenyl-

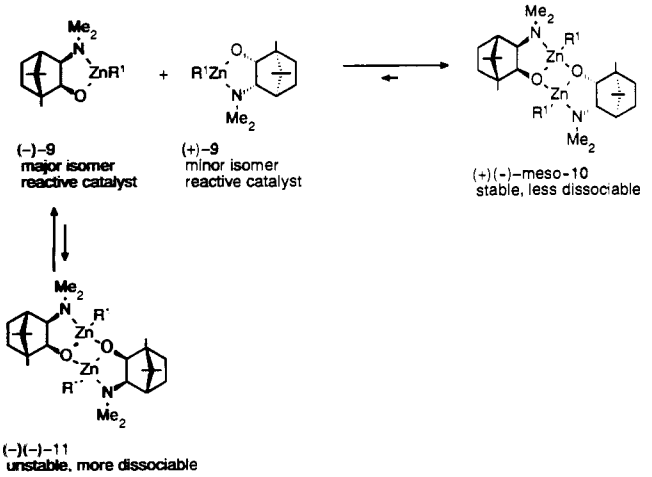
Table 1. Enantioselective Addition of Dialkylzincs to Aldehydes Catalyzed by Camphor-Derived Amino Alcohol 8

entry	R^1	R^2	catalyst (mol %)	solvent	T, °C	t, h	yield, %	ee, %	config	ref
1	Ph	Et	(−)-8 (2)	ether/toluene	0	6	98	99	*S*	13
2	Ph	Me	(−)-8 (2)	toluene	0	70	59	91	*S*	13
3	4-ClC_6H_4	Et	(−)-8 (2)	toluene	0	12	86	93	*S*	13
4	4-$MeOC_6H_4$	Et	(−)-8 (2)	toluene	0	12	96	93	*S*	13
5	*n*-hexyl	Et	(−)-8 (2)	toluene	0	24	81	61	*S*	13
6	ferrocenyl	Me	(−)-8 (2)	toluene	20	170	60	81	*S*	17
7	Ph	Et 15% ee	(−)-8 (8)	toluene	0	7	92	95	*S*	16

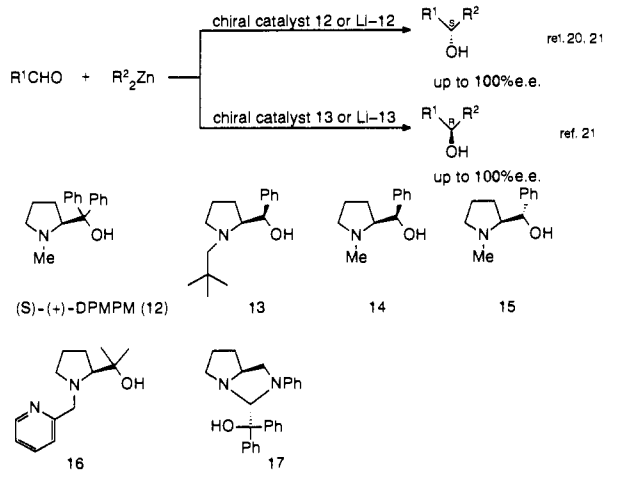
Scheme 4



Scheme 5



Scheme 6



propanol.[21] Thus, by employing chiral pyrrolidinylmethanols derived from (*S*)-proline, both enantiomers of the secondary alcohols desired are obtained in high ee's.

When lithium alkoxide of chiral (*S*)-DPMPM (12) is used in the reaction of aromatic aldehydes, better enantioselectivities (up to 100% ee) are observed than when (*S*)-DPMPM (12) itself is used. (The zinc alkoxide of DPMPM is formed in situ from the reaction with dialkylzinc.) In the addition of diethylzinc to benzaldehyde, the ee of 1-phenylpropanol increased to 99.5%. The higher enantioselectivity of the lithium alkoxide of (*S*)-DPMPM (12) than that of the zinc alkoxide is attributed to the stronger hard acid character of the lithium cation than zinc. Lithium cation may more easily coordinate with the oxygen atom (hard base) of the approaching aldehyde than zinc does. Thus, this coordination may restrict the number of the possible stereochemical courses of the reaction to afford high ee's.

By using (*S*)-DPMPM (12) as a chiral catalyst, optically active fluorine-containing alcohol[22] and deuterio alcohol[23] of high optical purities were synthesized.[24]

A chiral prolinol derivative with a 2-pyridylmethyl substituent on the nitrogen atom, 16, was reported by Chelucci et al.[25] Lithium alkoxide of 16 catalyzes the addition of diethylzinc to benzaldehyde to afford (*R*)-1-phenylpropanol in 60% ee. On the other hand, the enantioselectivity of the addition, when 16, without lithiation, was used, dropped to 37% ee. The enantioselectivity of 16 is opposite to that of (*S*)-DPMPM (12).

Chiral hydroxy aminal 17 derived from (*S*)-proline was reported by Asami and Inoue to catalyze the addition of diethylzinc to aldehydes to afford (*S*) alcohols of high optical purities.[26]

Cinchona Alkaloid. Smaardijk and Wynberg reported the enantioselective addition of diethylzinc to aromatic aldehydes[27] using cinchona alkaloids[28] as chiral catalysts (Scheme 7). Quinine (2 mol %) catalyzes the reaction with benzaldehyde to afford (*R*)-1-phenylpropanol with 68% ee in 92% yield (Table 3, entry 1). When 2-ethoxybenzaldehyde is employed, the ee of the obtained alcohol reached 92% (entry 3). The hydroxy group of quinine (probably via the formation of zinc alkoxide) is essential for this reaction because acetylquinine shows low enantioselectivity (14% ee) (entry 5). On the other hand, quinidine affords (*S*)-1-phenylpropanol with 48% ee.

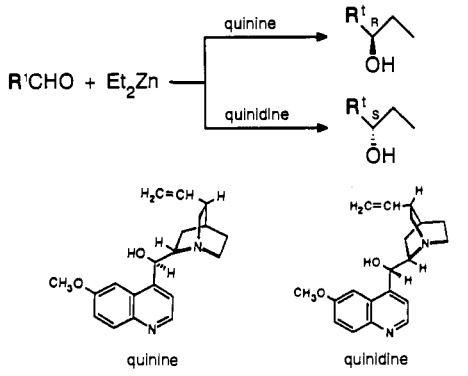
Buono et al. reported an interesting temperature effect on the enantioselective addition of diethylzinc to benzaldehyde using quinine as a chiral catalyst.[29] Unlike many other asymmetric syntheses, the reaction that is run for a short reaction time at elevated temperature (100 °C) affords alcohol with higher ee (73% ee) (entry 7) than that run at room temperature (64% ee) (entry 6).

Ephedrine Derivatives. One of the advantages of the use of ephedrine and norephedrine as chiral sources in asymmetric synthesis is that both enantiomers are readily available. Thus both enantiomers of the chiral catalysts can be derived from ephedrine or norephedrine. By using the appropriate enantiomer of the catalyst, either enantiomer of the product (alcohol) desired is synthesized in the same synthetic yield and the same enantioselectivity within experimental error. This predictable chemical access to either enantiomer

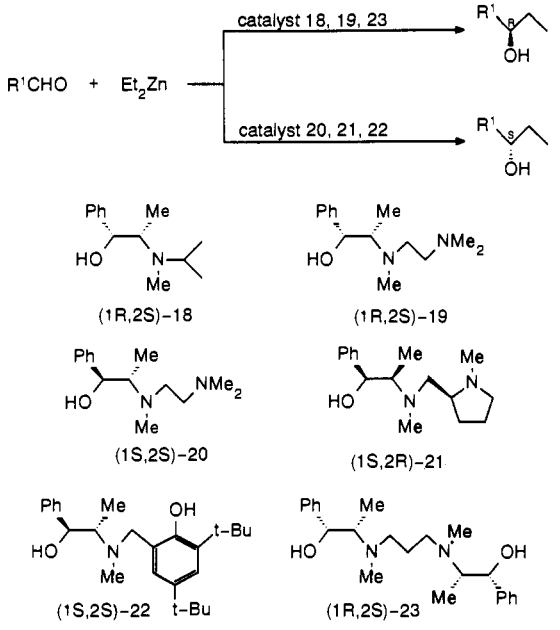
Table 2. Enantioselective Addition of Dialkylzincs to Aldehydes Catalyzed by Proline-Derived Amino Alcohol

entry	R^1	R^2	catalyst (mol %)	solvent	T, °C	t, h	yield, %	ee, %	config	ref
1	Ph	Et	(*S*)-DPMPM (12) (2)	hexane	0	4	100	97	*S*	21
2	4-ClC_6H_4	Et	(*S*)-DPMPM (12) (2)	hexane	0	4	100	98	*S*	21
3	4-$MeOC_6H_4$	Et	(*S*)-DPMPM (12) (2)	hexane	0	4	100	81	*S*	20
4	4-$MeOC_6H_4$	Et	(*S*)-DPMPM (12) (2)	cyclohexane/hexane	0	4	100	96	*S*	21
5	*n*-hexyl	Et	(*S*)-DPMPM (12) (2)	cyclohexane/hexane	0	4	96	91	*S*	21
6	Ph	Et	**13** (5)	hexane	0	4	100	100	*R*	21
7	4-ClC_6H_4	Et	**13** (5)	hexane	0	4	100	100	*R*	21
8	4-$MeOC_6H_4$	Et	**13** (5)	hexane	0	4	100	100	*R*	21
9	cyclohexyl	Et	**13** (5)	hexane	0	4	100	86	*R*	21
10	Ph	Et	**14** (5)	toluene/hexane	0	4	100	72	*R*	21
11	Ph	Et	**15** (5)	toluene/hexane	0	4	90	31	*S*	21
12	Ph	Et	Li-(*S*)-DPMPM (12) (2)	hexane	0	4	100	99.5	*S*	21
13	4-ClC_6H_4	Et	Li-(*S*)-DPMPM (12) (2)	cclohexane/hexane	0	4	91	100	*S*	21
14	4-$MeOC_6H_4$	Et	Li-(*S*)-DPMPM (12) (2)	cyclohexane/hexane	0	4	96	100	*S*	21
15	Ph	Et	Li-**13** (5)	hexane	0	4	100	100	*R*	21
16	4-$CF_3C_6H_4$	Et	Li-(*S*)-DPMPM (12) (6)	hexane	0	24	80	91	*S*	22
17	PhCDO	Et	(*S*)-DPMPM (12) (6)	hexane	0	22	86	91	*S*	23
18	Ph	Et	Li-**16** (6)	hexane	rt	6–24	97	60	*R*	25
19	Ph	Et	Li-**16** (6)	hexane	rt	6–24	99	37	*R*	25
20	Ph	Et	**17** (5)	hexane	rt	15	92	96	*S*	26
21	4-ClC_6H_4	Et	**17** (5)	hexane	rt	15	87	95	*S*	26
22	*n*-hexyl	Et	**17** (5)	hexane	rt	15	82	75	*S*	26

Scheme 7



Scheme 8



of the product is superior to biochemical (biological) methods in which the access to both enantiomers of the product is usually difficult or, at least, the synthetic yield and the enantioselectivity are not predictable.

Chaloner et al. found that (1*R*,2*S*)-*N*-isopropylephedrine (**18**) catalyzes the addition of diethylzinc to benzaldehyde to afford (*R*)-1-phenylpropanol with 80% ee in 72% yield (Scheme 8; Table 4, entry 1).[30] The catalyst is also effective for other aromatic aldehydes. However, in the addition to aliphatic cyclohexanecarboxaldehyde, only the racemic alcohol was obtained in 40% yield (entry 4). Recently, they reported that the enantioselectivities increase when an excess amount of diethylzinc was used in proportion to aldehydes.[31] When the molar ratio of diethylzinc to cyclohexanecarboxaldehyde was 4.5, ee of 1-cyclohexylpropanol reached 97% (entry 5). The enantioselectivities of the addition to other aldehydes also increased according to the increase in the ratio of diethylzinc.

A similar effect of the increase in enantioselectivity using an excess amount of diethylzinc was also observed with chiral pyrrolidinylmethanols.[32]

When dialkylzinc adds to aldehyde, alkyl zinc alkoxide is formed in situ. This alkylzinc alkoxide may also form a complex with the chiral catalyst and may reduce the enantioselectivity of the chiral catalyst. On the other hand, when an excess amount of dialkylzinc is present, an enantioselective chiral complex may be more easily formed between dialkylzinc and the chiral catalyst.

Corey and Hannon reported that the lithium salt of (1*R*,2*S*)-*N*-[2-(dimethylamino)ethyl]ephedrine (**19**), which is a chiral ligand in the conjugate addition of organocopper reagent,[33] catalyzes the addition of diethylzinc to benzaldehyde to afford (*R*)-1-phenylpropanol with 90% ee (entry 6).[34] When (1*S*,2*S*)-pseudoephedrine was used as a precursor of the chiral catalyst **20**, (*S*)-1-phenylpropanol with 91% ee was obtained (entry 7). The reversal of the enantioselectivity shows that the enantioselectivity is dependent on the configuration of the alcohol part of the chiral catalyst. The same type of reversal of the enantioselectivity by the configuration of the alcohol of the catalyst was observed in the chiral catalyst of pyrrolidinylmethanols.[21]

When the lithium salt of (*S*)-*N*-[(1-methylpyrrolidin-2-yl)methyl] derivative of (1*S*,2*R*)-ephedrine (**21**) was employed as a chiral catalyst, (*S*)-1-phenylpropanol with 95% ee was obtained (entry 8). Chiral phenol derived from 2,4-di-*tert*-butylphenol and (1*S*,2*S*)-pseu-

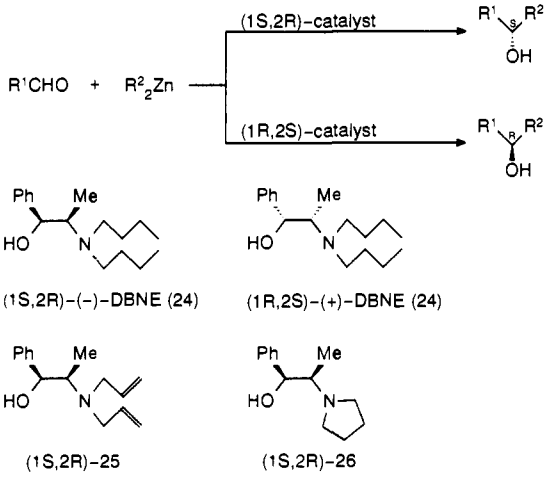
Table 3. Enantioselective Addition of Dialkylzincs to Aldehydes Catalyzed by Cinchona Alkaloid

entry	R^1	R^2	catalyst (mol %)	solvent	T, °C	t, h	yield, %	ee, %	config	ref
1	Ph	Et	quinine (2)	toluene	20	overnight	92	68	*R*	27
2	2-$MeOC_6H_4$	Et	quinine (2)	toluene	20	overnight	83	83		27
3	2-$EtOC_6H_4$	Et	quinine (2)	toluene	20	overnight	72	92		27
4	2-$EtOC_6H_4$	Et	quinine (2)	ether	20	overnight	90	90		27
5	2-$MeOC_6H_4$	Et	acetylquinine (2)	toluene	20	overnight	78	14		27
6	Ph	Et	quinine (3)	toluene	rt	16	97	64	*R*	29
7	Ph	Et	quinine (3)	toluene	100	0.25	95	73	*R*	29

