Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds

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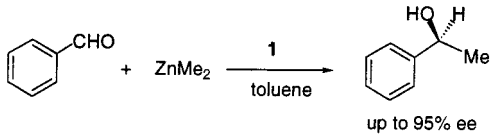
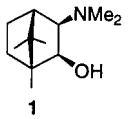
1. Introduction

Since the initial report of Oguni and Omi on the reaction of diethylzinc with benzaldehyde in the presence of a catalytic amount of (*S*)-leucinol with moderate enantioselectivity (49% ee) in 1984,[1] research on asymmetric organozinc additions to carbonyl compounds has grown dramatically. In 1986, (−)-3-exo-dimethylaminoisobornenol [(−)-DAIB, **1**] was discovered by Noyori and co-workers to be the first highly enantioselective ligand for the dialkylzinc addition to aldehydes.[2] In the presence of 2 mol % of **1**, reaction of dimethylzinc with benzaldehyde at 25−40 °C in toluene gave (*S*)-1-phenylethanol with up to 95% ee after aqueous work up (Scheme 1). Such

Scheme 1. Dimethylzinc Addition to Benzaldehyde Catalyzed by 1





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asymmetric organozinc additions allow the synthesis of chiral alcohols that are ubiquitous in the structures of natural products and drug compounds. They are also important precursors to many other functional organic molecules. Over the past decades, a large number of chiral catalysts have been developed and high enantioselectivities have been achieved.[3−6] In addition, the reaction of diethylzinc with aldehydes has also become a classical test in the design of new ligands for catalytic enantioselective syntheses.

Previous studies have shown that coordination of ligands to dimethylzinc converts its linear structure into an approximate tetrahedral structure.[7,8] This reduces the bond order of the Zn−C bond and increases the nucleophilicity of the zinc alkyl groups. Thus, chiral ligands not only control the stereochemistry of the organozinc addition, but also activate the zinc reagents. A number of chiral ligands developed for the asymmetric organozinc additions are derived from amino alcohols. These compounds react with dialkylzincs to generate a zinc-based chiral Lewis acid complex which can further coordinate with both the aldehyde substrates and the dialkylzinc reagents to conduct the catalytic addition. Thus, the in situ generated zinc complex is a multifunctional catalyst. It acts as a Lewis acid to activate the carbonyl substrates and also as a Lewis base to activate the organozinc reagents. The chiral environment of the ligand controls the stereoselectivity.

In 1992, Soai and Niwa published a comprehensive review for the work on the asymmetric reaction of

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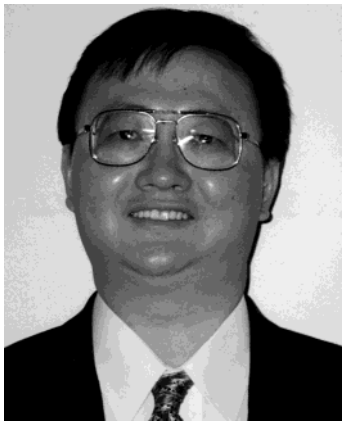


Lin Pu was born in 1965 in Xuyong, Sichuan Province, P. R. China. He received his B.S. degree in Chemistry from Sichuan University in 1984. He then obtained the Doering Fellowship (the Chemistry Graduate Program of China) for graduate study in the United States and enrolled in the Department of Chemistry at the University of California at San Diego in 1985. Under the supervision of Professor Joseph M. O'Connor, he obtained his Ph.D. degree in 1990. From January 1991 to November 1992, he studied in Professor Henry Taube's laboratory at Stanford University as a postdoctoral fellow. From November 1992 to August 1994, he joined Professor Robert H. Grubbs' research group at California Institute of Technology to continue his postdoctoral training. In the fall of 1994, he became an Assistant Professor in the Department of Chemistry at North Dakota State University. In fall 1997, he moved to the University of Virginia as an Associate Professor in the Department of Chemistry. The research projects in his laboratory focus on the design and synthesis of novel chiral materials and the study of their applications in areas such as asymmetric catalysis, enantioselective sensors, chiral separation, and electrical and optical materials.

Hong-Bin Yu was born in 1969 in Shanghai, P. R. China. She received her B.S. degree in Chemistry from Shanghai Jiaotong University in 1991. She then enrolled as a graduate student in Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. In 1994, she obtained her M.S. degree in Polymer Chemistry and Physics. In 1997, she earned her Ph.D. degree in Organic Chemistry at the same institute under the supervision of Professor Wei-Yuan Huang. From August 1997 to August 1999, she worked in Professor Lin Pu's research group at the University of Virginia as a postdoctoral fellow. Her research interests include reaction methodology development and study of novel chiral polymers for asymmetric catalysis as well as materials application.

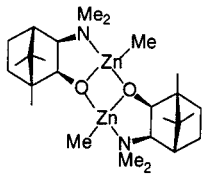
aldehydes with organozincs.[3,4] Since then, further progress have been made in this area. In this review article, we attempt to summarize the recently discovered catalysts that have shown good enantioselectivity for the organozinc addition to carbonyl compounds. In most cases, the results of the catalysts with enantioselectivity over 90% ee are tabulated. The catalytic asymmetric reactions of various zinc reagents including alkyl-, aryl-, alkenyl-, and alkynylzincs with carbonyls, mostly aldehydes, are discussed. Macromolecule-based chiral catalysts and catalysis on inorganic supports are also described.

2. Dialkylzinc Additions to Aldehydes Catalyzed by Amino Alcohols

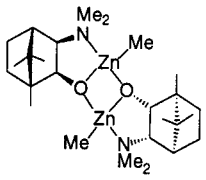
a. Acyclic Amine-Based Amino Alcohols

Amino alcohols constitute an important part of the chiral ligands developed for dialkylzinc additions to aldehydes. Noyori and co-workers conducted extensive experimental and theoretical studies on the mechanism of the dialkylzinc addition to aldehydes catalyzed by **1**.[5,6,9,10] Houk and co-workers also carried out a theoretical analysis of an dialkyzinc addition.[11,12] Scheme 2 shows a proposed mechanism for the reaction catalyzed by **1**.[9,10] In the first step, **1** reacts with dimethylzinc to generate the zinc complex **2**. It was found that 1 equiv of **2** cannot react with benzaldehyde. That is, the Zn−Me group of **2** cannot add to an aldehyde and a second equivalent of dimethylzinc is needed. The alkoxy oxygen atom in **2** coordinates with dimethylzinc to give **3**. Coordination of benzaldehyde with **3** generates **4**. Molecular orbital and density functional calculations indicate that the anti coordination of benzaldehyde (with respect to the chiral ligand) in **4** and a 5/4/4 tricyclic transition state **5** are most favorable. In transition state **5**, methyl migrates to the *si* face of the aldehyde to form **6**, which can react with dimethylzinc to dissociate (*S*)-(1-phenyl)ethoxy−ZnMe and regenerate **3**. Aqueous workup gives (*S*)-1-phenylethanol.

In 1988, Oguni and co-workers observed that the enantioselectivity of the amino alcohol-catalyzed dialkylzinc addition to aldehydes was not linear with the enantiomeric purity of the catalyst.[13] A lower enantiomeric purity led to higher enantioselectivity.[14] Noyori found that ligand **1** exhibited a large positive nonlinear effect.[15] For example, **1** with 15% ee led to the diethylzinc addition product with 95% ee. It was found that the racemic **1** reduced the reaction rate by 13 times as compared to the use of the enantiomerically pure **1**. The zinc complex **2** was able to form the homodimer **7a**. Combination of **2** with its enantiomer generated the heterodimer **7b**. The heterodimer was found to be more stable than the homodimer by ca. 3.4 kJ/mol.[16] Thus, the less stable homodimer dissociated much more easily to carry out the alkylation, but the more stable heterodimer consumed the minor enantiomer of the ligand, leading to the observed large positive nonlinear effect. The dialkylzinc addition was also carried out in the presence of a mixture of the diastereomers of **1**. These studies demonstrated that both the kinetics and enantioselectivity of this catalytic process were con-