Table 4. Enantioselective Addition of Dialkylzincs to Aldehydes Catalyzed by Ephedrine-Derived Amino Alcohol

entry	R^1	R^2	catalyst (mol %)	solvent	T, °C	t, h	yield, %	ee, %	config	ref
1	Ph	Et	**18** (10)	hexane	25	48	72	80	*R*	30
2	3-ClC_6H_4	Et	**18** (10)	hexane	25	48	60	78	*R*	30
3	*n*-hexyl	Et	**18** (10)	hexane	25	48	88	79	*R*	31
4	cyclohexyl	Et (1 equiv)	**18** (10)	hexane	25	48	40	0	–	30
5	cyclohexyl	Et (4.5 equiv)	**18** (10)	hexane	25	48	90	97		31
6	Ph	Et	Li-**19** (10)	toluene	23	14	81	90	*R*	34
7	Ph	Et	Li-**20** (10)	toluene	23	14	69	91	*S*	34
8	Ph	Et	Li-**21** (10)	toluene	0	7	68	95	*S*	34
9	Ph	*n*-Bu	Li-**21** (10)	toluene	0	7	68	84	*S*	34
10	Ph	Et	**22** (13)	toluene	23	8	93	86	*S*	35
11	Ph	Et	Li-**23** (4)	toluene/hexane	0	48	59	85	*R*	36
12	2-$MeOC_6H_4$	Et	Li-**23** (4)	toluene/hexane	0	48	93	73		36

Scheme 9



doephedrine (**22**) also catalyzed the addition of diethylzinc to benzaldehyde to afford (*S*)-1-phenylpropanol with 86% ee (entry 10).[35]

Chiral diaminodiol **23**, derived from 2 mol of (1*R*,2*S*)-ephedrine with a trimethylene chain, has a C_2 symmetry axis. The dilithium salt of **23** catalyzes the ethylation of benzaldehyde to afford (*R*)-1-phenylpropanol with 85% ee (entry 11).[36]

Norephedrine Derivatives. The chiral *N,N*-dialkylnorephedrines catalyzed the addition of dialkylzincs to aliphatic and aromatic aldehydes to afford optically active secondary alcohols with high ee's (Scheme 9).[37]

N-Alkyl substituents on the (1*S*,2*R*)-*N,N*-di-*n*-alkylnorephedrines had a significant effect on the enantioselectivity of the addition of diethylzinc to 3-methylbutanal and nonanal. As shown in Figure 3, the optical purity of the product increases as the chain length of the *N*-*n*-alkyl substituent increases and peaks at a chain length of four carbons (93% ee; Table 5, entry 5). Thus, (1*S*,2*R*)-*N,N*-DBNE (**24**) gave the best results.

The catalyst was highly enantioselective for the addition to aliphatic aldehydes (entries 5–8) as well as

Figure 3. Relationship between the ee's of the product aliphatic alcohols and the carbon number of the *N*-alkyl substituents (R) of the chiral catalyst [(1*S*,2*R*)-*N,N*-di-*n*-alkylnorephedrines] in the enantioselective addition of diethylzinc to 3-methylbutanal and nonanal: (○) (*S*)-5-methylhexan-3-ol, (△) (*S*)-3-undecanol (reprinted from ref 38; copyright 1991 American Chemical Society).

to aromatic aldehydes (entries 1, 2, and 4). As shown in Figure 4, various types of optically active aliphatic alcohols of high enantiomeric purities were first synthesized using DBNE. (Information on the structure of the aliphatic alcohols that have been prepared by the asymmetric *reduction* of ketones or by the asymmetric *hydroboration* of alkenes has been somewhat limited.)

(1*S*,2*R*)-*N,N*-Diallylnorephedrine (**25**) and (1*S*,2*R*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (**26**) were also

Scheme 10. Proposed Mechanism (reprinted from ref 38; copyright 1991 American Chemical Society)

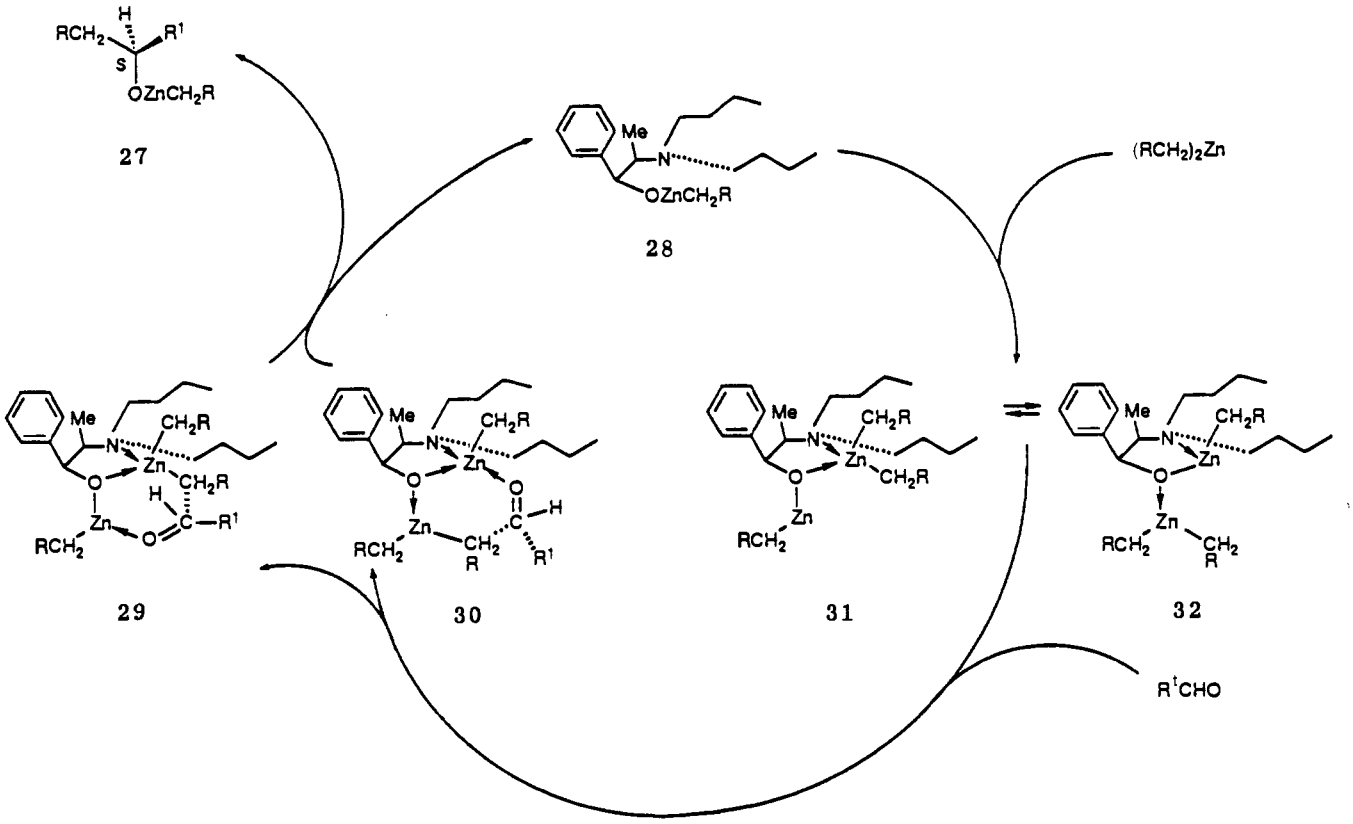


Table 5. Enantioselective Addition of Dialkylzincs to Aldehydes Catalyzed by Norephedrine-Derived Amino Alcohol

entry	R^1	R^2	catalyst (mol %)	solvent	T, °C	t, h	yield, %	ee, %	config	ref
1	Ph	Et	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	16	100	90	*S*	37
2	2-$MeOC_6H_4$	Et	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	16	100	94	*S*	37
3	$C_6H_5(CH_2)_2$	Et	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	16	94	95	*S*	38
4	Ph	*i*-Pr	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	16	53	75	*S*	38
5	$(CH_3)_2CHCH_2$	Et	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	16	92	93		37
6	*n*-hexyl	Me	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	16	70	90	*S*	38
7	*n*-hexyl	*n*-Pr	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	16	100	90		38
8	*n*-octyl	Et	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	16	95	87	*S*	38
9	*n*-octyl	Et	(1*S*,2*R*)-**26** (6)	hexane	0	16	87	>95	*S*	38
10	*n*-octyl	Et	(1*S*,2*R*)-**25** (6)	hexane	0	16	61	88	*S*	38
11	4-$CF_3C_6H_4$	Et	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	22	92	91	*S*	22
12	4-FC_6H_4	Et	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	24	83	93	–	22
13	PhCDO	Et	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	22	92	94	*S*	23
14	$CH_3(CH_2)_5CDO$	Et	(1*S*,2*R*)-DBNE (**24**) (6)	hexane	0	15	79	84	*S*	23

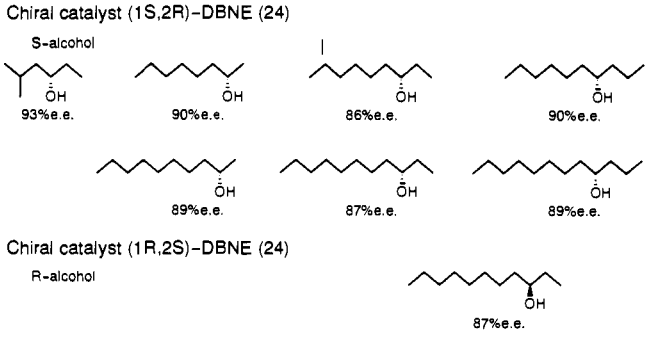


Figure 4. Optically active aliphatic alcohols synthesized using DBNE (**24**) as chiral catalyst.

effective chiral catalysts.[38] Diisopropylzinc possessing branched substituents can also be used (entry 4). A similar effect of the bulkiness of the *N*-alkyl substituents was observed in chiral 2-(dialkylamino)-1,2-diphenylethanol. The enantioselectivity of (1*S*,2*R*)-2-(*diethylamino*)-1,2-diphenylethanol was 94% ee ((*S*) configuration) in the ethylation of benzaldehyde, whereas that of the *dimethylamino* derivative dropped to 73% ee.[17]

Optically active fluorine-containing alcohols (entries 11 and 12)[22] and deuterio alcohols (entries 13 and 14)[23] were synthesized using DBNE.

A tentative mechanism for the reaction is shown in Scheme 10.[38] Zinc monoalkoxide (**28**) of (1*S*,2*R*)-DBNE and dialkylzinc are believed to form complex(es) **31** and **32**. The coordination geometry of the zinc atom is tetrahedral[11,39] with the coordination of the oxygen or the nitrogen atom of the catalyst, and the nucleophilicity of the alkyl group of the dialkylzinc is increased.[2d] The aldehyde is attacked at the *si* face via a six-center transition state (**29** or **30**,[34] respectively) to afford (*S*) chiral alkylzinc alkoxide (**27**). The bulkiness and the stereoelectronic effect of the substituents on the nitrogen atom of the chiral catalyst may affect the formation and stability of the six-center transition

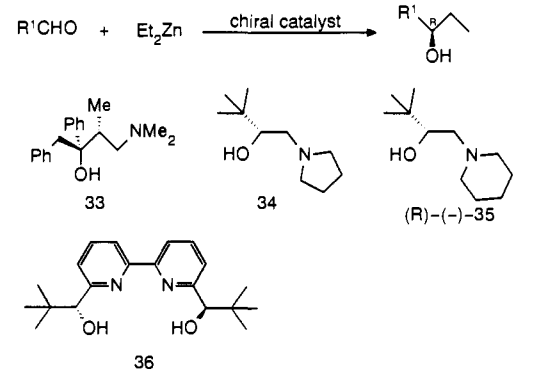
Table 6. Enantioselective Addition of Dialkylzincs to Aldehydes Catalyzed by Various Chiral Amino Alcohols

entry	R^1	R^2	catalyst (mol %)	solvent	T, °C	t, h	yield, %	ee, %	config	ref
1	Ph	Et	**33** (14)	toluene	−10	38	66	87	*R*	29
2	Ph	Et	**33** (14)	toluene	rt	16	98	83	*R*	29
3	Ph	Et	(*R*)-**34** (2)	hexane	0	24	95	98	*R*	17
4	Ph	Et	20% ee (+)-(*S*)-**34** (2)	hexane	−10		92	73	*S*	41
5	Ph	Et	77% ee (+)-(*S*)-**35** (2)	hexane	−10		96	94	*S*	41
6	Ph	Et	**36** (5)	toluene	−25	48	94	92	*R*	42
7	4-ClC_6H_4	Et	**36** (5)	toluene	0	3	65	90	*R*	42
8	4-$MeOC_6H_4$	Et	**36** (5)	toluene	0	9.5	96	80	*R*	42
9	*n*-hexyl	Et	**36** (5)	toluene	0	3	ca. 75	70	*R*	42

Table 7. Enantioselective Addition of Dialkylzincs to Aldehydes Catalyzed by Chiral Secondary Amino Alcohol

entry	R^1	R^2	catalyst (mol %)	solvent	T, °C	t, h	yield, %	ee, %	config	ref
1	Ph	Et	**37** (5)	toluene	rt		90	92	*R*	43
2	Ph	Et	**38** (5)	toluene	rt		87	88	*S*	43
3	*n*-hexyl	Et	**37** (5)	toluene	rt		82	75	*R*	43
4	*n*-hexyl	Et	**38** (5)	toluene	rt		86	74	*S*	43
5	Ph	Et	**39** (10)	toluene	0	16	94	95	*S*	45
6	4-$CF_3C_6H_4$	Et	**39** (10)	toluene	0	3	100	96	*S*	45
7	4-$MeOC_6H_4$	Et	**39** (10)	toluene	23	18	90	83	*S*	45
8	Ph	Et	**40** (6)	hexane	0	24	100	96	*S*	46
9	4-MeC_6H_4	Et	**40** (6)	hexane	0	24	100	95	*S*	46
10	4-$MeOC_6H_4$	Et	**40** (6)	hexane	0	24	100	97	*S*	46
11	Me_2CHCH_2	Et	**41** (6)	hexane	0	24	40	81	*S*	46

Scheme 11

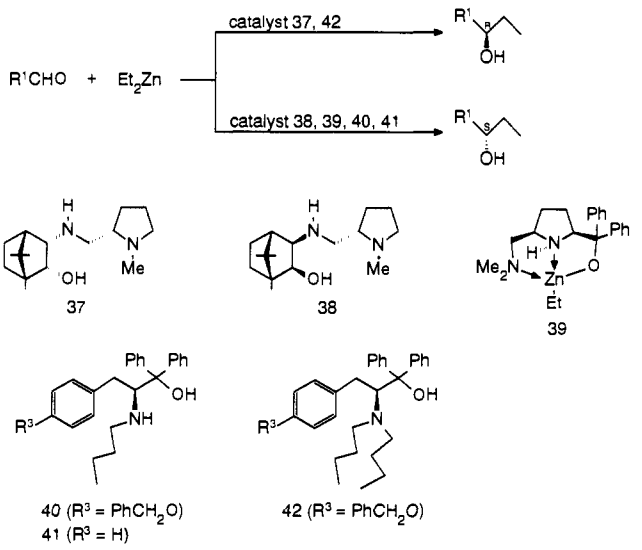


states. *N*-Alkyl substituents must possess at least one β-carbon atom to achieve high enantioselectivity. When the *N*-alkyl substituents are suitably large, they may block the approach of the attacking species to one of the enantiotopic faces of the aldehyde leading to a high level of enantioselection. On the other hand, when the *N*-alkyl substituents are bulkier than *n*-butyl, the formation of the six-center transition states (**29** or **30**) may be more or less inhibited, leading to low enantioselection.

Various Tertiary Amino Alcohols and Chiral Bipyridyldiol. (2*S*,3*R*)-4-(Dimethylamino)-1,2-diphenyl-3-methyl-2-butanol (**33**, Chirald)[40] is a rare example of a γ-amino alcohol which catalyzes the enantioselective ethylation of benzaldehyde to afford (*R*)-1-phenylpropanol with 87% ee (Scheme 11; Table 6, entry 1).[29]

(*R*)-1-Pyrrolidino-3,3-dimethyl-2-butanol (**34**) as a chiral catalyst affords (*R*)-1-phenylpropanol with 98% ee in the enantioselective ethylation of benzaldehyde (entry 3).[17] Like the reaction with (−)-**8**, a nonlinear relationship between the optical purities of the chiral catalysts and those of the products were observed. When (*S*)-**34** with 20% ee was used as catalyst, (*S*)-1-phenylpropanol with 73% ee was obtained (entry 4).[41] Similarly, (*S*)-1-piperidino-3,3-dimethyl-2-butanol (**35**) with 77% ee afforded the corresponding (*S*)-1-phenylpropanol with 94% ee (entry 5).

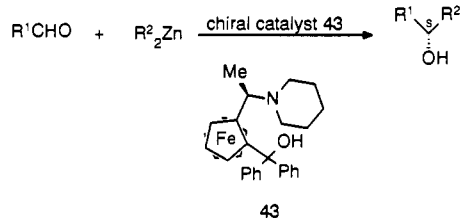
Scheme 12



Enantioselective ethylation using a chiral (*R*,*R*)-bipyridyl diol **36** which was reported by Bolm et al. afforded optically active aromatic alcohols with 80–92% ee's (entries 6–8).[42] Ethylation of heptanal gave (*R*)-3-nonanol with 70% ee (entry 9).

β-Secondary Amino Alcohol. Some chiral amino alcohols possessing secondary amino groups were found to be enantioselective catalysts for the addition of diethylzinc to aldehydes (Scheme 12; Table 7). Tanaka et al. reported[43] that *N*-alkyl derivative **37** of *endo*-3-amino-*endo*-2-hydroxybornane[44] prepared from D-camphor catalyzes the addition of diethylzinc to benzaldehyde to afford (*R*)-1-phenylpropanol with 92% ee (Table 7, entry 1). On the other hand, *exo*-3-amino-*exo*-2-hydroxybornane (**38**) prepared from D-camphor afforded (*S*)-1-phenylpropanol with 88% ee (entry 2). Thus either enantiomer of the alcohols is obtained by using the appropriate amino alcohol. The secondary amine hydrogen of the catalyst is intact during the reaction and does not form zinc amide.

Scheme 13



43

Table 8. Enantioselective Addition of Dialkylzincs to Aldehydes Catalyzed by Chiral Ferrocenyl Amino Alcohol (43)[a]

entry	R^1	R^2	T, °C	t, h	yield, %	ee, %	config
1	Ph	Et	rt	1	99	99	*S*
2	4-ClC_6H_4	Et	rt	1	100	100	*S*
3	2-naphthyl	Et	rt	3	91	97	*S*
4	*n*-hexyl	Et	rt	3	93	59	*S*
5	cyclohexyl	Et	0	3	92	>98	*S*
6	*t*-Bu	Et	rt	3	93	98	*S*
7	$(CH_3)_2CHCH_2$	Et	rt	2	70	62	*S*

[a] Reference 47. **43**, 5 mol %, was used in hexane.

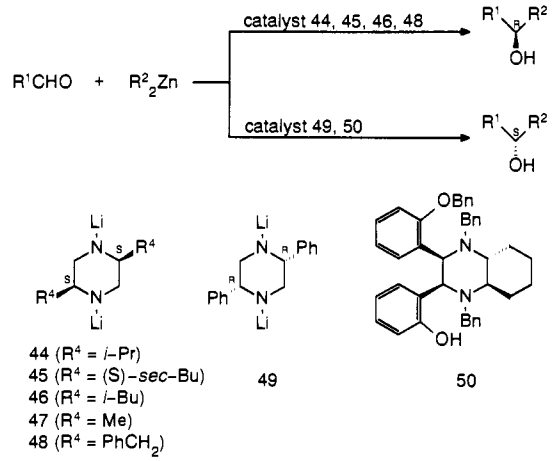
Chiral diamino alcohol possessing a secondary amino group was synthesized from (*S*)-proline.[45] Ethyl zinc alkoxide (**39**) derived from chiral diamino alcohol and diethylzinc has been used as a chiral catalyst for the enantioselective addition of diethylzinc to aromatic aldehydes.[45] The reaction of diethylzinc with benzaldehyde in the presence of 10 mol % of **39** afforded (*S*)-1-phenylpropanol with 94% ee in 95% yield (entry 5). The (*S*) configuration of the obtained alcohol is the same as that obtained by using DPMPM. The structure of the catalyst is confirmed by X-ray diffraction and ^1H NMR analyses. The coordination geometry of the zinc atom of the catalyst is tetrahedral. It should be noted that the N–H bond (not the N–Zn bond) is present in the catalyst. The dimethylamino ligand is considered to be replaced by the oxygen atom of the aldehyde. When diethylzinc coordinates to the oxygen atom of the catalyst, the ethyl group of diethylzinc transfers to the aldehyde via a six-membered cyclic structure.

Chiral secondary amino alcohols (**40** and **41**) derived from (*S*)-tyrosine catalyze the addition of diethylzinc to both aromatic and aliphatic aldehydes to afford (*S*) alcohols in 81–97% ee.[46] When tertiary dibutylamino alcohol (**42**) was used, enantioselectivity was reversed. Thus, the secondary amino alcohol is remarkably different from the corresponding tertiary amino alcohol.

Chiral Ferrocenyl Amino Alcohol. The use of chiral 1,2-disubstituted ferrocenyl amino alcohols as catalysts for the addition of dialkylzincs to aldehydes was reported by Butsugan et al.[47]

Ferrocenyl amino alcohol **43** catalyzed the addition of diethylzinc to aromatic aldehydes to afford optically active alcohols with high ee's (Scheme 13; Table 8, entries 1–3). With concern to the addition to aliphatic aldehydes, aldehydes with the substituent *not branched* at the α-carbon, such as heptanal, afforded optically active aliphatic alcohols in moderate ee's (entries 4 and 7); however, the addition to aliphatic aldehydes with the substituent *branched* at the α-carbon, such as pivaldehyde, afforded the corresponding alcohols in very high ee's (entries 5 and 6). This difference in the enantioselectivity according to the structure of the aliphatic aldehydes is a characteristic point when compared with

Scheme 14



44 (R^4 = *i*-Pr)
45 (R^4 = (S)-*sec*-Bu)
46 (R^4 = *i*-Bu)
47 (R^4 = Me)
48 (R^4 = $PhCH_2$)

49 50

DBNE (**24**)[38] which is enantioselective toward both kinds of aliphatic aldehydes.

When the alcohol of the amino alcohol is secondary, the carbon atom bearing the hydroxyl group becomes an asymmetric carbon. However, regardless of the stereochemistry of the asymmetric carbon bearing the hydroxyl group of the catalyst, the sense of the enantioselectivity is constant. This point is different for other β-amino alcohols (**14** and **15**) in which the sense of the enantioselectivity is dependent on the configuration of the asymmetric carbon bearing the hydroxyl group.

2. Chiral Piperazine

Chiral 2,5-disubstituted piperazines are cyclic diamines and are readily available by the reduction of the corresponding 2,5-diketopiperazines derived from α-amino acids.[48]

A series of 2,5-disubstituted piperazines, as their dilithium salts, have been examined as chiral catalysts for the enantioselective addition of diethylzinc to benzaldehyde (Scheme 14).[49] Chiral 2(*S*),5(*S*)-disubstituted piperazines possessing branched substituents such as diisopropyl, di-(*S*)-*sec*-butyl, and diisobutyl catalyze the reaction and (*R*)-1-phenylpropanol with 89–91% ee's were obtained (Table 9, entries 2–4). When 2(*S*),5(*S*)-diisopropylpiperazine is used without lithiation, enantioselectivity dropped slightly to 81% ee (entry 1). On the other hand, 2(*S*),5(*S*)-dimethylpiperazine possessing substituents of smaller size does not afford the optically active alcohol (entry 5). 2(*S*),5(*S*)-Diisopropylpiperazine is effective not only with other di-primary-alkylzincs (up to 94% ee) but also with di-*sec*-alkylzinc (diisopropylzinc) (73% ee) (entry 9). Enantioselective propylation and butylation also afforded the corresponding secondary alcohols in 92% and 96% ee's, respectively (entries 8 and 10). The catalyst was effective for other aromatic aldehydes, too (entries 11–14).

One of the probable stereochemical courses of the reaction is postulated as shown in Figure 5.[50] The zinc atom of dialkylzinc is chelated with two nitrogen atoms of the piperazine ring, which has a boat configuration with two bulky isopropyl substituents in the pseudoequatorial positions. The configuration of dialkylzinc becomes tetrahedral, and subsequently the nucleophilicity of dialkylzinc increased. The chiral complex has a C_2 symmetry axis which reduces the number of possible transition states.[51] The aldehyde

Table 9. Enantioselective Addition of Dialkylzincs to Aldehydes Catalyzed by Chiral Piperazines[a]

entry	R^1	R^2	catalyst (mol %)	yield, %	ee, %	config	ref
1[b]	Ph	Et	(2*S*,5*S*)-**44** (6)	73	81	*R*	49
2	Ph	Et	(2*S*,5*S*)-**44** (6)	69	90	*R*	49
3	Ph	Et	(2*S*,5*S*)-**45** (6)	75	89	*R*	50
4	Ph	Et	(2*S*,5*S*)-**46** (6)	76	91	*R*	50
5	Ph	Et	(2*S*,5*S*)-**47** (6)	54	0	–	50
6	Ph	Et	(2*S*,5*S*)-**48** (6)	70	68	*R*	49
7	Ph	Et	(2*R*,5*R*)-**49** (6)	32	13	*S*	50
8	Ph	*n*-Pr	(2*S*,5*S*)-**44** (6)	48	92	*R*	50
9	Ph	*i*-Pr	(2*S*,5*S*)-**44** (6)	44	73	*R*	50
10	Ph	*n*-Bu	(2*S*,5*S*)-**44** (6)	44	96	*R*	50
11	4-ClC_6H_4	Et	(2*S*,5*S*)-**44** (6)	77	90	*R*	49
12	4-ClC_6H_4	Me	(2*S*,5*S*)-**44** (6)	23	94	*R*	49
13	4-$MeOC_6H_4$	Et	(2*S*,5*S*)-**44** (6)	65	79	*R*	49
14	1-naphthyl	Et	(2*S*,5*S*)-**44** (6)	69	63	*R*	50
15	$Ph(CH_2)_2$	Et	(2*S*,5*S*)-**44** (6)	55	31	*R*	50
16	Ph	Et	**50** (5)	85	>99	*S*	52
17	4-$MeOC_6H_4$	Et	**50** (5)	95	>99	*S*	52
18	n-hexyl	Et	**50** (5)	91	81	*S*	52

[a] The reactions were run in mixed solvent of toluene and hexane at room temperature for 20 h (entries 1–15) or for 15–24 h (entries 16–18). [b] Piperazine was used without lithiation.

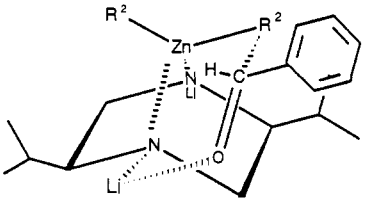


Figure 5. Proposed stereochemical course of the enantioselective addition of R^2_2Zn with benzaldehyde using **44** as a chiral catalyst.

approaches the chiral complex from a direction which avoids the bulky isopropyl group of the piperazine and reacts via a six-center mechanism with a bulky phenyl group at the equatorial position. An alcohol of (*R*) configuration is thus formed.

A convenient synthesis of chiral tetrasubstituted piperazines by electroreduction of the corresponding 1,2-diimines is reported by Shono et al.[52] One of the piperazines (**50**) with *N*,*N*-dibenzyl substituents and with a phenolic substituent is an efficient chiral catalyst for the enantioselective addition of diethylzinc to both aromatic and aliphatic aldehydes (81 to >99% ee's) (entries 16–18). Because the phenolic group plays an important role in the reaction, the catalyst may be more appropriately categorized as a chiral aminophenol.

3. Chiral Quaternary Ammonium Salt

Chiral quaternary ammonium salts, (1*S*,2*R*)-*N*-benzyl-*N*-methylephedrinium halides (**51** and **52**), catalyze the enantioselective addition of diethylzinc to aldehydes to afford optically active alcohols in good ee's (up to 74% ee)[53] (Scheme 15).

The effect of the solvents was important. The chiral ammonium catalyst in the solid state in hexane (and benzene) revealed much higher enantioselectivities than those in the solution state. The reaction of benzaldehyde with diethylzinc using a *solid* state catalyst in hexane affords an alcohol of 74% ee (Table 10, entry 1). However, the same reaction using a *solution* of chiral catalyst in dimethylformamide (DMF)–hexane showed no enantioselectivity. This is a very rare

Scheme 15

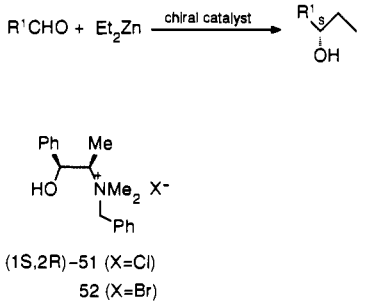


Table 10. Enantioselective Addition of Diethylzinc to Aromatic Aldehydes Catalyzed by (1*S*,2*R*)-*N*-Benzyl-*N*-Methylephedrinium Halides[a]

entry	R^1	catalyst (mol %)	solvent	yield, %	ee, %	config
1	Ph	**51** (6)	hexane	90	74	*S*
2	Ph	**51** (6)	benzene/hexene	76	73	*S*
3	Ph	**51** (6)	DMF/hexane	71	0	–
4	Ph	**52** (6)	hexane	72	62	*S*
5	4-Me-C_6H_4	**51** (6)	hexane	81	61	*S*

[a] Reference 53. Reactions were run at room temperature.

Scheme 16

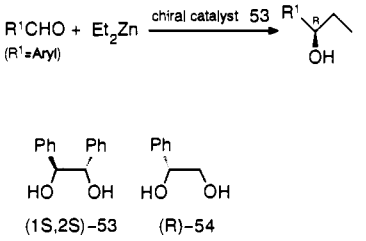


Table 11. Enantioselective Addition of Diethylzinc to Aryl Aldehydes Catalyzed by Chiral Diol 53[a]

entry	R^1	solvent	*t*, h	yield, %	ee, %	config
1	2-naphthyl	toluene	20	99	72	*R*
2	2-naphthyl	ether	27	71	75	*R*
3	Ph	toluene	69	99	77	*R*
4	2-$MeOC_6H_4$	toluene	20	95	78	*R*

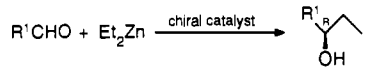
[a] Reactions were craried out at room temperature in the presence of 6 mol % catalyst **53**.