7a



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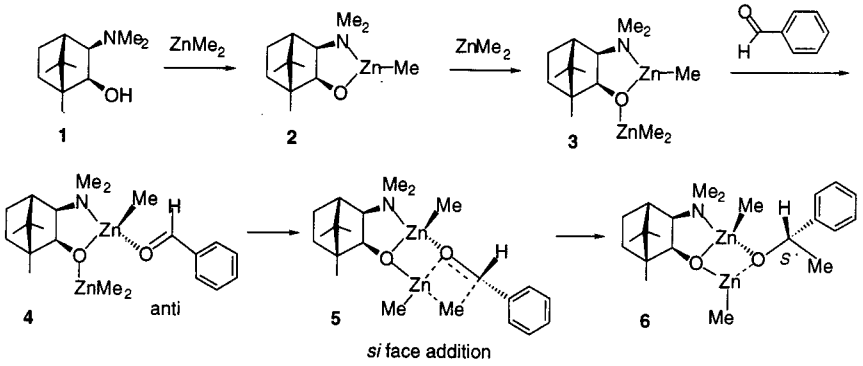
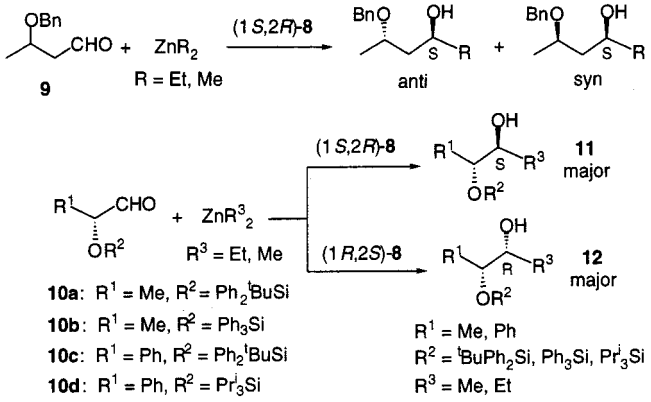
Scheme 2. Proposed Mechanism for the Catalytic Dimethylzinc Addition to Benzaldehyde



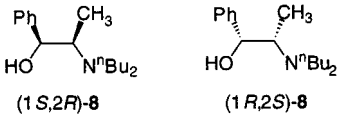
Scheme 3. Dialkylzinc Additions to Functional Aldehydes Catalyzed by 8



trolled by the self-recognition (homodimer formation) and non-self-recognition (heterodimer formation) of the catalysts in solution.[17]

To determine whether the catalytically active species are the monomeric zinc complexes such as **2** or the dimeric zinc complexes such as **7** in the asymmetric dialkylzinc addition, Noyori and co-workers studied the relative reactivity of various substituted benzaldehydes in the presence of either the optically active ligand **1** or its racemic mixture.[18] Although the racemic mixture of **1** showed much lower catalytic activity, the relative rate of the substituted benzaldehydes remained the same for both the optically active ligand and the racemic mixture. The authors concluded that the catalytically active species should be the monomeric zinc complex of **1** rather than its dimeric zinc complexes. In the dialkylzinc addition, the enantiomerically pure ligand can only form one type of dimeric complex, a homodimer, but the racemic mixture can generate a mixture of three dimeric complexes including two enantiomeric homodimers and a heterodimer. When all three dimeric complexes generated from the racemic ligand are catalyzing the dialkylzinc addition, the relative rates of the substituted benzaldehydes should be different from the use of the optically active ligand. The fact that the same relative reaction rate was observed indicates that the same catalytically active species may be involved in the reactions catalyzed by both the optically active and racemic ligands. However, this experiment would be inconclusive if the two enantiomeric homodimers were much more active catalysts than the heterodimer and controlled the reaction rate when the racemic ligand was used.

The ephedrine-based amino alcohol ligand **8** was previously found by Soai and co-workers to catalyze highly enantioselective reactions of a number of aromatic and aliphatic aldehydes with dialkylzincs.[3]



This ligand was used to catalyze the reaction of functionalized aldehydes such as the β-alkoxy aldehyde **9**[19] and the α-alkoxy aldehyde **10**[20] with alkylzincs (Scheme 3). In the reaction of **9** with dialkylzincs in the presence of (1*S*,2*R*)-**8**, both the anti and syn products preferred a *S* configuration for the hydroxyl carbon. The ee's of these products were in the range of 61−85%.[19] For the reaction of **10a**−**d** with dialkylzincs, (1*S*,2*R*)-**8** led to **11** as the major product with a *S* configuration for the hydroxyl carbon and (1*R*,2*S*)-**8** led to **12** as the major product with a *R* configuration. The ratio of these two diastereomeric products in the reactions was in the range from 85/15 to 98/2 (Table 1).[20] Thus, in the

Table 1. Dialkylzinc Additions to 10a−d Catalyzed by (1*S*,2*R*)-8 and (1*R*,2*S*)-8[a]

entry	R_2Zn	aldehyde	catalyst (mol %)	*T* (°C)	*t* (h)	yield (%) of **11**+**12**	ratio of **11**/**12**
1	Et_2Zn	**10a**	(1*S*,2*R*)-**8** (5)	0	16	46	95/5
2	Et_2Zn	**10a**	(1*R*,2*S*)-**8** (5)	0	16	56	4/96
3	Me_2Zn	**10a**	(1*S*,2*R*)-**8** (5)	0	26	24	85/15
4	Me_2Zn	**10a**	(1*R*,2*S*)-**8** (5)	0	26	32	7/93
5	Et_2Zn	**10b**	(1*S*,2*R*)-**8** (20)	r.t.	20	46	98/2
6	Et_2Zn	**10b**	(1*R*,2*S*)-**8** (20)	r.t.	20	50	7/93
7	Et_2Zn	**10c**	(1*S*,2*R*)-**8** (20)	r.t.	22	46	97/3
8	Et_2Zn	**10c**	(1*R*,2*S*)-**8** (20)	r.t.	23	46	8/92
9	Et_2Zn	**10d**	(1*S*,2*R*)-**8** (20)	r.t.	22	57	96/4
10	Et_2Zn	**10d**	(1*R*,2*S*)-**8** (20)	r.t.	21	68	7/93

[a] The reactions were carried out in toluene solution.

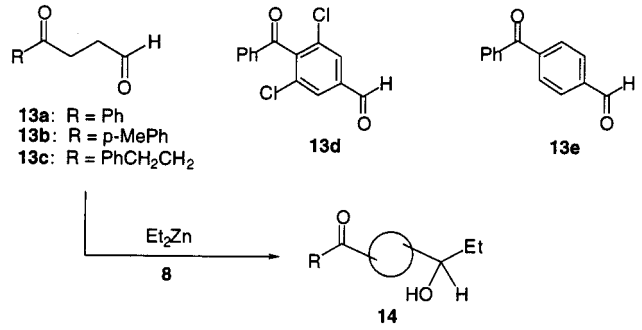
Table 2. Dialkylzinc Additions to 15a,b Catalyzed by (1*S*,2*R*)-8

entry	R_2Zn	aldehyde	solvent	*T* (°C)	equiv of (1*S*,2*R*)-**8**	yield (%)	ee (%)	DL/meso
1	Et_2Zn	**15a**	THF−hexane	r.t.	0.2	74	>99	80/20
2	$^iPr_2Zn$	**15a**	toluene−hexane	0	0.5	66	>99	91/9
3	Et_2Zn	**15b**	toluene−hexane	0	0.2	70	>99	89/11
4	$^iPr_2Zn$	**15b**	toluene−hexane	0	0.2	60	>99	>99/1

reactions of both **9** and **10**, the chiral configuration of the products was controlled by the chiral ligands rather than by the chiral center adjacent to the carbonyl group of the substrates.

Ligands (1*R*,2*S*)-**8** and (1*S*,2*R*)-**8** were used to catalyze the reaction of the keto aldehydes **13a**−**e** with diethylzinc to generate the chiral hydroxyl ketones **14** (Scheme 4).[21] In the presence of 12 mol

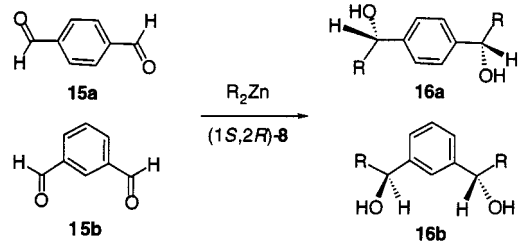
Scheme 4. Diethylzinc Additions to Keto Aldehydes Catalyzed by 8



% of either (1*S*,2*R*)-**8** or (1*R*,2*S*)-**8**, diethylzinc added to **13e** with 91% ee and 82% yield at 0 °C in toluene. The reaction of other substrates gave 81−87% ee. In these reactions, the keto function remained unreactive.