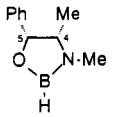
example in that the solid-state catalyst is more enantioselective than the solution-state catalyst. The degree of solvation of the ammonium cation of the catalyst is different between hexane and other polar solvents. Very little solvation of the ammonium cation in hexane is essential for the asymmetric induction. On the other hand, the oxygen or nitrogen atom of DMF strongly solvates the ammonium cation and may subsequently destroy the chiral complex of ammonium catalyst and diethylzinc.

4. Chiral 1,2-Diol

(1*S*,2*S*)-1,2-Diphenylethane-1,2-diol (**53**), a chiral diol with C_2 symmetry axis, is reported by Salvadori et al. to be an enantioselective catalyst for the addition of diethylzinc to aromatic aldehydes (Scheme 16, Table 11).[54] (*R*) alcohols of up to 78% ee are obtained (Table 11, entry 4). On the other hand, (*R*)-1-phenylethane-1,2-diol (**54**) which contains both primary and secondary alcohols does not cause any asymmetric induction.

Scheme 17





(4S,5R)-55

Table 12. Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Chiral Oxazaborolidine 55[a]

entry	R^1	t, h	yield, %	ee, %	config
1	Ph	30	>85	95	*R*
2	4-MeO-C_6H_4	48	>85	93	*R*
3	4-Cl-C_6H_4	48	>85	96	*R*
4	*n*-hexyl	88	>85	52	*R*

[a] Reference 55. Reactions were run at −25 °C in toluene in the presence of 5 mol % catalyst **55**.

5. Chiral Oxazaborolidine

Srebnik and Brown reported that (4*S*,5*R*)-3,4-dimethyl-5-phenyl-1,3,2-oxazaborolidine (**55**), prepared from (1*R*,2*S*)-(−)-ephedrine and borane–methyl sulfide complex, is an efficient chiral catalyst for the addition of diethylzinc to aromatic aldehydes to afford (*R*) alcohol of up to 96% ee (Scheme 17; Table 12, entry 3).[55] This catalyst is the first example of a chiral boron compound for the addition of diethylzinc to aldehydes. The ee of the addition to aliphatic aldehyde with this catalyst is moderate (entry 4).

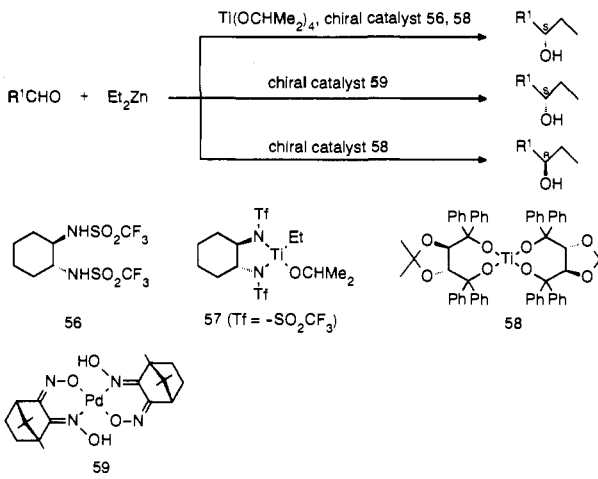
The role of the centered atom in the metalated oxaza ring system is important. When boron (86% ee) is replaced by aluminum, lithium, or zinc, the ee of the product dropped to 58%, 70%, and 71%, respectively. The reason for the superiority of boron over other metals in the catalyst is considered to be the shorter bond lengths of the B–O and B–N bonds than the bond lengths of other metal–O and –N bonds.

6. Transition Metal Complex with Chiral Ligands

The addition reaction of diethylzinc to benzaldehyde in the presence of titanium tetrachloride is described by Reetz.[56]

Yoshioka and Ohno found that the chiral orthotitanate complex prepared in situ from titanium tetraisopropoxide and bistrifluoromethanesulfonamide of *trans*-cyclohexane-1,2-diamine (**56**) works as a highly enantioselective catalyst for the addition of dialkylzincs to aldehydes (Scheme 18).[57] Optically active (*S*)-1-phenylpropanol in 98–99% ee's is obtained from the enantioselective ethylation of benzaldehyde (Table 13, entries 1 and 2). The catalyst is also effective even for the aliphatic aldehyde. In fact, alcohol of 99% ee is obtained in 78% yield from the addition of diethylzinc to aliphatic hexanal (−20 °C, 5 h) (entry 5). It should be noted that the turnover of the catalyst reaches about 2000. Chiral disulfonamide accelerates the reaction rate considerably. The reaction of diethylzinc with benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$, only, and without the disulfonamide is rather slow (24 h at room temperature). Therefore, the Lewis acidity of the Ti compound is considered to be increased by the electron-withdrawing disulfonamide. A key reactive species is considered to be ethyltitanium reagent **57**.[58]

Scheme 18



59

Schmidt and Seebach reported the enantioselective addition of diethylzinc to aldehydes using a chiral spirotitanate **58** prepared from the corresponding diol derived from (*R*,*R*)-tartaric acid. In the presence of 10 mol % of **58**, (*R*)-1-(4-methoxyphenyl)propanol of 82% optical purity was obtained in 15% yield from the reaction of diethylzinc with anisaldehyde (entry 6).[59] Of particular interest is the reversal of the sense of the enantioselectivity in the presence of 120 mol % of Ti(O-*i*-Pr)$_4$ in addition to 10 mol % of **58**. When anisaldehyde is reacted with diethylzinc in the presence of **58** (10 mol %) and Ti(O-*i*-Pr)$_4$, (*S*)-1-(4-methoxyphenyl)propanol of 94% optical purity is obtained in 86% yield (entry 7). The method is also applicable to aliphatic and α,β-unsaturated aldehydes, and optically active alcohols of over 90% ee's are obtained (entries 9–12). The mixing of chiral spirotitanate **58** with Ti(O-*i*-Pr)$_4$ causes an exchange of the alkoxy ligands, presumably leading to the formation of a monocyclic titanate with two isopropoxy groups. The results show that the chiral titanate derived from the chiral diol accelerates the reaction rate more efficiently than Ti(O-*i*-Pr)$_4$.

Besides the chiral orthotitanate-catalyzed reaction, an enantioselective addition of diethylzinc to benzaldehyde catalyzed by chiral bis[(−)-camphorquinone-α-dioximato]palladium(II) (**59**)[60] affords optically active (*S*)-1-phenylpropanol with 58% ee (entry 13).[61]

B. Heterogeneous Chiral Catalysts

Heterogeneous catalysts have advantages over homogeneous catalysts in their easier separation and recovery from the reaction mixture. The number of turnovers of the reaction may be increased by the repeated use of a heterogeneous chiral catalyst.

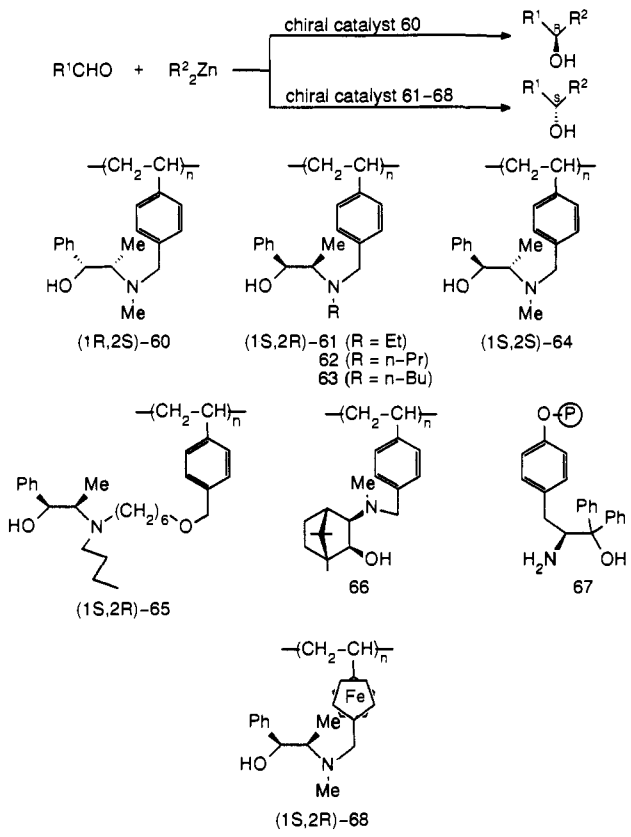
1. Polymer-Supported Chiral Catalysts

Polymer-supported reagents[62] and catalysts[63] have been utilized in organic synthesis. However, the enantioselectivities have been low to moderate in asymmetric carbon–carbon-bond-forming reactions[64] using polymer-

Table 13. Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Chiral Transition Metal Complexes

entry	R^1	ligand (mol %)	$Ti(O\text{-}i\text{-}Pr)_4$, equiv	solvent	T, °C	t, h	yield, %	ee, %	config	ref
1	Ph	**56** (2)	0.2	hexane/toluene	0	2	99	99	*S*	57
2	Ph	**56** (0.05)	1.2	hexane/toluene	−20	2	97	98	*S*	57
3	*trans*-PhCH=CH	**56** (2)	0.3	hexane/toluene	−50	6.5	85	99	*S*	58
4	$Ph(CH_2)_2$	**56** (1)	0.6	hexane/toluene	0	4.5	95	92	*S*	58
5	*n*-hexyl	**56** (4)	0.6	hexane/toluene	−20	5	78	99	*S*	58
6	4-MeO-C_6H_4	**58** (10)	–	toluene	0 to rt	15–70	15	82	*R*	59
7	4-MeO-C_6H_4	**58** (10)	1.2	toluene	−75 to rt	15–24	86	94	*S*	59
8	Ph	**58** (10)	1.2	toluene	−75 to rt	15–24	75	99	*S*	59
9	*n*-hexyl	**58** (10)	1.2	toluene	−75 to rt	15–24	75	92	*S*	59
10	$Ph(CH_2)_2$	**58** (10)	1.2	toluene	−75 to rt	15–24	85	82	*S*	59
11	*i*-Pr	**58** (10)	1.2	hexane	−75 to rt	15–24	44	94	*S*	59
12	*trans*-PhCH=CH	**58** (10)	1.2	toluene	−75 to rt	15–24	89	96	*S*	59
13	Ph	**59** (1)	–	toluene	30	48	98	58	*S*	61

Scheme 19



supported chiral catalysts.[63] Thus, the design of highly effective polymer-bound chiral catalysts is important.

Several polymer-supported chiral catalysts have been reported for the enantioselective addition of dialkylzincs to aldehydes (Scheme 19).

The enantioselective addition of dialkylzincs to aromatic aldehydes in the presence of polymer-supported (1*R*,2*S*)-ephedrine (**60**) as a catalyst afforded optically active alcohols in high ee's (Table 14).[65] The catalyst, **60**, was easily recovered and used repeatedly without a considerable change in enantioselectivity (Table 14, entries 5–7). The enantioselective ethylation of benzaldehyde in the presence of catalyst **60** afforded (*R*)-1-phenylpropanol with 89% ee in 83% yield (Table 14, entry 1). On the other hand, when polymer-bound (1*S*,2*S*)-pseudoephedrine (**64**, diastereoisomer of **60**) was used as a catalyst for the same reaction, (*S*)-1-phenylpropanol with 44% ee was obtained in 84% yield (Table 14, entry 2).[66] This result

Table 14. Enantioselective Addition of Dialkylzincs to Aldehydes Using (1*R*,2*S*)-60 and (1*S*,2*S*)-64 as Polymer-Supported Catalysts[a]

		alcohol				
entry	catalyst	R^1	R^2	yield, %	ee, %	config
1	(1*R*,2*S*)-**60**	Ph	Et	83	89	*R*
2	(1*S*,2*S*)-**64**	Ph	Et	84	44	*S*
3	(1*R*,2*S*)-**60**	Ph	*n*-Pr	57	86	*R*
4	(1*R*,2*S*)-**60**	Ph	*n*-Bu	21	68	*R*
5	(1*R*,2*S*)-**60**	4-Cl-C_6H_4	Et	78	83	*R*
6[b]	(1*R*,2*S*)-**60**	4-Cl-C_6H_4	Et	77	77	*R*
7[c]	(1*R*,2*S*)-**60**	4-Cl-C_6H_4	Et	69	76	*R*

[a] Reference 67. Chloromethylated polystyrene cross-linked with 1% divinylbenzene was used as a support. The reactions were run in hexane at room temperature using 10 mol % (calculated as the content of the amino alcohol part) of catalyst. [b] First recycle. [c] Second recycle.

suggests that, as in the case of monomeric chiral catalysts (**14** and **15**, the configuration of the formed alcohol was attributed to the configuration of the carbon atom of the catalyst to which the hydroxyl group of the catalyst was attached.

Although catalyst **60** was effective for aromatic aldehydes, the enantioselectivity was low in the ethylation of heptanal (aliphatic aldehyde). However, by using polymer-supported (1*S*,2*R*)-*N*-ethylnorephedrine (**61**), an increase in the enantioselectivity was observed in the enantioselective ethylation of aliphatic aldehydes.[67] The results of the enantioselective ethylation of aldehydes using various polymer-supported *N*-alkylnorephedrines (**60–63**) are shown in Figure 6. The following observations can be drawn from Figure 6: (1) For the alkylation of benzaldehyde (aromatic aldehyde), catalyst **60** was the most enantioselective. (2) For the alkylation of aliphatic aldehydes, catalyst **61** was the most enantioselective.

In contrast, DBNE (**24**)[37,38] is an efficient chiral catalyst for the enantioselective alkylation of both aromatic and aliphatic aldehydes. Polymer-supported (1*S*,2*R*)-DBNE containing a hexamethylene spacer (**65**) was found to be an effective chiral catalyst for the enantioselective alkylation of both aromatic and aliphatic aldehydes (Table 15).[68] Among the polymer catalysts reported so far, catalyst **65** is the most enantioselective in the addition of diethylzinc to aliphatic aldehyde (69–70% ee's) (Table 15, entries 2 and 3). The polymer catalyst **65** was easily recovered, and the recovered catalyst showed no loss of the enantioselectivity (Table 15, entry 3). The reason for the high enantioselectivity of **65** in the ethylation of the aliphatic aldehyde may

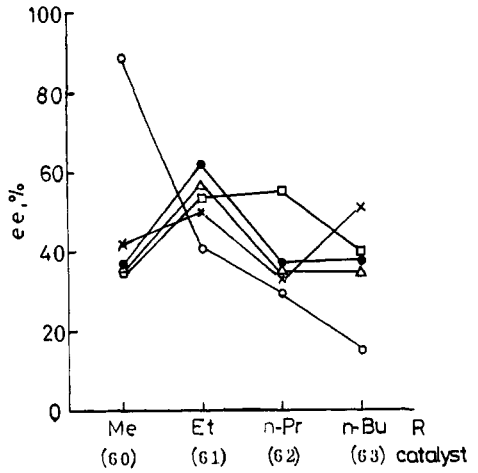


Figure 6. Relation between *N*-alkyl groups (R) of the catalyst **60–63** and ee's of the alcohols obtained from the enantioselective addition of diethylzinc to aldehydes (R^1CHO): R^1 = ●, *n*-hexyl; △, *n*-octyl; □, Me_2CHCH_2; ×, cyclohexyl; ○, phenyl.

Table 15. Enantioselective Addition of Diethylzinc to Aldehydes Using Polymer-Supported Catalyst (1*S*,2*R*)-65[a]

		(*S*) alcohol	
entry	R^1	yield, %	ee, %
1	Ph	91	82
2	*n*-octyl	75	69
3[b]	*n*-octyl	80	70
4	$PhCH_2CH_2$	77	75

[a] Reference 68. [b] Recycled catalyst **65** was used.

be the presence of the hexamethylene spacer which assures the freedom of the active site of DBNE (**24**).

Itsuno and Fréchet et al. reported the enantioselective addition of diethylzinc to aromatic aldehydes using a polymer-supported chiral catalyst, **66**,[69] derived from (−)-**8** (Table 16).[13,14] Aromatic aldehydes were ethylated in high ee's (Table 16, entries 1–3).

It is also reported that cross-linked polymers containing a chiral primary amino and tertiary alcohol, **67**, catalyzed the enantioselective ethylation.[70] Optically active (*S*) alcohols with moderate to high ee's were obtained using **67** (Table 16, entries 4–7). The primary amino group of the chiral amino alcohols reacts with the aldehydes to afford a Schiff base, which accelerates the enantioselective addition of diethylzinc to aldehydes. Furthermore, the asymmetric ethylation of 4-chlorobenzaldehyde in a continuous-flow system using polymer-supported **67** afforded (*S*)-1-(4-chlorophenyl)-propanol with 94% ee.[70]

In contrast, chiral polymers possessing *N*-ferrocenylephedrine (**68**) also catalyzed the enantioselective addition of Et_2Zn to benzaldehyde.[71] By using 5 mol % of chiral polymer **68** containing 33 mol % of (1*S*,2*R*)-ephedrine unit gave (*S*)-1-phenylpropanol with 72% ee (Table 16, entry 8).

2. Chiral Catalysts Supported on Silica Gel and Alumina

Silica gel and alumina are widely utilized as the stationary phase in chromatographic separations, as acidic or basic catalysts,[72] and insoluble supports for reagents in organic synthesis.[73]

Chiral *N*-alkylnorephedrines are immobilized on (3-chloropropyl)silyl-functionalized alumina or silica gel using a silane coupling reagent (3-chloropropyl)-trimethoxysilane. Optically active secondary (*R*) alcohols are obtained in moderate ee's using (1*R*,2*S*)-**69** (Table 17) and (1*R*,2*S*)-**70** (Table 18) (Scheme 20).[74] (1*R*,2*S*)-Ephedrine immobilized on silica gel coated with polystyrene (**71**) is also a chiral catalyst which affords optically active secondary alcohol in moderate ee's (Table 19).[74]

Although the ee's are moderate, these chiral catalysts represent the first example of the use of silica gel and alumina as heterogeneous supports for chiral catalysts in an asymmetric carbon–carbon-bond-forming reaction.

III. Enantioselective Addition of Various Organozinc Reagents to Aldehydes

A. Alkynylzinc Reagents

The enantioselective addition of dialkynylzinc reagents to aldehydes in the presence of a chiral amino alcohol as catalyst (5 mol %) afforded optically active alkynyl alcohols in moderate ee's (Scheme 21; Table 20).[75] Treatment of bis(2-phenylethynyl)zinc with benzaldehyde at room temperature in the presence of 5 mol % of (1*S*,2*R*)-(−)-DBNE (**24**) in hexane–tetrahydrofuran (2:3, v/v) afforded (*R*)-1,3-diphenyl-1-propyn-3-ol with 34% ee in 99% yield (Table 20, entry 1). When 20 mol % of DBNE was used, a higher enantioselectivity (43% ee) was observed (Table 20, entry 2). Dialkynylzinc reagents attacked aldehydes from the same side as the dialkylzinc reagents[37] did. In addition the results using alkylalkynylzinc reagents during the 2-phenylethynylation of benzaldehyde are also shown in Scheme 21. The enantioselectivity increased when ethyl- or methyl(2-phenylethynyl)zinc was used instead of the dialkynylzinc in the presence of 5 mol % (1*S*,2*R*)-DBNE. When alkylalkynylzinc reagents were used, only alkynylation of the aldehyde occurred and alkylation did not occur.

Tombo et al. reported the enantioselective addition of alkynylzinc bromide to aldehyde (Table 21).[76] The reaction of 3-phenoxy-4-(fluorophenyl)benzaldehyde with 2 equiv of 2-phenylzinc bromide in the presence of 1 equiv of the lithium salt of (1*R*,2*S*)-(−)-*N*-methylephedrine (**72**) afforded the corresponding (*S*) alcohol in 88% ee. The latter is an alcohol moiety of an insecticide, **73**, with low fish toxicity.

B. Divinylzinc and Alkenylzinc Bromides

Enantioselective addition of divinylzinc to both aromatic and aliphatic aldehydes was reported by Oppolzer and Radinov using **74** as a chiral catalyst.[77] Optically active allyl alcohols were obtained in 82 to >96% ee's (Scheme 22; Table 22, entries 1–5). Matsutakeol (1-octen-3-ol) was synthesized in 88 to >96% ee's by the enantioselective addition of divinylzinc to hexanal (entries 2 and 3).

Optically active allyl alcohols are important synthetic intermediates. This method is complimentary to the enantioselective addition of dialkylzinc to α,β-unsaturated aldehydes which is described in section IV.H.

Table 16. Enantioselective Ethylation of Aldehydes Catalyzed by Polymer-Supported Catalysts

entry	R^1	catalyst (mol %)	solvent	T, °C	t, h	yield, %	ee, %	config	ref
1	Ph	**66** (5)	toluene	0	73	91	92	*S*	69
2	2-MeO-C_6H_4	**66** (5)	toluene	0	24	88	93		69
3	2-EtO-C_6H_4	**66** (5)	toluene	0	24	92	95		69
4	Ph	**67** (5)	toluene	0	24	90	75	*S*	70
5	2-MeO-C_6H_4	**67** (5)	toluene	0	24	94	54	*S*	70
6	2-EtO-C_6H_4	**67** (5)	toluene	0	24	95	99	*S*	70
7	*n*-Bu	**67** (5)	toluene	rt	120	84	65	*S*	70
8	Ph	**68** (5)	hexane		8	85	72	*S*	71

Table 17. Enantioselective Addition of Dialkylzincs to Aromatic Aldehydes Using a Heterogeneous Chiral Catalyst Immobilized on Alumina, (1*R*,2*S*)-69[a]

entry[b]	R^1	R^2	solvent	t, days	yield, %	ee, %	config
1	Ph	Et	hexane	2	81	43	*R*
2	Ph	Et	hexane	5	79	59	*R*
3	Ph	*n*-Bu	hexane	5	13	40	*R*
4	4-CH_3-C_6H_4	Et	hexane	5	58	55	*R*
5	Ph	Et	hexane/benzene	3	66	50	*R*

[a] Reference 74. Reactions were run at 0 °C. [b] Amounts of aldehyde, catalyst, and dialkylzinc are 0.98 mmol, 0.130 g, and 2.2 mmol, respectively.

Table 18. Enantioselective Addition of Dialkylzincs to Aldehydes Using a Heterogeneous Chiral Catalyst Immobilized on Silica Gel, (1*R*,2*S*)-70[a]

entry	R^1	R^2	solvent	yield, %	ee, %	config
1	Ph	Et	hexane	47	37	*R*
2	Ph	*n*-Pr	hexane	12	38	*R*
3	2-naphthyl	Et	hexane	56	33	*R*
4	4-CH_3-C_6H_4	Et	hexane	33	40	*R*
5	Ph	Et	hexane/benzene	69	39	*R*

[a] Reference 74. Reactions were run at 0 °C for 4–5 days.

Table 19. Enantioselective Addition of Diethylzinc to Aldehydes Using (1*R*,2*S*)-Ephedrine Immobilized on Silica Gel Coated with Polystyrene as Chiral Catalyst (1*R*,2*S*)-71[a]

entry	R^1	solvent	T, °C	t, days	yield, %	ee, %	config
1	Ph	hexane	0	5	56	36	*R*
2	Ph	hexane/benzene	0	5	64	56	*R*
3	Ph	hexane/benzene	rt	3	66	49	*R*
4[b]	Ph	hexane/benzene	rt	3	78	49	*R*
5	Ph	benzene	rt	5	63	48	*R*
6	*n*-octyl	hexane/benzene	rt	5	40	48	*R*

[a] Reference 74. [b] Recycled catalyst is used.

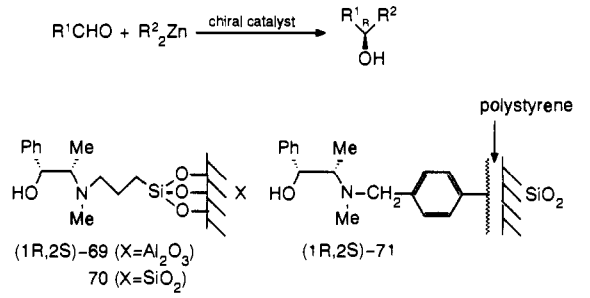
Amino alcohol **74** is also effective in the enantioselective addition of diethylzinc to benzaldehyde (92% ee, (*S*)-1-phenylpropanol).

As also shown in Scheme 22, alkenylzinc bromides add to aldehydes to afford optically active allylalcohols in high ee's in the presence of a stoichiometric amount of the lithium salt of (1*S*,2*R*)-*N*-methylephedrine (**72**) or the lithium salt of (1*S*,2*R*)-(dimethylamino)-1,2-diphenylethanol (**75**) (entries 6–8).[78]

C. Enantioselective Phenylation

Enantioselective addition of phenylmetal reagent to aldehydes affords optically active aromatic alcohols. Some of the aromatic alcohols are natural products,

Scheme 20



Scheme 21

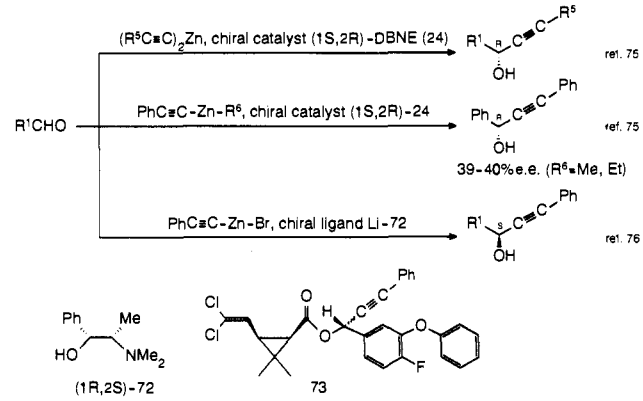


Table 20. Enantioselective Addition of Alkynylzinc Reagent to Aldehydes Using (1*S*,2*R*)-(−)-DBNE (24) as a Catalyst[a]

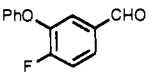
				alkynyl alcohol		
entry	R^1	R^5	t, h	yield, %	ee, %	config
1	Ph	Ph	14	99	34	*R*
2[b]	Ph	Ph	14	99	43	*R*
4	*trans*-PhCH=CH	Ph	14	97	10	
5	Ph	*n*-hexyl	44	81	22	
6	Ph	*n*-Bu	52	93	20	
7	Ph	Me_3Si	168	36	21	*R*
8	*n*-octyl	Me_3Si	48	80	24	*R*

[a] Reference 75. The reactions were carried out at room temperature in hexane/THF (2:3) in the presence of (1*S*,2*R*)-DBNE (24). Unless otherwise noted, molar ratio: R^1CHO/dialkynylzinc/DBNE = 1.0:2.0:0.05. [b] Molar ratio: R^1CHO/dialkynylzinc/DBNE = 1.0:2.0:0.2.

and the phenyl group can be oxidatively converted to carboxylic acid.[79] Therefore, enantioselective phenylation is of synthetic importance. However, there are very few enantioselective phenylations[80] compared with the reactions with dialkylzincs.

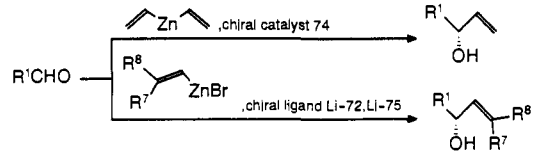
Organo phenylmetal reagent (PhM), prepared from phenylmagnesium bromide and zinc chloride, adds to aliphatic, aromatic, and α,β-unsaturated aldehydes in high ee's (up to 82% ee) in the presence of (1*R*,2*S*)-DBNE (24) (Scheme 23; Table 23).[81]

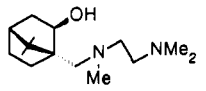
Table 21. Enantioselective Addition of 2-Phenylethynylzinc Bromide to Aldehydes Using Lithium Salt of 72 as a Chiral Ligand[a]

entry	R^1CHO	T, °C	t, h	alcohol yield, %	alcohol ee, %	alcohol config
1		0 to 5	20	80	88	*S*
2	PhCHO	−30	19	70	80	*S*
3	*t*-BuCHO	−30	24	50	67	
4	*n*-BuCHO	−30	20	90	19	

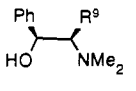
[a] Reference 76.

Scheme 22





74



(1S,2R)-72 (R^9=Me)
(1S,2R)-75 (R^9=Ph)

The kinetically formed (0 °C, 20 s) chiral complex between PhM and DBNE is more enantioselective than the thermodynamically formed chiral complex. Aldehydes react with organo phenylmetal reagent from the *si* face in the presence of (1*R*,2*S*)-(+)-DBNE. This enantioselectivity is *opposite* to that observed with dialkylzincs[38] which react with aldehydes from the *re* face in the presence of (1*R*,2*S*)-DBNE (**24**).

It is known that Grignard reagent and zinc chloride form an equilibrium mixture of diphenylzinc and magnesium halide. However, the actual reactive species of this enantioselective phenylation is not considered to be diphenylzinc itself, because the reaction of pure diphenylzinc (crystalline) with aromatic aldehyde in the presence of DBNE is very sluggish.

In contrast, Hübscher and Barner reported the diastereoselective synthesis of a key intermediate for the synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol (**76**) in 92% de by the addition of diarylzinc, prepared from aryl Grignard reagent and zinc chloride, to phytenal in the presence of 1-*endo*-aminoborneol (**77**) (2 mol %).[82]

D. Enantioselective Furylation

Optically active furyl alcohols **78** form an important class of compounds because the furyl group can be easily converted into many other functionalities.[83] Although diastereoselective furylation of aldehyde has been reported,[84] no report has appeared on the enantioselective furylation of aldehydes.

Difurylzinc, prepared in situ from furyllithium and zinc chloride adds to aromatic and α,β-unsaturated aldehyde in the presence of either a stoichiometric or a catalytic amount of (1*S*,2*R*)-*N*,*N*-di(4-phenylbutyl)-norephedrine (**79**) to afford optically active furyl alcohols **78** in good ee's (up to 73% ee) (Scheme 24; Table 24, entry 2).[85] The presence of lithium chloride increases the enantioselectivity, which is probably due to the effect of the chelation of lithium cation with the oxygen atom of the furan ring.

(1*S*,2*R*)-DBNE (**24**) is also an effective chiral ligand. In the presence of (1*S*,2*R*)-DBNE, difurylzinc approaches benzaldehyde from the *re* face to afford the furyl alcohol of (*S*) configuration. It should be noted that the stereochemical course is the *reverse* of that for dialkylzincs[38] where the aldehyde is attacked from the *si* face to afford (*S*) alcohol.