Ligand (1*S*,2*R*)-**8** catalyzed the reaction of terephthaldehyde (**15a**) and isophthaldehyde (**15b**) with dialkylzincs to generate the chiral diols **16a** and **16b** both enantioselectively and diastereoselectively (Scheme 5).[22] As shown in Table 2, the DL products

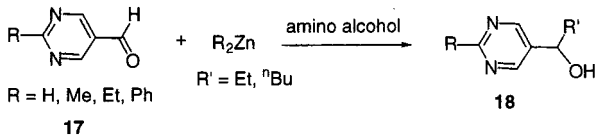
Scheme 5. Dialkylzinc Additions to Phthaldehydes Catalyzed by (1*S*,2*R*)-8



were obtained with very high enantioselectivity. Formation of the meso products was also observed in most cases. The chiral diols generated from these reactions were observed to carry out an autocatalytic addition of dialkylzincs to the phthaldehydes in the presence of $Ti(O^iPr)_4$ with up to 91% yield but only ≤44% ee.

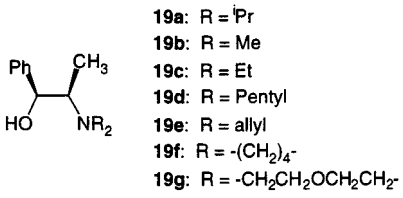
The reaction of pyrimidine-5-carboxaldehydes (**17**) with dialkylzincs in the presence of several *β*-amino alcohols was studied by Soai and co-workers (Scheme 6). They found that (1*S*,2*R*)-**8** catalyzed this reaction

Scheme 6. Dialkylzinc Additions to Pyrimidine-5-carboxaldehydes



to generate the corresponding (*S*)-5-pyrimidyl alkanols (**18**) with up to 94% ee.[23]

The amino alcohol ligands **19a**−**g** and (1*S*,2*R*)-**8** were examined for the diisopropylzinc addition to aldehydes among which (1*S*,2*R*)-**8** and **19a** were found to be most enantioselective.[24a] These com-



pounds catalyzed the reaction of a variety of aldehydes with diisopropylzinc with over 90% ee (Table 3). Ligands **8** and **19** were used in a solvent-free

Table 3. Diisopropylzinc Additions to Aldehydes Catalyzed by (1*S*,2*R*)-8 and 19a

entry	catalyst	aldehyde	yield (%)	ee (%)	config
1	(1*S*,2*R*)-**8**	benzaldehyde	73	92	*S*
2	**19a**	benzaldehyde	73	91	*S*
3	**19b**	benzaldehyde	69	36	*S*
4	**19c**	benzaldehyde	72	88	*S*
5	**19d**	benzaldehyde	61	90	*S*
6	**19e**	benzaldehyde	63	87	*S*
7	**19f**	benzaldehyde	68	86	*S*
8	**19g**	benzaldehyde	72	88	*S*
9	(1*S*,2*R*)-**8**	cinnamaldehyde	73	93	*S*
10	**19a**	cinnamaldehyde	63	91	*S*
11	(1*S*,2*R*)-**8**	3-phenylpropionaldehyde	62	96	*S*
12	**19a**	ferrocenecarboxaldehyde	97	98	*S*
13	(1*S*,2*R*)-**8**	ferrocenecarboxaldehyde	92	97	*S*
14	**19a**	ferrocene-1,1′-dicarboxaldehyde	39	100	*SS*
15	(1*S*,2*R*)-**8**	ferrocene-1,1′-dicarboxaldehyde	47	100	*SS*

[a] The reactions were carried out at 0 °C in hexane in the presence of 10 mol % of the catalyst.

system to catalyze the reaction of diethylzinc with aldehydes with 84−91% ee.[24b] Accelerated reaction rate was observed compared to the reactions using solvent.

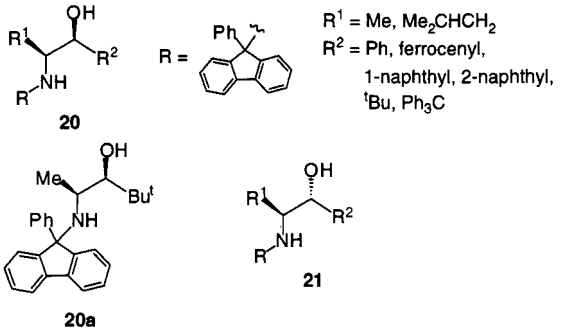
The *β*-amino alcohols **20** and **21** were studied by Paleo et al. for the dialkylzinc addition.[25] Among these ligands, **20a** showed the highest enantioselectivity for the diethylzinc addition to benzaldehyde (97% ee, entry 1, Table 4). High enantioselectivity was also observed for both aromatic and aliphatic aldehydes (Table 4). Ligands **21**, the diastereomers

Table 4. Diethylzinc Additions to Aldehydes Catalyzed by 20a[a]

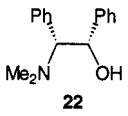
entry	aldehyde	*T* (°C)	*t* (h)	yield (%)	ee (%)
1	benzaldehyde	18	0.3	98	97
2	1-naphthaldehyde	18	1.2	85	86
3	2-naphthaldehyde	0	16	91	97
4	*p*-phenylbenzaldehyde	0	1.5	98	98
5	*o*-bromobenzaldehyde	0	16	82	94
6	*p*-bromobenzaldehyde	0	18	73	96
7	*p*-chlorobenzaldehyde	18	0.7	96	96
8	*p*-methoxybenzaldehyde	0	16	98	93
9	*m*-methoxybenzaldehyde	18	1	97	97
10	3,4-methyleneoxybenzaldehyde	18	7	98	88
11	3,4-dimethoxybenzaldehyde	18	1	99	54
12	cyclohexanecarboxaldehyde	18	4	94	97
13	nonyl aldehyde	18	18	98	98

[a] The reactions were carried out in toluene in the presence of 3 mol % of **20a**.

of **20**, generally showed lower enantioselectivity than **20** probably due to a unfavorable steric interaction between R^1 and R^2 in the intermediate formed by chelation of the amino alcohols with zinc.



Jiang and co-workers found that the amino alcohol **22** and its enantiomer catalyzed the diethylzinc addition to benzaldehyde to give (*S*)-1-phenylpropanol or (*R*)-1-phenylpropanol with 97% ee.[26] Other



derivatives of **22** with various alkyl substituents on nitrogen showed much lower enantioselectivity. They also found that (*R*)-1-phenylpropanol was capable of asymmetric autocatalysis for the reaction but with very low chemical activity as well as low chiral induction (14% ee).[27] Addition of sterically bulky achiral amines such as biscyclohexylamine improved both the chemical reactivity and asymmetric autoinduction (up to 49% ee).

Luche and co-workers prepared the optically active *β*-amino alcohols **23**−**25** from L-valine[28a] and studied their use in diethylzinc additions.[28b] As shown in

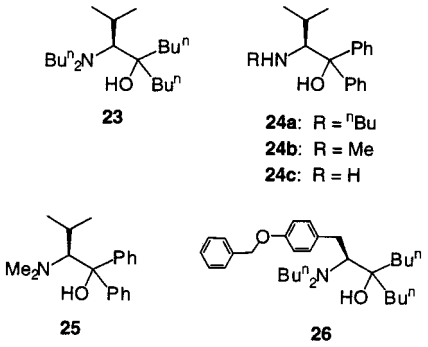
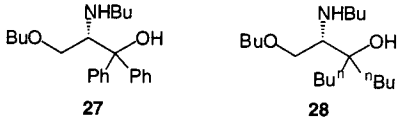


Table 5, ligand **23** with flexible butyl groups on both the nitrogen and hydroxyl carbon showed much better enantioselectivity (97% ee) than ligands **24** and **25** (2−75% ee) that contain rigid diphenyl substituents on the hydroxyl carbon. In the presence of 10 mol % of **23**, diethylzinc added to certain aliphatic and aromatic aldehydes to give the corresponding (*R*)-alcohols with 82−97% ee (entries 1 and 6−9, Table 5). Ligand **26**, structurally similar to **23**, was made from (*S*)-tyrosine by Kragl and co-workers. This ligand also showed good enantioselectivity (86−95% ee, entries 10−12, Table 5).[29]

Sibi and co-workers studied amino alcohols such as **27** and **28**.[30] In the presence of ^{n}BuLi, **27** catalyzed



the reaction of diethylzinc with benzaldehyde to give (*S*)-1-phenylpropanol with 83% ee. However, under the same conditions, **28** gave (*R*)-1-phenylpropanol with 79% ee even though both **27** and **28** had the same chiral configuration.