E. Enantioselective Reformatsky Reaction

The Reformatsky reaction affords synthetically useful β-hydroxy esters from alkyl haloacetates, zinc, and aldehydes.[86]

An early example of the enantioselective Reformatsky reaction, employing (−)-sparteine (a di-tertiary-amine) as a chiral ligand, affords a β-hydroxy ester of high ee in low yield in one case (the reaction of ethyl bromoacetate and benzaldehyde).[87] However, the reaction lacks generality and the ee's of other β-hydroxy esters are low to moderate (Table 25, entry 1).

Optically active (*S*)-DPMPM (**12**) is an efficient chiral ligand for the enantioselective Reformatsky reaction with aromatic and aliphatic aldehydes to afford optically active β-hydroxy esters (**80**) of good enantiomeric purities (up to 78% ee) (Scheme 25; Table 25, entry 3).[88] Optically active (*S*)-β-hydroxy ester **80** of 44% ee is obtained when a catalytic amount of (*S*)-DPMPM (**12**) was employed (entry 5). Aldehydes are attacked from the *si* face in the presence of (*S*)-DPMPM. This stereochemical course is the *same* as that of dialkylzincs to afford β-hydroxy esters.[21] When the methyl ether of (1*R*,2*S*)-DBNE was used, enantioselectivity was very low (1% ee). Therefore, the hydroxy group of the amino alcohol, which becomes zinc alkoxide during the reaction, is essential for this reaction.

IV. Enantioselective and Chemoselective Addition to Aldehydes with Functional Groups

A. Addition to Formyl Esters. Enantioselective Synthesis of Hydroxy Ester and Lactone

The optically active hydroxy esters, 4-alkyl-γ-butyrolactone (**82**) and 5-alkyl-δ-valerolactone (**83**), are important compounds. Some of the lactones are pheromones and key intermediates of a pheromone and a retro steroid.

A new method for the asymmetric synthesis of 2-substituted lactones which includes a *catalytic* asymmetric alkylation of prochiral 3- and 4-formyl esters was reported (Scheme 26).[89]

When ethyl 4-formylbutanoate was reacted with Et_2Zn using (1*S*,2*R*)-DBNE (**24**), the corresponding (*S*)-5-hydroxyheptanoic acid ethyl ester (**81**, n = 2) was obtained in 87% yield (Table 26, entry 6). This shows that Et_2Zn reacted with the aldehyde in enantioselective and chemoselective manner in the presence of an ester group. The subsequent hydrolysis of the ester group and the following spontaneous cyclization afforded (*S*)-(−)-5-heptanolide (**83**), a key intermediate of a retro steroid,[90] with 95% ee in 98% yield (entry 6). When (1*R*,2*S*)-DBNE (**24**) was used as a chiral catalyst, (*R*)-**83** with 95% ee was obtained in 97% yield (entry

Table 22. Enantioselective Addition of Divinylzinc and Alkenylzinc Bromides to Aldehydes Catalyzed by or in the Presence of Chiral Amino Alcohol[a]

entry	R^1	Zn reagent	catalyst/ligand (mol %)	yield, %	ee, %	config	ref
1	Ph	$(CH_2{=}CH)_2Zn$	**74** (2)	96	87	*S*	77
2	*n*-pentyl	$(CH_2{=}CH)_2Zn$	**74** (2)	88	88	*R*	77
3	*n*-pentyl	$(CH_2{=}CH)_2Zn$	**74** (20)	90	>96	*R*	77
4	*n*-hexyl	$(CH_2{=}CH)_2Zn$	**74** (2)	86	87	*R*	77
5	cyclohexyl	$(CH_2{=}CH)_2Zn$	**74** (2)	83	82	*S*	77
6	Ph	(*Z*)-$CH_3CH{=}CHZnBr$	**72** (100)	68	86	*S*	78
7	*t*-Bu	(*E*)-$CH_3CH{=}CHZnBr$	**72** (100)	48	>98	*S*	78
8	Ph	(*Z*)-$CH_3CH{=}CHZnBr$	**75** (100)	82	93	*S*	78

[a] Reactions were carried out in a mixed solvent of hexane and ether at 0 °C for 1–3 h.

Scheme 23

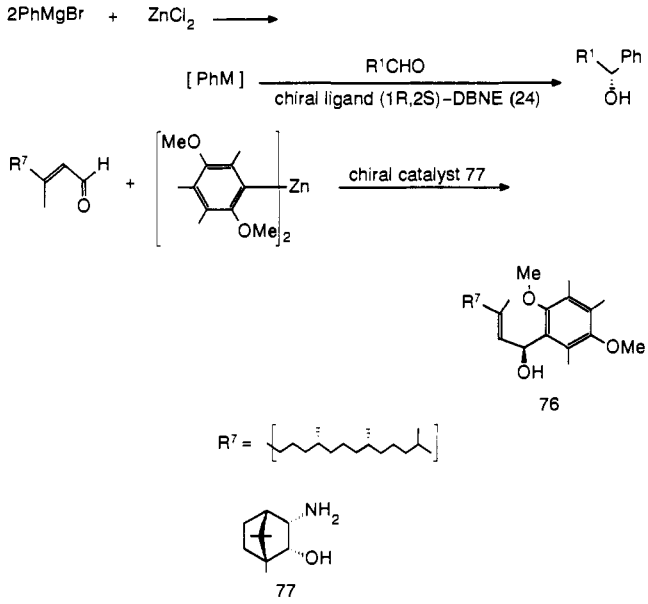
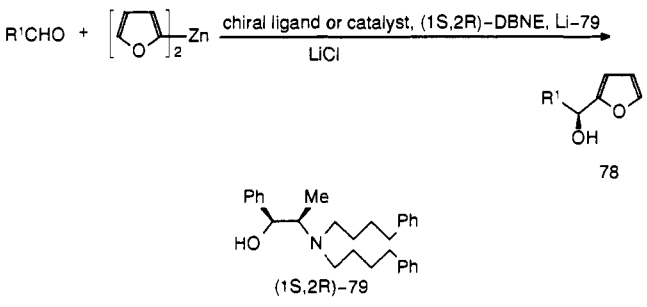


Table 23. Enantioselective Phenylation of Aldehydes Using a Kinetically Formed Chiral Complex between Grignard–Zinc Halide Reagent and (1*R*,2*S*)-(+)-DBNE (24)[a]

entry	R^1	yield, %	ee, %	config
1	2-naphthyl	83	79	
2	4-MeO-C_6H_4	41	68	*S*
3	*trans*-PhCH=CH	90	82	*R*
4	*i*-Pr	44	78	*R*
5	*n*-hexyl	43	79	*R*

[a] Reference 81. Reactions are run in a mixed solvent of THF and hexane at room temperature for 30 min.

Scheme 24



7). Similarly, (*S*)-(−)-4-hexanolide (**82**) was obtained in 92% ee (entry 3); it is a key intermediate in the synthesis of chalcograne (a pheromone of a species of beetle).[91]

Table 24. Enantioselective Furylation of Aldehydes Using Lithium Salt of (1*S*,2*R*)-*N*,*N*-Di(4-phenylbutyl)norephedrine (79) as a Chiral Ligand or a Catalyst in the Presence of Lithium Chloride[a]

entry	R^1	yield, %	ee, %	config
1[b]	Ph	62	72	*S*
2[b]	4-MeO-C_6H_4	58	73	
3[b]	2-Naphthyl	68	59	
4[b]	*trans*-PhCH=CH	79	45	
5[c]	Ph	53	30	*S*

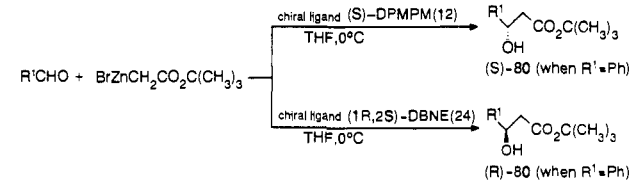
[a] Reference 85. Reactions were run in a mixed solvent of THF and hexane at 0 °C. [b] Molar ratio: R^1CHO/difurylzinc/chiral ligand/LiCl = 1:2.5:1:4.9–5.0. [c] Molar ratio: R^1CHO/difurylzinc/chiral ligand/LiCl = 1:2.5:0.3:5.7.

Table 25. Enantioselective Reformatsky Reaction of $BrZnCH_2CO_2CMe_3$ with Aromatic and Aliphatic Aldehydes Using Chiral Ligand or Catalyst[a]

entry	R^1	ligand	yield, %	ee, %	config	ref
1	Ph	(−)-sparteine	62	53		87
2[b]	Ph	(*S*)-DPMPM (**12**)	91	75	*S*	88
3[b]	2-naphthyl	(*S*)-DPMPM (**12**)	82	78		88
4[b]	*n*-Pr	(*S*)-DPMPM (**12**)	60	56	*R*	88
5[c]	Ph	(*S*)-DPMPM (**12**)	81	44	*S*	88
6[c]	Ph	(1*R*,2*S*)-DBNE (**24**)	89	37	*R*	88

[a] For entries 2–6, reactions were run in THF at 0 °C for 24 h. [b] Molar ratio: R^1CHO/(*S*)-DPMPM/Reformatsky reagent = 1:1:3. [c] Molar ratio: R^1CHO/(*S*)-DPMPM/Reformatsky reagent = 1:0.4:3.

Scheme 25



B. Addition to Keto Aldehydes. Synthesis of Optically Active Hydroxy Ketones

Optically active hydroxy ketones **85** are important synthetic intermediates. Various organometallic reagents[92] have been used for the chemoselective *non asymmetric* alkylation of aldehydes in the presence of ketones. However, no *catalytic asymmetric* synthesis of **85** from keto aldehydes **84** has been reported. In contrast, hydroxy ketones were obtained in high yields by the chemoselective nonasymmetric alkylation of the formyl group of keto aldehydes with dialkylzincs in the presence of *achiral* catalysts.[12]

The *first catalytic* asymmetric synthesis of hydroxy ketones **85** by the chemo- and enantioselective alky-

Scheme 26

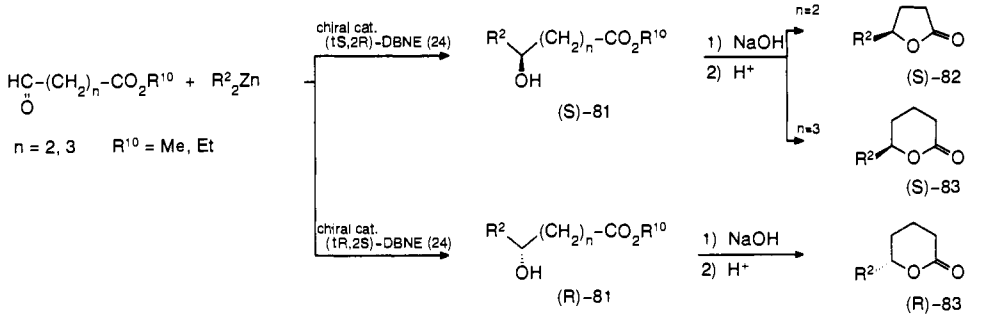
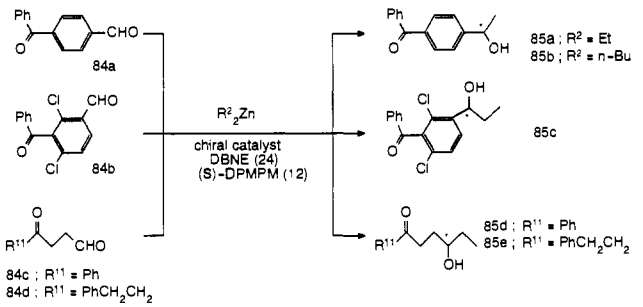


Table 26. Enantioselective Synthesis of Hydroxy Esters and Lactones[a]

	formyl ester			hydroxy ester	lactone			
entry	n	R^{10}	R^2	yield, %		yield, %	ee, %	config
1	2	Me	Et	88	**82**	96	85	*S*
2	2	Et	Me	78	**82**	95	90	*S*
3	2	Et	Et	90	**82**	97	92	*S*
4	3	Me	Et	83	**83**	97	88	*S*
5	3	Et	Me	88	**83**	97	91	*S*
6	3	Et	Et	87	**83**	98	95	*S*
7[b]	3	Et	Et	85	**83**	97	95	*R*

[a] Unless otherwise noted, (1*S*,2*R*)-DBNE (**24**) was used. [b] (1*R*,2*S*)-DBNE was used.

Scheme 27



lation of **84** with dialkylzincs was reported using (*S*)-DPMPM (**12**) and (1*S*,2*R*)- and (1*R*,2*S*)-DBNE (**24**) as chiral catalysts (Scheme 27).[93]

When 4-benzoylbenzaldehyde (**84a**) was treated with diethylzinc using (*S*)-DPMPM (**12**) as a catalyst, 4-(1-hydroxypropyl)benzophenone (**85a**) with 93% ee was obtained in 99% yield as a result of the enantioselective and chemoselective alkylation of aldehyde (Table 27, entry 1). The use of (1*S*,2*R*)-DBNE (**24**) as a catalyst afforded **85a** with 91% ee (entry 2).

Both enantiomers of γ-hydroxy ketone **85d** were obtained with the same ee's and yields within experimental error using (1*S*,2*R*)- and (1*R*,2*S*)-DBNE (**24**) (entries 5 and 6). The method is a unique approach to optically active γ-hydroxy ketones **85d,e**, which have the same structure of the product of homoaldol reaction.

C. Addition to Alkynyl Aldehydes. Synthesis of Optically Active Alkynyl Alcohols

Optically active *sec*-alkynyl alcohols **87** are an important class of compounds such as in natural products and biologically active compounds.[94] Conventional methods of the asymmetric synthesis of **87** require *stoichiometric amounts* of chiral auxiliaries.[95]

Catalytic enantioselective synthesis of alkynyl alcohols **87** by the enantioselective addition of dialkylzincs to alkynyl aldehydes **86** in the presence of a chiral catalyst was reported (Scheme 28).

When 3-(trimethylsilyl)-2-propynal (**86a**) was treated with diethylzinc using (*S*)-DPMPM (**12**) as a catalyst, (−)-1-(trimethylsilyl)-1-pentyn-3-ol (**87a**) with 78% ee was obtained in 67% yield (Table 28, entry 1).[96] Various optically active alkynyl alcohols **87** were obtained in the same manner. Furthermore, the addition of dipentylzinc to **86a** afforded (*S*)-1-(trimethylsilyl)-1-octyn-3-ol (**87c**) in reasonable ee (70% ee, entry 3).[75] Removal of the trimethylsilyl group from (*S*)-**87c** afforded (*S*)-(−)-1-octyn-3-ol (**88**) with 70% ee which is a building block for prostaglandin synthesis.[97]

The method is complimentary to the enantioselective synthesis of alkynyl alcohols by alkynylation of aldehydes which is described in section III.A.

D. Synthesis of Optically Active Hydroxy Aldehydes

Optically active hydroxy aldehydes are versatile synthetic intermediates for the synthesis of natural products[98] and liquid crystals.[99] However, only limited methods have been reported for the asymmetric synthesis of hydroxy aldehydes.[100]

Optically active hydroxy aldehydes **91** are synthesized in high ee by the catalytic enantioselective addition of dialkylzincs using (1*R*,2*S*)-DBNE (**24**) (Scheme 29).[101] When 4-(diethoxymethyl)benzaldehyde (**89**) was reacted with diethylzinc using (1*R*,2*S*)-DBNE (**24**), the corresponding hydroxy acetal (**90**) was obtained, and subsequent acidic hydrolysis afforded (*R*)-(+)-**91b** with 94% ee in 76% yield.