Table 5. Diethylzinc Additions to Aldehydes Catalyzed by Compounds 23−26

entry	aldehyde	catalyst (mol %)	solvent	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	**23** (10)	*a*	r.t.	48	100	97	*R*
2	benzaldehyde	**24a** (10)	*a*	r.t.	48	88	75	
3	benzaldehyde	**24b** (10)	*a*	r.t.	48	52	53	
4	benzaldehyde	**24c** (10)	*a*	r.t.	48	58	2	
5	benzaldehyde	**25** (10)	*a*	r.t.	48	80	73	
6	cinnamaldehyde	**23** (10)	*a*	r.t.	48	95	88	
7	heptanal	**23** (10)	*a*	r.t.	48	86	84	
8	cyclohexanecarboxaldehyde	**23** (10)	*a*	r.t.	48	75	82	
9	isovaleraldehyde	**23** (10)	*a*	r.t.	48	44	86	
10	benzaldehyde	**26** (10)	toluene	0	8	98[b]	93	*R*
11	heptanal	**26** (10)	toluene	0	48	100[b]	86	
12	*p*-chlorobenzaldehyde	**26** (10)	toluene	0	45	98[b]	95	

[a] Toluene−hexane (5:4). [b] Conversion.

Table 6. Diethylzinc Additions to Aldehydes Catalyzed by 29−31

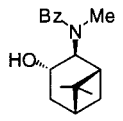
entry	aldehyde	catalyst (mol %)	solvent	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	**29** (10)	THF	0	12	>95	80	*R*
2	*p*-chlorobenzaldehyde	**29** (10)	THF	0	12		75	*R*
3	*p*-methylbenzaldehyde	**29** (10)	THF	0	12		73	*R*
4	*p*-methoxybenzaldehyde	**29** (10)	THF	0	12		52	*R*
5	benzaldehyde	**30a** (20)	toluene	r.t.	24	91	96	*S*
6	heptanal	**30a** (20)	toluene	r.t.	24	81	88	*S*
7	benzaldehyde	**30b** (20)	toluene	r.t.	24	80	98	*R*
8	heptanal	**30b** (20)	toluene	r.t.	24	70	66	*R*
9	benzaldehyde	**31a**	toluene	r.t.	24	96	94	*S*
10	benzaldehyde	**31b**	toluene	r.t.	24	69	58	*S*

Table 7. Diethylzinc Additions to Aldehydes Catalyzed by 33[a]

entry	aldehyde	mol (%) of **33**	yield (%)	ee (%)
1	benzaldehyde	5	99	94
2	benzaldehyde	1	97	91
3	*p*-methoxybenzaldehyde	5	98	88
4	*o*-methoxybenzaldehyde	5	99	73
5	*p*-methylbenzaldehyde	5	99	95
6	1-naphthaldehyde	5	96	83
7	cinnamaldehyde	5	98	60
8	3-phenylpropionaldehyde	5	80	54

[a] All the reactions were carried out in the presence of 2 equiv of diethylzinc at room temperature in toluene over 24 h.

The use of the amino alcohol ligand **29** for the asymmetric diethylzinc addition was studied by Goralski et al.[31] In the presence of 10 mol % of **29**,



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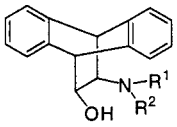
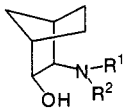
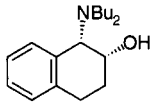


30a: $R^1 = R^2 = Me$
30b: $R^1 = SO_3CF_3$, $R^2 = H$



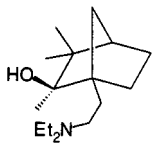
31a: $R^1 = R^2 = Me$
31b: $R^1 = SO_3CF_3$, $R^2 = H$



32

the addition of diethylzinc to aryl aldehydes generated (*R*)-1-arylpropanols with 52−80% ee (entries 1−4, Table 6). Compounds **30a,b**, prepared by Kunieda and co-workers, are sterically very similar to each other but electronically quite different due to the different substituents on the nitrogen.[32] Both showed high enantioselectivity (96% and 98% ee, respectively) for the diethylzinc addition to benzaldehyde but gave the opposite enantiomeric product (entries 5 and 7, Table 6). Such opposite enantioselectivity was, however, not observed for ligands **31a,b**, even though these two ligands were also electronically very different. Compounds **31a,b** catalyzed the diethylzinc addition to benzaldehyde with 94% and 58% ee, respectively (entries 9 and 10, Table 6).[32] The tetrahydronaphthalene-derived amino alcohol **32** prepared by Umani-Ronchi and co-workers gave low enantioselectivity for the diethylzinc addition to benzaldehyde (44% ee).[33]

Ligand **33** was prepared by Fujita and co-workers for the diethylzinc addition.[34] It showed good enantioselectivity for the reaction of benzaldehyde as well as a couple of *para*-substituted benzaldehydes (88−95% ee, entries 1−3 and 5, Table 7) but much lower enantioselectivity for aliphatic and α,*β*-unsaturated aldehydes (60% and 54% ee, entries 7 and 8, Table 7). Another ligand **34** was found to have much lower enantioselectivity for the reaction of diethylzinc with aldehydes (44−62% ee).[35a] Other derivatives of **33** and **34** were also studied.[35b]



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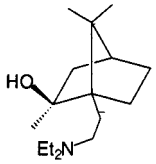
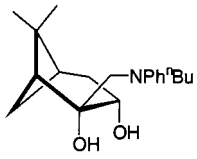


34

A large number of pinane derivatives were prepared by Lu and co-workers, among which compounds **35** and **36** exhibited good enantioselectivity for the reaction of diethylzinc with benzaldehyde.[36] They produced (*S*)-1-phenylpropanol with 88% and 86% ee, respectively. For the reaction of other aryl aldehydes, 54−84% ee was obtained.



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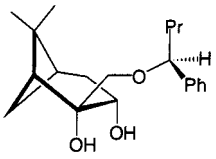
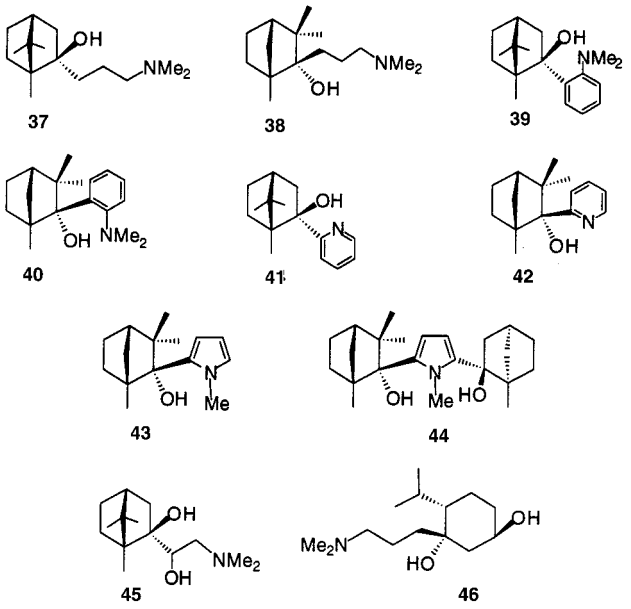
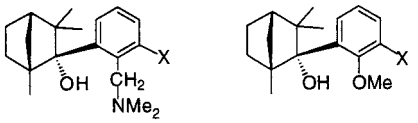


36

Dimitrov and co-workers prepared ligands **37**−**44** from the reaction of alkyl- or aryllithium reagents with camphor or fenchone.[37] These compounds produced a range of ee's, 10−64%, for the diethylzinc addition to benzaldehyde with compound **43** giving the best results. The amino diol **45** was found to catalyze the reaction of diethylzinc with benzaldehyde to give (*S*)-1-phenylpropanol with 80% ee.[38] The addition of ^{n}BuLi reduced the enantioselectivity. The *δ*-amino alcohol **46** gave 89% ee for the reaction of diethylzinc with both benzaldehyde and ferrocenecarboxaldehyde.[39] It showed 86% ee for the dimethylzinc addition to 2-naphthaldehyde.

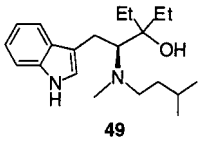


The fechone-based amino alcohols **47** and alcohols **48** were used by Goldfuss et al. to catalyze the reaction of benzaldehyde with diethylzinc.[40] It was

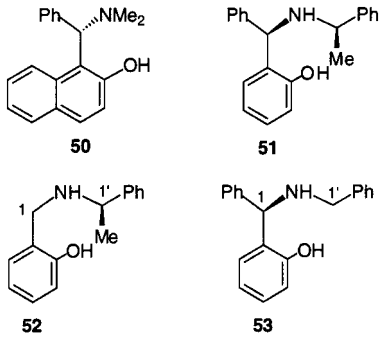


found that **47b** showed up to 93% ee, but the enantioselectivity of ligands **47a** and **48a,b** was low (26−73% ee). Ligands **47b** and **48b** with the bulky trimethylsilyl group were better catalysts than **47a** and **48a**. This was explained by the stronger tendency of the dimeric zinc complexes of **47b** and **48b** to undergo dissociation to generate the catalytically active monomeric zinc complexes. The structures of the dimeric zinc complexes of these ligands were studied by X-ray as well as computational analyses.

Dai and co-workers found that the tryptophan-derived amino alcohol **49** had very good enantioselectivity for diethylzinc additions to certain aromatic and aliphatic aldehydes (up to 97% ee, Table 8).[41] However, very low enantioselectivity (5−24% ee) was observed for pyridinecarboxaldehydes (entries 15−17, Table 8), probably because the resulting products from these substrates could also catalyze the reaction but with low ee.



Compound **50** is a derivative of the Betti base. Naso



and co-workers found that this compound had high enantioselectivity for the diethylzinc addition to aromatic aldehydes (92−99% ee, Table 9).[42] Palmieri found that ligand **51** showed good enantioselectivity for the reaction of diethylzinc with the aromatic and aliphatic aldehydes listed in Table 10.[43] For other aldehydes, the enantioselectivity was much lower. This secondary amine ligand contains two chiral carbon centers connected to the nitrogen atom. It also catalyzed the reaction of dimethylzinc and dibutylzinc with benzaldehyde with 87% and 91% ee, respectively. A pronounced nonlinear effect was observed for **51**. The diastereomer of **51** gave a lower enanti-

Table 8. Diethylzinc Additions to Aldehydes Catalyzed by 49[a]

entry	aldehyde	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	96	70	88	*R*
2	*p*-chlorobenzaldehyde	96	99	97	*R*
3	*m*-chlorobenzaldehyde	117	92	97	*R*
4	*p*-bromobenzaldehyde	117	93	96	*R*
5	*o*-bromobenzaldehyde	117	82	85	*R*
6	*p*-methylbenzaldehyde	96	90	96	*R*
7	*p*-methoxybenzaldehyde	96	90	96	*R*
8	*p*-*N*,*N*-dimethylaminobenzaldehyde	116	94	80	*R*
9	3,5-dichlorobenzaldehyde	116	94	95	*R*
10	3,5-dimethoxybenzaldehyde	116	93	94	*R*
11	1-naphthaldehyde	116	90	94	*R*
12	2-naphthaldehyde	96	99	96	*R*
13	cyclohexanecarboxaldehyde	40	65	95	*R*
14	cinnamaldehyde	48	100	81	*R*
15	2-pyridinecarboxaldehyde	116	41	5	*R*
16	3-pyridinecarboxaldehyde	116	81	24	*R*
17	4-pyridinecarboxaldehyde	116	79	8	*R*
18	2-furaldehyde	96	72	78	*R*
19	2-thiophenecarboxaldehyde	96	84	95	*R*

[a] The reactions were carried out in toluene at room temperature using 10 mol % of **49** and 1 M hexane solution of diethylzinc.

Table 9. Diethylzinc Additions to Aromatic Aldehydes Catalyzed by 50[a]

entry	aldehyde	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	12	93	96	*R*
2	*p*-fluorobenzaldehyde	24	91	92	*R*
3	*p*-chlorobenzaldehyde	24	92	94	*R*
4	*o*-methylbenzaldehyde	72	78	>99	*R*
5	*m*-methylbenzaldehyde	24	89	93	*R*
6	*p*-methylbenzaldehyde	24	94	96	*R*
7	*o*-methoxybenzaldehyde	24	93	96	*R*

[a] The reactions were carried out in toluene at room temperature in the presence of 13 mol % of **50**.

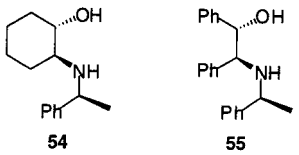
Table 10. Diethylzinc Additions to Aromatic Aldehydes Catalyzed by 51[a]

entry	aldehyde	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	4	93	89	*S*
2	*p*-methoxybenzaldehyde	4	92	94	*S*
3	*p*-chlorobenzaldehyde	5	93	86	*S*
4	3-ethylbutyraldehyde	8	83	94	*S*
5[b]	isobutyraldehyde	4	86	98	*S*
6[c]	cyclohexanecarboxaldehyde	4	82	97	*S*
7	*p*-methylbenzaldehyde	4	92	86	*S*
8	*m*,*p*-dimethoxybenzaldehyde	4	92	94	*S*
9	*m*,*m*′,*p*-trimethoxybenzaldehyde	5	88	86	*S*

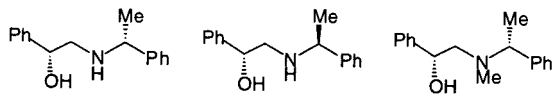
[a] The reactions were carried out in toluene at room temperature in the presence of 6 mol % of **51**. [b] In ref 43b, $t = 8$ h, yield = 86%, and ee = 97%. [c] In ref 43b, $t = 4$ h, yield = 82%, and ee = 93%.

oselectivity. Compound **52**, which contains no chiral center at C1, was found to give only 16% ee for the diethylzinc addition to benzaldehyde, whereas **53** with an achiral C1′ gave 42% ee. Thus, both chiral centers at C1 and C1′ are important for the asymmetric induction.

The amino alcohols, such as **54** and **55**, prepared by Juaristi and co-workers, also had an additional chiral center on the alkyl substituents of the nitrogen.[44] These ligands showed very low enantioselectivity for the diethylzinc addition to benzaldehyde (2−47% ee), even with the use of various additives such as ^{n}BuLi, HCl, and LiCl. The amino alcohols **56**−**58** were prepared from mandelic acid and 1-phenylethylamine.[45] Salvadori and co-workers found that **56** catalyzed the diethylzinc addition to aldehydes with up to 88% ee. The enantioselectivity of **57** and **58** was lower.