E. Addition to Furyl Aldehydes. Synthesis of Optically Active Furyl Alcohols

Optically active furyl alcohols form an important class of compounds, because the furyl group is recognized as a substrate for the facile introduction of further functionalities.[83,84]

Optically active 2- and 3-furyl alcohols were synthesized in high ee by the enantioselective addition of dialkylzinc reagents to 2-furyl aldehydes (**92**) or 3-furyl aldehyde (**92e**) using DBNE (**24**) and (*S*)-DPMPM (**12**) as chiral catalysts (Scheme 30; Table 29).[102] The method is complimentary to the enantioselective furylation of aldehydes (section III.D).

Feringa et al. independently reported[103] the enantioselective synthesis of 5-substituted-2-furyl alcohols using quinine, (−)-8, DBNE (**24**), and (*S*)-DPMPM (**12**) as catalysts. One of the optically active furyl alcohols obtained was converted to the optically active butenolide **94** (Scheme 30).[103]

Table 27. Catalytic Asymmetric Synthesis of Hydroxy Ketones[a]

entry	ketoaldehyde 84	R^2	catalyst	hydroxy ketone 85	yield, %	ee, %	config[b]
1	**84a**	Et	(*S*)-DPMPM (**12**)	**85a**	99	93	*S*
2	**84a**	Et	(1*S*,2*R*)-DBNE (**24**)	**85a**	84	91	*S*
3	**84a**	*n*-Bu	(*S*)-DPMPM (**12**)	**85b**	64	92	*S*
4	**84b**	Et	(*S*)-DPMPM (**12**)	**85c**	100	88	*S*
5	**84c**	Et	(1*S*,2*R*)-DBNE (**24**)	**85d**	52	87	
6	**84c**	Et	(1*R*,2*S*)-DBNE (**24**)	**85d**	48	85	
7	**84d**	Et	(1*S*,2*R*)-DBNE (**24**)	**85e**	47	81	

[a] Reference 93. [b] Tentatively assigned.

Scheme 28

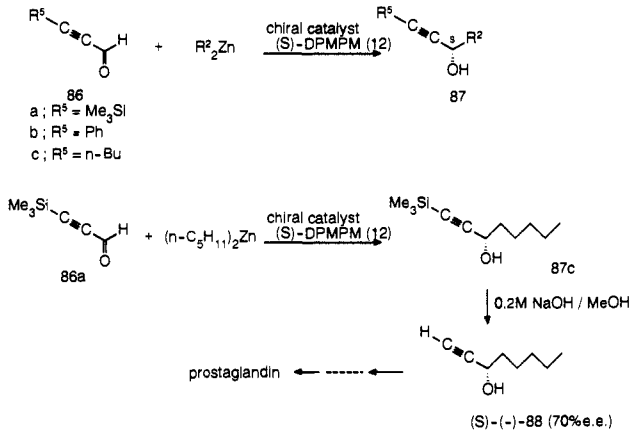
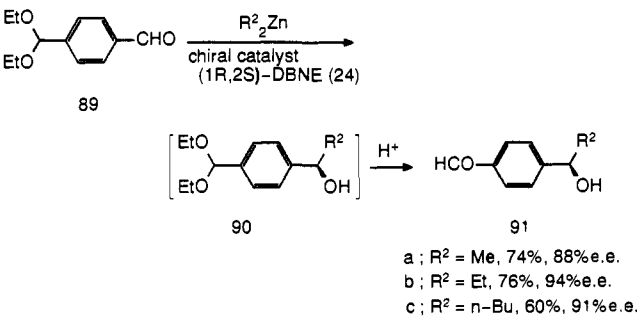


Table 28. Catalytic Asymmetric Synthesis of Optically Active Alkynyl Alcohols by Enantioselective Alkylation of Alkynyl Aldehydes Using (*S*)-DPMPM (**12**) as a Chiral Catalyst[a]

entry	aldehyde 86 R^5	aldehyde 86 R^2	alkynyl alcohol 87	yield, %	ee, %	config
1	Me_3Si (**86a**)	Et	**87a**	67	78	
2	Me_3Si (**86a**)	*n*-Bu	**87b**	54	72	*S*
3	Me_3Si (**86a**)	*n*-pentyl	**87c**	55	70	*S*
4	Me_3Si (**86a**)	*i*-Pr	**87d**	52	43	
5	Ph (**86b**)	Me	**87e**	26	40	*S*
6	Ph (**86b**)	Et	**87f**	70	70	*S*
7	Ph (**86b**)	*n*-Bu	**87g**	61	67	
8	*n*-Bu (**86c**)	Et	**87h**	71	64	*S*

[a] Reference 96.

Scheme 29



Chiral amino alcohol (**35**) was also used as a chiral catalyst for this reaction.[104]

F. Addition to Pyridyl Aldehydes. Synthesis of Optically Active Pyridyl Alcohols

Optically active pyridylalkyl alcohols are important synthetic intermediates.[105] Asymmetric reduction of acylpyridines by biochemical[105a,106] and chemical[107] methods has been reported. Biochemical reduction can afford only one enantiomer, and it is difficult to obtain the enantiomer of the opposite configuration. On the other hand, chemical methods require stoichiometric amounts of chiral auxiliaries and most of the chemical reductions afford optically active pyridylalkyl alcohols with low to moderate ee's.

The addition of diisopropylzinc to 3-pyridinecarbaldehyde in the presence of (1*S*,2*R*)-DBNE (**24**) (mol ratio to aldehyde was 0.75) afforded (−)-2-methyl-1-(3-pyridyl)propanol (**95**, R^2 = *i*-Pr) in 86% ee (Scheme 31).[108] Other pyridylalkyl alcohols were obtained in moderate to good ee's. Unlike the reaction with benzaldehyde, isopropylation of nicotinaldehyde afforded the corresponding alcohol in higher enantioselectivity than other dialkylzincs with straight carbon chains.

G. Addition to Terephthalyl Aldehyde. Enantioselective Synthesis of Diol

Optically active diols with C_2 symmetry axis have been utilized as chiral auxiliaries in asymmetric synthesis and in chiral recognition chemistry.[51]

Enantioselective addition of dialkylzinc to dialdehyde may afford the optically active diol.

When terephthalyl aldehyde is treated with diethylzinc in a mixed solvent of THF and hexane at refluxing temperature for 40 min using (1*S*,2*R*)-DBNE (**24**) as a chiral catalyst, the corresponding diol [1,4-bis(1-hydroxypropyl)benzene (**96**)] was obtained in 74% yield (ratio *dl*/*meso* = 80:20). The ee of the optically active diol is 100% (Scheme 32).[109] When the same reaction is run at room temperature, the diol of 100% ee was obtained (54%, *dl*/*meso* = 84:16). The opposite enantiomer of the diol of 100% ee was obtained using (*S*)-DPMPM (**12**) as a chiral catalyst.

H. Addition to α,β-Unsaturated Aldehyde. Asymmetric Synthesis of Allyl Alcohol

Optically active allyl alcohols are useful synthetic intermediates. Enantioselective 1,2-addition of dialkylzincs to α,β-unsaturated aldehyde provides optically active allyl alcohols **97** (Scheme 33). The results using various chiral catalysts are shown in Table 30. Various optically active allyl alcohols **97** were obtained in high ee's. The method is complimentary to the enantioselective alkenylation (vinylation) of aldehydes which is described in section III.B.

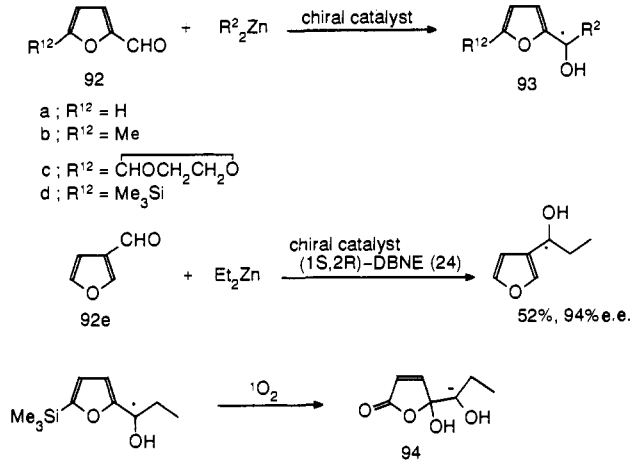
I. Enantioselective Synthesis of 3-Alkylphthalide

Optically active 3-alkylphthalides are substances present in naturally occurring compounds such as celery

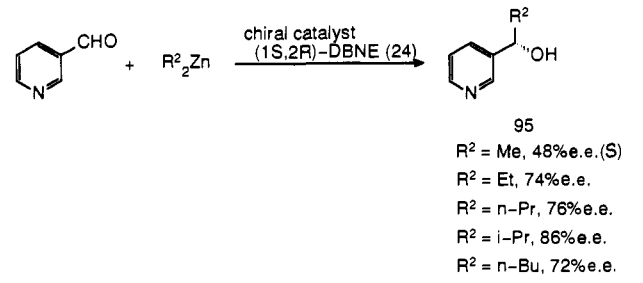
Table 29. Synthesis of Furyl Alcohols by the Enantioselective Alkylation of Furyl Aldehydes

entry[a]	aldehyde, 92	R^2	catalyst	solvent	T, °C	93 yield, %	93 ee, %	93 config	ref
1	**92a**	Me	(*S*)-DPMPM (**12**)	hexane	0	53	70	*S*	102
2	**92a**	Me	(*R*)-**35**	Et_2O	15	76	75	*R*	104
3	**92a**	Et	quinine	toluene	4	83	60	*S*	103
4	**92a**	Et	(−)-**8**	toluene	−	68	65	*S*	103
5	**92a**	Et	(*S*)-DPMPM (**12**)	hexane	0	94	88	*S*	102
6	**92a**	Et	(1*S*,2*R*)-DBNE (**24**)	hexane	0	83	89	*S*	102
7	**92a**	Et	(1*R*,2*S*)-DBNE (**24**)	hexane	0	74	88	*R*	102
8	**92a**	Et	(1*S*,2*R*)-DBNE (**24**)	hexane	−	82	93	*S*	103
9	**92a**	*n*-Bu	(1*S*,2*R*)-DBNE (**24**)	hexane	0	58	90	−	102
10	**92a**	Et	(*R*)-**35**	hexane	−10	96	92	*R*	104
11	**92b**	Et	(1*S*,2*R*)-DBNE (**24**)	hexane	0	79	87	*S*	102
12	**92b**	Et	(1*S*,2*R*)-DBNE (**24**)	hexane	−	88	91	*S*	103
13	**92b**	Et	(−)-**8**	toluene	−	91	97	*S*	103
14	**92c**	Et	(*S*)-DPMPM (**12**)	hexane	−	77	72	*S*	103
15	**92d**	Et	(*S*)-DPMPM (**12**)	hexane	−	84	94	*S*	103
16	**92e**	Et	(1*S*,2*R*)-DBNE (**24**)	hexane	0	52	94	−	102

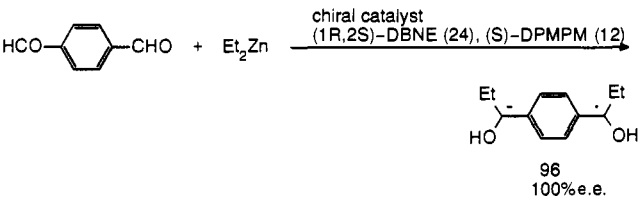
Scheme 30



Scheme 31



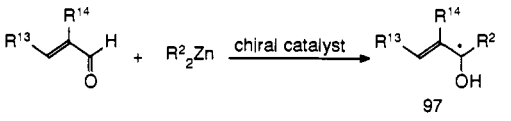
Scheme 32



oil[110] and alkaloids.[111] Most of their asymmetric syntheses are diastereoselective reactions[112] which require stoichiometric amounts of chiral auxiliaries and require the steps of the introduction/removal of chiral auxiliaries to/from the substances.

A catalytic enantioselective synthesis of optically active 3-alkylphthalides (**100**) was reported (86–90% ee) (Scheme 34).[113] The key step is the enantioselective addition of dialkylzincs to 2-bromobenzaldehyde

Scheme 33



(**98**) using DBNE (**24**) as a chiral catalyst. The obtained optically active alcohols **99** were derived into optically active **100** without any racemization. When (1*R*,2*S*)-DBNE (**24**) was used in the enantioselective addition of di(*n*-butyl)zinc to aldehyde **98**, (*R*)-(+)-3-*n*-butylphthalide (**100b**), a component of celery oil, with 86% ee was synthesized. On the other hand, (1*S*,2*R*)-DBNE afforded (*S*)-3-*n*-butylphthalide. Enantioselective addition of diethylzinc afforded 3-ethylphthalide (**100a**) with 90% ee.

V. Stereoselective Addition to Chiral Aldehydes

A. Diastereoselective Addition to 2-Phenylpropanal Using Achiral Catalyst

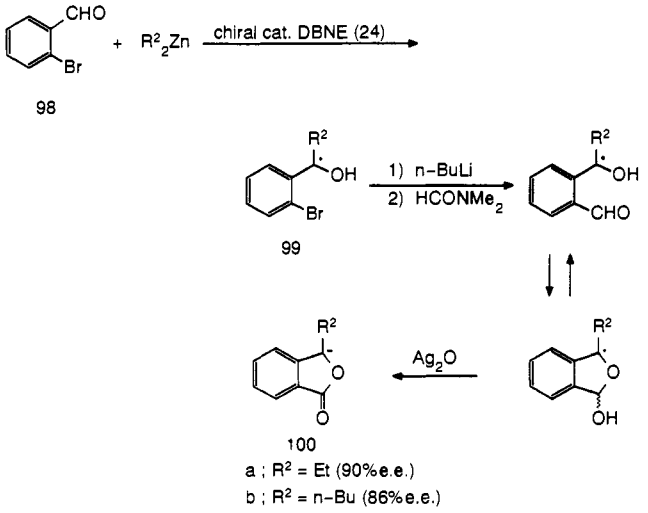
Diastereoselective 1,2-asymmetric alkylation of *chiral* carbonyl compounds has been well studied, and the useful models for predicting the relative stereochemistry have been provided.[114] Among chiral carbonyl compounds, 2-phenylpropanal (**101**) has been one of the most widely used aldehydes in the diastereoselective 1,2-asymmetric induction by the addition reaction of organometallic reagents.[115] However, the diastereomeric excess (de) of the product from the Cram-type selective addition has been low to moderate. It is only recently that more diastereoselective methods using organometallic reagents with certain auxiliaries have been reported.[116] These methods require stoichiometric amounts of auxiliaries such as Lewis acid ($TiCl_4$) and crown ether.