54 **55**



56 **57** **58**

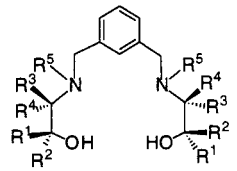
Compounds **59a**−**j** containing two amino alcohol units were prepared and studied by Pedrosa and co-workers.[46] The results of using these ligands in the diethylzinc addition to aldehydes are summarized in Table 11. Ligands **59b**,**h,i** gave 90−98% ee for the

Table 11. Diethylzinc Additions to Aldehydes Catalyzed by 59a−j[a]

entry	aldehyde	catalyst (mol %)	yield (%)	ee (%)	config
1	*p*-chlorobenzaldehyde	**59a** (10)	95	78	*S*
2	*p*-chlorobenzaldehyde	**59b** (10)	82	95	*S*
3	*p*-chlorobenzaldehyde	**59c** (10)	80	78	*S*
4	*p*-chlorobenzaldehyde	**59d** (10)	82	78	*R*
5	*p*-chlorobenzaldehyde	**59e** (10)	85	75	*S*
6	*p*-chlorobenzaldehyde	**59f** (10)	75	75	*S*
7	*p*-chlorobenzaldehyde	**59g** (10)	84	79	*S*
8	*p*-chlorobenzaldehyde	**59h** (10)	81	98	*R*
9	*p*-chlorobenzaldehyde	**59i** (10)	87	91	*R*
10	*p*-chlorobenzaldehyde	**59j** (10)	82	87	*R*
11	benzaldehyde	**59a** (20)	72	80	*S*
12	benzaldehyde	**59b** (10)	85	93	*S*
13	benzaldehyde	**59f** (10)	60	64	*S*
14	benzaldehyde	**59g** (10)	80	69	*S*
15	benzaldehyde	**59h** (10)	83	90	*R*
16	benzaldehyde	**59i** (10)	84	96	*R*
17	2-naphthaldehyde	**59a** (10)	84	87	*S*
18	2-naphthaldehyde	**59b** (10)	85	94	*S*
19	2-naphthaldehyde	**59e** (10)	90	90	*S*
20	2-naphthaldehyde	**59f** (10)	85	87	*S*
21	2-naphthaldehyde	**59g** (10)	89	92	*S*
22	2-naphthaldehyde	**59h** (10)	93	94	*R*
23	2-naphthaldehyde	**59i** (10)	87	93	*R*

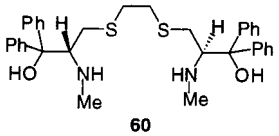
[a] The reactions were carried out in toluene:hexane (2:1) at room temperature.

reaction of several aromatic aldehydes. Ligands **59a**−**c** are different only in their nitrogen substituents (R^5), but the ethyl-substituted **59b** had much higher enantioselectivity (95% ee) than the methyl- and benzyl-substituted **59a,c** (entries 1−3, Table 11). Compound **59d** was the enantiomer of **59c** and showed the expected opposite enantioselectivity (entry 4, Table 11).



59a: R^1 = Ph, R^2 = H, R^3 = Me, R^4 = H, R^5 = Me
59b: R^1 = Ph, R^2 = H, R^3 = Me, R^4 = H, R^5 = Et
59c: R^1 = Ph, R^2 = H, R^3 = Me, R^4 = H, R^5 = Bn
59d: R^1 = H, R^2 = Ph, R^3 = H, R^4 = Me, R^5 = Bn
59e: R^1 = Ph, R^2 = H, R^3 = Ph, R^4 = H, R^5 = Me
59f: R^1 = Me, R^2 = Me, R^3 = Ph, R^4 = H, R^5 = Me
59g: R^1 = Me, R^2 = Me, R^3 = Ph, R^4 = H, R^5 = Et
59h: R^1 = Me, R^2 = Me, R^3 = H, R^4 = ^{t}Bu, R^5 = Me
59i: R^1 = Me, R^2 = Me, R^3 = H, R^4 = ^{t}Bu, R^5 = Et
59j: R^1 = Ph, R^2 = Ph, R^3 = H, R^4 = ^{t}Bu, R^5 = Me

The C_2-symmetric amino alcohols such as **60** were prepared by Kossenjans and Martens from (*R*)-cysteine for asymmetric catalysis.[47] Compound **60** catalyzed the reaction of diethylzinc with benzaldehyde with up to 94% ee at room temperature.



60

Table 12. Diethylzinc Additions to Aldehydes Catalyzed by 61 and 62[a]

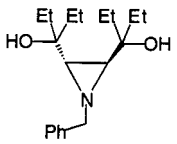
entry	aldehyde	catalyst (mol %)	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	*p*-chlorobenzaldehyde	**61** (3)	−23	60	85	91	*S*
2	*m*-methoxybenzaldehyde	**61** (3)	−23	60	>95	97	*S*
3	*p*-methoxybenzaldehyde	**61** (3)	−23	60	>95	94	*S*
4	isovaleraldehyde	**61** (3)	−23	60	>70	65	*S*
5	cyclohexanecarboxaldehyde	**61** (3)	−23	60	>95	10	*R*
6	benzaldehyde	(*S*)-**62** (5)	0	24	90	99	*S*
7	benzaldehyde	(*R*)-**62** (5)	0	24	90	99	*R*
8	*p*-methoxybenzaldehyde	(*S*)-**62** (5)	0	24	91	99	*S*
9	*p*-chlorobenzaldehyde	(*S*)-**62** (5)	0	24	80	99	*S*
10	2-furaldehyde	(*S*)-**62** (5)	0	24	69	99	*S*
11	cyclohexanecarboxaldehyde	(*S*)-**62** (5)	0	24	90	99	*S*
12	cyclohexanecarboxaldehyde	(*R*)-**62** (5)	0	24	90	95	*R*
13	3-isovaleraldehyde	(*S*)-**62** (5)	0	24	50	96	*S*
14	3-isovaleraldehyde	(*R*)-**62** (5)	0	24	45	96	*R*
15	heptanal	(*S*)-**62** (5)	0	24	48	80	*S*

[a] The reactions were carried out in toluene solution.

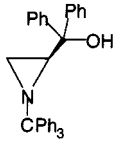
b. Cyclic Amine-Based Amino Alcohols

i. Three- and Four-Membered Rings

A family of chiral aziridino alcohols was prepared by Tanner and co-workers for the diethylzinc addition among which **61** was found to gave the highest ee.[48] In the presence of 3 mol % of **61**, the addition to aromatic aldehydes proceeded with 91−97% ee (Table 12). However, the addition to aliphatic aldehydes such as isovaleraldehyde and cyclohexanecarboxaldehyde gave only 65% and 10% ee, respectively (entries 4 and 5, Table 12). Zwanenburg and co-workers reported a more effective aziridino alcohol ligand **62**.[49] This compound catalyzed the reaction of aromatic, β-branched aliphatic and cyclic aliphatic aldehydes with diethylzinc with 95−99% ee (entries 6−14, Table 12). For a linear aliphatic aldehyde, heptanal, **62** showed 80% ee (entry 15, Table 12).

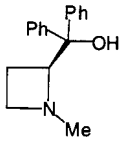


61



(*S*)-**62**

The optically active amino alcohol **63** containing a four-membered cyclic amine substituent was studied by Martens and co-workers.[50] It was found that the catalysis by **63** required the addition of ^{n}BuLi. In the presence of 5 mol % of **63**, as well as 11 mol % of ^{n}BuLi, the reaction of diethylzinc with aromatic aldehydes produced the corresponding (*S*)-alcohols with 94−100% ee (entries 1−5, Table 13). Lower enantioselectivity was observed for the reaction of nonyl aldehyde, a linear aliphatic aldehyde (67% ee, entry 8, Table 13).



63

The C_2-symmetric 2,4-disubstituted azetidines **64a−c** were reported by Shi and Jiang as chiral ligands for the addition of diethylzinc to aldehydes.[51] Ligand **64a** showed good enantioselectivity (83−93% ee) for aromatic aldehydes but much lower for aliphatic and α,β-unsaturated aldehydes (65 and 63% ee) (entries 1−7, Table 14). Its enantioselectivity was much better than that of the bulky silyl group-protected ligands **64b,c** (20% ee's, entries 8−10, Table 14).

Table 13. Diethylzinc Additions Catalyzed by 63 in the Presence of ^{n}BuLi[a]

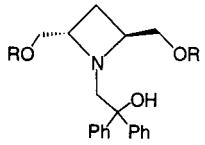
entry	aldehyde	ee (%)	config
1	benzaldehyde	98	*S*
2	*p*-chlorobenzaldehyde	100	*S*
3	*o*-methoxybenzaldehyde	94	*S*
4	*p*-methoxybenzaldehyde	100	*S*
5	*p*-methylbenzaldehyde	99	*S*
6	cinnamaldehyde	80	*S*
7	2-furaldehyde	94	*S*
8	nonyl aldehyde	67	*S*

[a] The reaction were carried out in toluene in the presence of 5 mol % of **63** at 22 °C over 40 h.