The diastereoselective addition of dialkylzinc reagents to racemic **101** using *achiral* amino alcohol as catalyst afforded *erythro* alcohols (**102**) (Cram selectivity) in high de (up to 88% de) (Scheme 35).[117] The de observed here is much higher than those of the conventional organozinc reagents [MeZnX (ca. 20% de),[118] Et_2Zn–$TiCl_4$ (54% de)[56]]. The high diastereoselectivity of the amino alcohol catalyzed addition of dialkylzinc may be due to the steric bulkiness of the activated dialkylzinc coordinated with amino alcohol

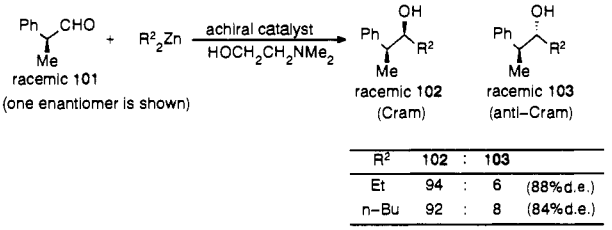
Table 30. Asymmetric Synthesis of Allyl Alcohol 97 by the Enantioselective Alkylation and Arylation of α,β-Unsaturated Aldehyde

entry	R^{13}	R^{14}	R^2	catalyst	allyl alcohol 97 yield, %	ee, %	config	ref
1	Ph	H	Et	(−)-8	81	96	S	13
2	n-Bu_3Sn	H	n-pentyl	(−)-8	84	85	S	17
3	Ph	H	Et	(S)-DPMPM (12)	91	97	S	20
4	Ph	H	Me	Li-(S)-DPMPM (12)	47	89	S	21
5	Ph	H	Et	13	89	89	R	21
6	Ph	H	Et	17	90	73	S	26
7	H	H	Et	(R)-35	72	88	R	104
8	H	Me	Et	(R)-35	67	95	R	104
9	Ph	H	Et	(R)-35	86	84	R	17
10	Ph	H	Et	(S)-40	97	80	S	46
11	Ph	H	Et	39	100	70	S	45
12	Ph	H	Et	43	90	72	S	47
13	Ph	H	Et	50	90	88	S	52
14	Ph	H	Et	51	85	99	S	53
15	Ph	H	Et	53	89	96	S	54
16	Ph	H	Ph	(1R,2S)-DBNE (24)	90	82	R	81
17	Ph	H	2-furyl	(1S,2R)-79	79	45		85

Scheme 34



Scheme 35. Diastereoselective Alkylation of Racemic 101 Using Achiral Amino Alcohol as Catalyst



R^2	102	:	103	
Et	94	:	6	(88%d.e.)
n-Bu	92	:	8	(84%d.e.)

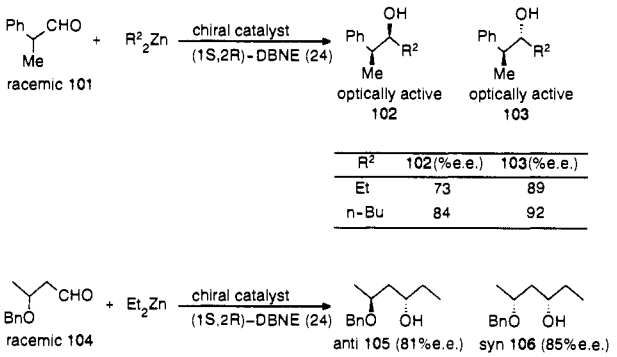
as a catalyst. These bulky alkylating reagents may be diastereoselective probably because of their effective steric interaction with the substituents of 101.

B. Enantioselective Addition to Chiral Aldehydes Using Chiral Catalysts

The addition reaction of dialkylzincs to chiral aldehyde using a *chiral* catalyst has different features from that of the reaction using the *achiral* catalyst described in the preceding section.

By starting from *racemic* 2-phenylpropanal (101), optically active alcohols with two chiral centers were obtained in good to high ee's by the diastereo- and enantioselective addition of dialkylzincs using (1S,2R)-DBNE (24) as a chiral catalyst (Scheme 36).[119]

Scheme 36. Enantioselective Addition of Chiral Racemic Aldehydes Using DBNE as a Chiral Catalyst



R^2	102(%e.e.)	103(%e.e.)
Et	73	89
n-Bu	84	92

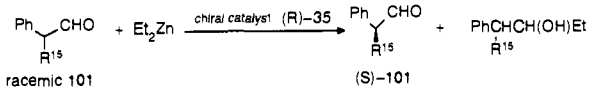
The reaction of *racemic* 101 with diethylzinc (mol ratio, aldehyde/Et_2Zn = 1) in hexane at room temperature using 10 mol % of (1S,2R)-DBNE (24) as a chiral catalyst afforded 2-phenylpentan-3-ol in 58% yield (erythro/threo = 81:19). Among the two pairs of enantiomers, (2S,3S)-102 for the erythro isomer and (2R,3S)-103 for the threo isomer were found to be the predominant isomers, respectively. The ee of 102 and 103 reached 73% and 89%, respectively. When di(*n*-butyl)zinc (mol ratio, aldehyde/n-Bu_2Zn = 2) was used, the ee's of 102 and 103 were 84% and 92%, respectively (erythro/threo = 83:17).[120]

For both *erythro*-102 and *threo*-103 of the predominant isomers formed in the presence of (1S,2R)-DBNE (24), the configuration of the carbon atom, to which the hydroxyl group is attached, is S in all cases. Formation of these predominant isomers is the result of the selective addition of R_2Zn to S and R *racemic* 101 from the *si* face of the aldehyde 101, regardless of the configuration of 101. Thus, the sense of the addition of dialkylzinc to 101 is determined by the chiral catalyst 24 and not by the configuration of 101.

The total yields of (2S,3S)-102 and (2S,3R)-103 are higher than those of the enantiomers (2R,3R)-102 and (2R,3S)-103. This result shows that, in the presence of (1S,2R)-DBNE (24), (S)-101 reacted with Et_2Zn faster than (R)-101 did.

In the reaction of diethylzinc with *racemic* 3-(benzyloxy)butanal (104) using (1S,2R)-DBNE (24) as a chi-

Scheme 37. Kinetic Resolution of Racemic Aldehyde Using (*R*)-35 as a Chiral Catalyst



R^{15}	recovery
Me	15% (91%ee)
Me	41% (52%ee)
Cl	25% (98%ee)

ral catalyst, optically active monoprotected 1,3-diols, *anti*-**105** with 81% ee and *syn*-**106** with 85% ee, were obtained.[121] The result shows that the sense of the enantioselectivity is determined by the chiral catalyst and not by the chirality of the aldehyde, **104**. This point is very different from the conventional diastereoselective 1,3-asymmetric induction.[122]

The kinetic resolution of racemic aldehydes by enantioselective alkylation was reported (Scheme 37).[123] An excess amount of racemic aldehyde **101** was reacted with diethylzinc in the presence of a catalytic amount of (*R*)-**35**. Aldehyde (*S*)-**101** with 91% ee was recovered in 15% yield (Scheme 37). The kinetic resolution of racemic chlorophenylacetaldehyde afforded an optically active aldehyde with 98% ee in 25% yield.[124]

VI. Asymmetric Self-Catalytic Reaction

The enantioselective addition of organozinc reagents to aldehydes using various chiral catalysts, as reviewed in sections I–V is an excellent method to increase the amount of the chirality of the molecule using a small amount of chiral catalyst. However, the structures of the chiral catalysts and the products are *different*.

One of the important characteristic features of animals and plants is their self-reproduction. The cell division increases the number of cells and the number of individuals. Is it possible for organic synthesis to achieve such a self-reproduction system? Because animals and plants are composed of many kinds of chiral compounds, self-reproduction of chiral molecules (i.e., asymmetric self-reproduction) should be of interest.

If the structures of the product and the chiral catalyst are the *same* (chiral self-recatalyst), the reaction system becomes a real self-reproduction system for chiral molecules. An asymmetric self-catalytic reaction may be one of the ideal reactions because the amount of the chiral catalyst (i.e., the product) increases during the reaction. If the reaction proceeds ideally, no separation of the chiral catalyst is required. However, no apparent asymmetric self-catalytic reaction has been reported.[125]

An asymmetric self-catalytic reaction in which a chiral molecule plays the role of a chiral catalyst to afford the same chiral molecule of the same configuration has been reported by us.[126] Optically active 3-pyridylalkyl alcohols, chiral self-catalysts, produced themselves in the same configuration in the enantioselective addition of dialkylzinc reagents to 3-pyridinecarbaldehyde (Scheme 38). The results are shown in Table 31.

When 3-pyridinecarbaldehyde was reacted with diisopropylzinc (2 mmol) using 86% ee (−)-2-methyl-1-(3-pyridyl)propanol (**95**, R^2 = *i*-Pr) as a chiral catalyst (20 mol %), an increased amount of (−)-**95** with 47% ee was obtained. The product with 47% ee contains 20

Scheme 38. Asymmetric Self-Catalytic Reaction

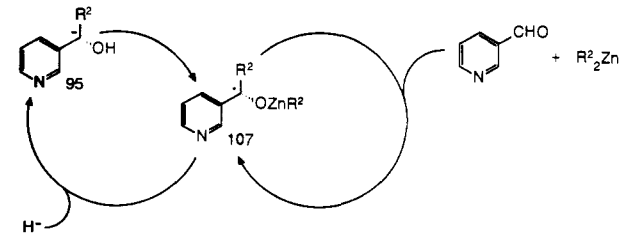


Table 31. Asymmetric Self-Catalytic Reaction

			ee of catalyst **95**		product **95**		
entry	catalyst **95**, R^2	R^2_2Zn, R^2	% ee	config	yield, %	% ee	config
1	Et	Et	(−) 56		66	(−) 14	
2	Me	Me	(−) 42	(*S*)	34	(−) 7	*S*
3	*n*-Pr	*n*-Pr	(−) 62		65	(−) 5	
4	*n*-Bu	*n*-Bu	(−) 72		82	(−) 6	
5	*i*-Pr	*i*-Pr	(−) 86		67	(−) 35	

mol % of (−)-**95** as a chiral catalyst with 86% ee and the newly formed (−)-**95** with 35% ee in 67% yield. This result shows that (−)-**95** (R^2 = *i*-Pr), to be more precise its alkylzinc alkoxide **107**, acts as a chiral self-catalyst to produce itself in the same configuration [(−)-(**95**), 67%, 35% ee] (entry 5). From the enantioselective additions of dimethyl-, diethyl-, dipropyl-, and dibutylzincs to 3-pyridinecarbaldehyde using the corresponding chiral 3-pyridylalkyl alcohols (**95**) as chiral catalysts, products of the same configuration as the chiral catalysts were obtained, respectively (entries 1–5).

It is clear that (−)-**95** (20 mol %, 86% ee) catalyzed the addition reaction, because (−)-**95** (20 mol %, 86% ee) is also a chiral catalyst for the ethylation of benzaldehyde to afford (*S*)-1-phenylpropanol with 16% ee in 87% yield.

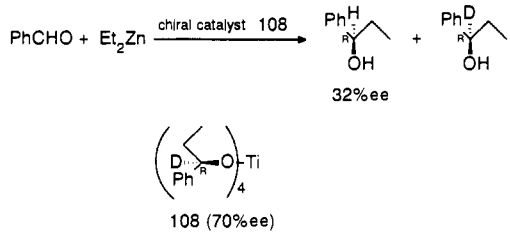
Thus, optically active 3-pyridylalkyl alcohols (**95**), especially **95** (R^2 = *i*-Pr), were shown to be chiral self-catalysts, producing themselves in the enantioselective addition of R_2Zn to 3-pyridinecarbaldehyde.

Alberts and Wynberg reported a catalytic asymmetric induction in which the product (1-phenylpropanol) has the same structure as the chiral *ligand* of the orthotitanate catalyst[57] in the enantioselective addition of diethylzinc to benzaldehyde (Scheme 39).[127] By using the orthotitanate derived from (*R*)-1-phenylpropanol-d_1 (**108**) (70% ee), the optically active (*R*)-1-phenylpropanol with 32% ee was obtained. In this reaction, the structure of the in situ formed product, i.e., ethylzinc alkoxide of 1-phenylpropanol, is different from that of the chiral orthotitanate catalyst. Ethylzinc alkoxide of 1-phenylpropanol is much less enantioselective. However, there is a possibility that the product acts as a chiral ligand if the ligand exchange occurs between the orthotitanate catalyst and the product (ethylzinc alkoxide).

VII. Conclusions

This review has presented the current stage of the asymmetric synthesis of alcohols and related compounds using homogeneous and heterogeneous chiral catalysts and chiral ligands by the enantioselective addition of organozinc reagents to aldehydes.

Scheme 39



Homogeneous chiral catalysts and ligands which have been utilized include amino alcohols, piperazines, transition metal salts with diols, quaternary ammonium salts, diols, and oxazaborolidines. By using these chiral catalysts and ligands, optically active secondary alcohols with high ee's are synthesized from the enantioselective addition of organozinc reagents to aldehydes. Each catalyst (or ligand) has its characteristic feature.

In contrast, heterogeneous chiral catalysts which have been utilized include polymer-supported, alumina-supported, and silica gel-supported chiral amino alcohols. Polymer-supported chiral catalysts afford secondary alcohols with high ee's. Judging from the yield and the ee of the products, these polymer supported catalysts are presently the most efficient ones among those utilized in catalytic enantioselective carbon–carbon-bond-forming reactions. Alumina-supported and silica gel-supported catalysts are the first examples of the use of inorganic alumina and silica gels as supports of the catalysts for asymmetric reactions.

Organozinc reagents which have been utilized in the enantioselective addition to aldehydes include dialkylzincs, dialkynylzincs, mixed alkylalkynylzincs, alkynylzinc halide, divinylzinc, alkenylzinc bromide, phenylzinc reagent, difurylzinc, and Reformatsky reagents. The caalytic enantioselective reactions are achieved with dialkylzincs, dialkynylzincs, mixed alkylalkynylzincs, and divinylzinc. For the reactions with alkynylzinc halide, alkenylzinc bromide, phenylzinc reagent, difurylzinc, and Reformatsky reagents, the catalytic enantioselective reactions are reported. However, the presence of a stoichiometric amount of a chiral catalyst is preferable for high enantioselectivities.

There are highly enantioselective and chemoselective catalytic addition reactions of dialkylzincs to functionalyzed aldehydes. The following highly enantioselective syntheses have been achieved: hydroxy esters and lactones from formyl esters, hydroxyl ketones from keto aldehydes, alkynyl alcohols from alkynyl aldehyde, hydroxy aldehyde from formyl acetal, furyl alcohols from furyl aldehydes, pyridylalkyl alcohols from pyridyl aldehyde, diol from terephthaldehyde, allyl alcohols from α,β-unsaturated aldehydes, and 3-alkylphthalides from aldehyde.

Diastereoselective addition of dialkylzincs to racemic chiral aldehyde in the presence of an *achiral* catalyst affords a Cram-type alcohol in high de.

In contrast, addition of dialkylzincs to racemic chiral aldehydes in the presence of *chiral* catalysts affords optically active alcohols, resulting from the enantioselective addition (and not from the diastereoselective addition). The selectivity of the addition to chiral aldehydes is affected more profoundly by the configuration of the chiral catalyst than by the chirality of the chiral aldehydes. Optically active aldehydes are obtained by the kinetic resolution using an excess amount of chiral aldehydes in the addition of diethylzinc using chiral catalysts.

Some chiral amino alcohols show a nonlinear effect in the relationship between the ee's of the chiral catalysts and the ee of the products. The ee's of the products are higher than those of the catalysts. This effect may throw light on the mechanism of the concentration of enantiomers in nature.

Chirality and self-reproduction are the most important features of all living things. Therefore, an asymmetric self-catalytic reaction, observed in the enantioselective synthesis of pyridylalkyl alcohols using chiral pyridylalkyl alcohols as catalysts, has two important features of living things.

As described, the enantioselective addition of organozinc reagents to aldehydes is at the forefront of asymmetric synthesis.

VIII. Abbreviations

DPMPM diphenyl(1-methylpyrrolidin-2-yl)methanol
DBNE *N,N*-di-*n*-butylnorephedrine

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