Table 14. Diethylzinc Additions to Aldehydes Catalyzed by 64a−c[a]

entry	aldehyde	catalyst (mol %)	yield (%)	ee (%)	config
1	benzaldehyde	**64a** (5)	99	92	*S*
2	*p*-methylbenzaldehyde	**64a** (5)	95	83	*S*
3	*p*-chlorobenzaldehyde	**64a** (5)	92	92	*S*
4	*p*-bromobenzaldehyde	**64a** (5)	94	93	*S*
5	1-naphthaldehyde	**64a** (5)	97	86	*S*
6	valeraldehyde	**64a** (5)	94	65	*S*
7	cinnamaldehyde	**64a** (5)	86	63	*S*
8	benzaldehyde	**64b** (5)	96	20	*S*
9	*p*-methylbenzaldehyde	**64b** (5)	96	20	*S*
10	*p*-methylbenzaldehyde	**64c** (5)	90	20	*S*

[a] The reactions were carried out in hexane at 0 °C over 24 h using 1.1 M hexane solution of diethylzinc.



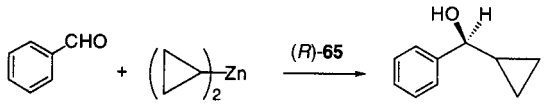
64a: R = Me
64b: R = TBDMS
64c: R = TBDPS

ii. Five-Membered Rings

Earlier, the proline-based ligand (*S*)-**65** was shown to be highly enantioselective for the diethylzinc

addition to aldehydes.[52] Soai and co-workers recently used (*S*)-**65** and (*R*)-**65** to catalyze the reaction of dicyclopropylzinc with benzaldehyde (Scheme 7).[53]

Scheme 7. Dicyclopropylzinc Addition to Benzaldehyde Catalyzed by (*R*)-65



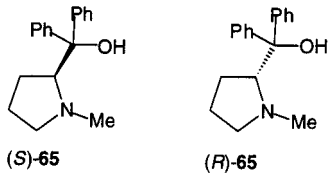
The *R* ligand led to the formation of a *S* alcohol product. The catalytic activity and enantioselectivity were very similar when the lithium salt of (*S*)-**65** was used. Table 15 summarizes the use of (*R*)-**65** for the

Table 15. Dicyclopropylzinc Additions to Aldehydes Catalyzed by (*R*)-65[a]

entry	aldehyde	mol % of catalyst	*t* (h)	yield (%)	ee (%)
1	benzaldehyde	20	5	90	86
2	*p*-methoxybenzaldehyde	5	3	97	86
3	*p*-chlorobenzaldehyde	5	2	97	84
4	1-naphthaldehyde	5	2	94	78
5	cinnamaldehyde	5	1.5	94	67
6	3-phenylpropionaldehyde	20	1	91	67
7	cyclohexanecarboxaldehyde	5	2	87	71

[a] All the reactions were carried out in the presence of 3 equiv of dicyclopropylzinc in a mixed solvent of hexane and toluene (4:1.5) at 0 °C.

reaction of dicyclopropylzinc with aromatic and aliphatic aldehydes. Up to 86% ee was observed for the reaction of aromatic aldehydes.



Soai et al. used (*S*)-**65** to catalyze the reaction of *p*-benzoylbenzaldehyde (**13e**) with dialkylzincs (see Scheme 4).[21] As shown in Table 16, these reactions

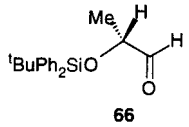
Table 16. Dialkylzinc Additions to *p*-Benzoylbenzaldehyde[a]

entry	R_2Zn	catalyst	*t* (h)	yield (%)	ee (%)
1	Et_2Zn	(*S*)-**65**	18	100	93
2	Et_2Zn	(*S*)-**65**−Li[b]	24	82	96
3	Me_2Zn	(*S*)-**65**	20	82	87
4	Me_2Zn	(*S*)-**65**−Li[b]	72	83	87
5	Bu_2Zn	(*S*)-**65**	72	64	92
6	Bu_2Zn	(*S*)-**65**−Li[b]	19	48	91
7	$(pentyl)_2Zn$	(*S*)-**65**	27	94	94
8	$(3\text{-methylbutyl})_2Zn$	(*S*)-**65**	78	100	95

[a] All the reactions were carried out at 0 °C in toluene in the presence of 8 mol % of (*S*)-**65**. [b] Prepared by treatment of (*S*)-**65** with butyllithium.

gave the corresponding keto alcohols **14** with 87−96% ee with no reaction occurring at the ketone group.

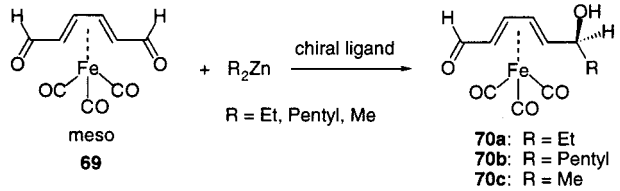
Ligand (*R*)-**65** was also used to catalyze the reaction of **66** with diethylzinc.[20] At 0 °C, 5 mol % of (*R*)-**65** gave the corresponding products **11** and **12** with a ratio of 6:94 and 54% yield (see Scheme 3). Under the same conditions, (*S*)-**65** gave a product ratio of 93:7 (**11**/**12**). This indicates that the stereoselectivity is provided by the structure of the chiral catalyst rather than that of the substrate. The bulky silyl group of **66** might have prevented the α oxygen atom from coordination with the metal center and allowed the catalyst to control the reaction.



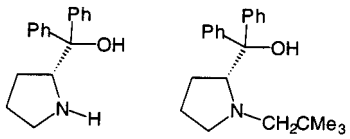
66

Takemoto et al. reported the use of (*R*)-**65**, (*R*)-**67**, and (*R*)-**68** to catalyze the dialkylzinc addition to the iron−diene complex-based meso dialdehyde **69** (Scheme 8).[54] In the presence of 0.5 equiv of (*R*)-**65**,

Scheme 8. Dialkylzinc Additions to 69 Catalyzed by (*R*)-65, (*R*)-67, and (*R*)-68



70a was obtained with >98% ee and 78% yield. Only a small amount of other products was observed. Thus, the diethylzinc addition proceeded with both high enantiotopic group selectivity and high diastereotopic face selectivity. A dipentylzinc addition gave similar results, but a dimethylzinc addition gave much lower conversion as well as lower enantiotopic group selectivity. When ligand **67** was used, a lower yield of **70a** was obtained but still with high enantioselectivity (96% ee). Ligand **68** gave both lower yield and lower enantioselectivity.



The kinetic resolution for the reaction of a racemic mixture of (sorbic aldehyde)$Fe(CO)_3$ (**71**) with diethylzinc was conducted in the presence of (*R*)-**65** (Scheme 9).[54] This process generated (3*S*,4*S*)-**72** with high enantioselectivity (>95% ee). The optically active (−)-(2*R*)-**71** was recovered with 22% ee. A small amount of another diastereomer (3*S*,4*R*)-**72** was also obtained with >95% ee. Complexes **73** and **74**, which contain more bulky triphenylphosphine and trimethyl phosphate ligands, could not undergo the dialkylzinc addition in the presence of (*R*)-**65**.

Ligands **75**−**78**, structurally similar to **65**, were shown by Wang and co-workers to have good enantioselectivity for the reaction of diethylzinc with

Scheme 9. Diethylzinc Addition to 71 Catalyzed by (*R*)-65

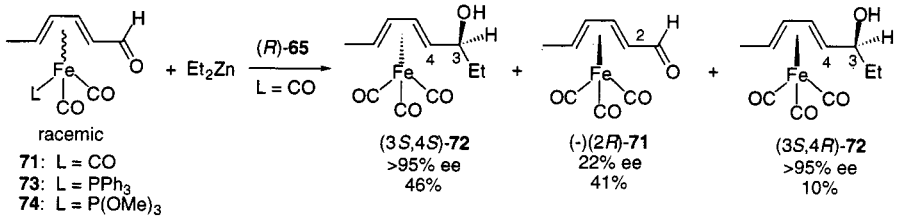
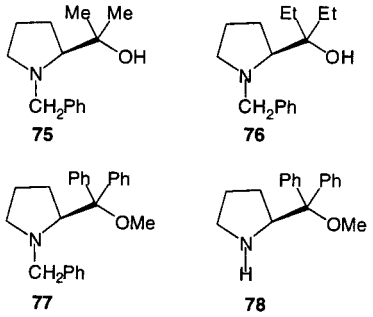


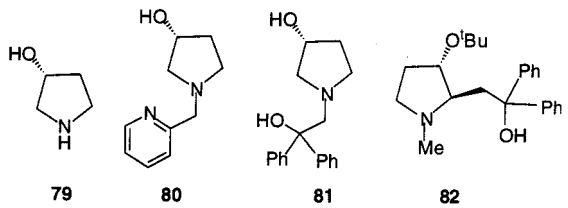
Table 17. Diethylzinc Additions to Aldehydes Catalyzed by 75−78

entry	catalyst	aldehyde	solvent	time and temperature	yield (%)	ee (%)	config
1	**75**	benzaldehyde	benzene	0 °C, 2 h; rt, 13 h	98	99	*R*
2	**75**	*p*-methoxybenzaldehyde	benzene	0 °C, 2 h; rt, 15 h	79	95	*R*
3	**76**	benzaldehyde	hexane	0 °C, 2 h; rt, 13 h	98	96	*R*
4	**76**	*p*-methoxybenzaldehyde	hexane	0 °C, 2 h; rt, 15 h	73	85	*R*
5	**77**	benzaldehyde	hexane	0 °C, 2 h; rt, 10 h	90	95	*S*
6	**78**	benzaldehyde	benzene	0 °C, 2 h; rt, 15 h	96	94	*R*

aromatic aldehydes (85−99% ee, Table 17).[55] Although the structure of **77** was similar to the other ligands, it gave the opposite enantiomeric product (entry 5, Table 17).



Ligands **79**−**81** were prepared by Martens and co-workers from L-hydroxyproline.[56] These compounds, as well as their lithium salts made by treatment with ^{n}BuLi, were used to catalyze the reaction of diethylzinc with benzaldehyde. It was found that the lithium salt of **79** gave the highest enantioselectivity (80% ee), much higher than the use of **79** itself (23% ee only). For the reaction of other aromatic aldehydes, the lithium salt of **79** gave 62−79% ee. Cicchi et al. reported the study of a series of γ-amino alcohols, such as **82**.[57] This ligand catalyzed the reaction of diethylzinc with benzaldehyde with only 54% ee.

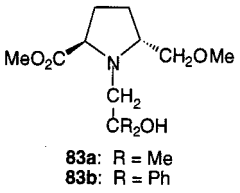


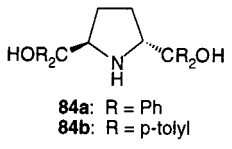
The use of the pyrolidine compounds **83a,b** in the reaction of aldehydes with diethylzinc was investigated by Masaki and co-workers.[58] Compound **83b** showed good reactivity and enantioselectivity for certain aromatic aldehydes (70−96% ee) (Table 18). Another type of pyrolidine-based C_2 symmetric ligands, **84a,b**, showed much lower enantioselectivity (10−53% ee).

Table 18. Diethylzinc Additions to Aldehydes Catalyzed by 83b[a]

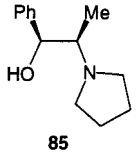
entry	aldehyde	yield (%)	ee (%)	config
1	benzaldehyde	99	91	*R*
2	*p*-methylbenzaldehyde	99	96	*R*
3	*o*-methoxybenzaldehyde	85	83	*R*
4	*p*-methoxybenzaldehyde	85	73	*R*
5	*p*-fluorobenzaldehyde	96	70	*R*
6	*m*-fluorobenzaldehyde	88	85	*R*
7	*p*-chlorobenzaldehyde	92	76	*R*
8	*m*-chlorobenzaldehyde	96	90	*R*
9	*o*-chlorobenzaldehyde	86	92	*R*

[a] The reactions were carried out in hexane at 0 °C over 24 h in the presence of 5 mol % of **83b**.





In 1991, Soai et al. reported that the amino alcohol **85** was an efficient chiral catalyst for the reaction of diethylzinc with aliphatic aldehydes.[59] They also found that this ligand was able to catalyze the reaction of dialkylzincs with aromatic aldehydes with very good enantioselectivity (87−92% ee, Table 19).[60] Ligand **85** and its enantiomer were used to catalyze the reaction of dialkylzincs with heteroaromatic aldehydes derived from furane, thiophene, and pyrrole, which gave the corresponding alcohols with 70−86% ee.[60b]



Yamada and co-workers found that ligands **86a,b** were highly enantioselective for the reaction of diethylzinc with benzaldehyde.[61] These two compounds

Table 19. Dialkylzinc Additions to Aromatic Aldehydes Catalyzed by 85[a]

entry	R_2Zn	aldehyde	yield (%)	ee (%)	config
1	Et_2Zn	benzaldehyde	91	88	S
2	Bu_2Zn	benzaldehyde	57	89	S
3	Et_2Zn	*p*-methylbenzaldehyde	93	88	S
4	Et_2Zn	*p*-methylbenzaldehyde[b]	87	92	S
5	Bu_2Zn	*p*-methylbenzaldehyde	64	91	S
6	$^{i}Pr_2Zn$	*p*-methylbenzaldehyde	71	92	S
7	Et_2Zn	*o*-methylbenzaldehyde	90	89	S
8	Et_2Zn	*p*-chlorobenzaldehyde	92	87	S
9	Et_2Zn	1-naphthaldehyde	86	92	S
10	Et_2Zn	2-naphthaldehyde	94	87	S
11	Et_2Zn	*p*-phenylbenzaldehyde	97	88	S
12	Et_2Zn	3,4-methylenedioxybenzaldehyde	91	91	S
13	Et_2Zn	*m*,*p*-dimethoxybenzaldehyde	96	88	S

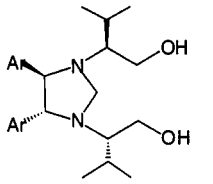
[a] The reactions were carried out in hexane at 0 °C in the presence of 10 mol % of **85**. [b] 5 mol % of **85** was used.

Table 20. Diethylzinc Additions to Aldehydes Catalyzed by 89−94[a]

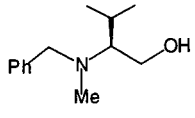
entry	aldehyde	catalyst (mol %)	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	**89** (5)	r.t.	48		99	*R*
2	2-naphthaldehyde	**89** (5)	r.t.	48	98	87	*R*
3	2-furaldehyde	**89** (5)	r.t.	48	98	67	*R*
4	*p*-chlorobenzaldehyde	**89** (5)	r.t.	48	98	99	*R*
5	*p*-methylbenzaldehyde	**89** (5)	r.t.	48	87	100	*R*
6	heptanal	**89** (5)	r.t.	48	78	66	*R*
7	isovaleraldehyde	**89** (5)	r.t.	48	22	86	*R*
8	benzaldehyde	**90** (10)	25		71	98	*R*
9	benzaldehyde	**91** (10)	22		76	98	*R*
10	benzaldehyde	**92** (10)	22		91	94	*R*
11	benzaldehyde	**93** (5)	23		76	12	*S*
12	benzaldehyde	**94** (5)	21		71	99	*R*

[a] The reactions were carried out in toluene.

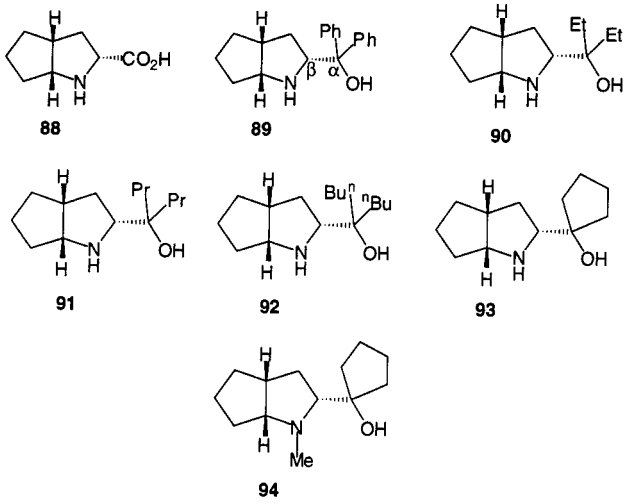
catalyzed the formation of (*R*)-1-phenylpropanol with 90% and 91% ee, respectively, at 0 °C. However, **87**, the monomeric model compound of **86a,b**, gave only 13% ee. Compound **86a** was used to catalyze the reaction of other aromatic aldehydes with up to 88% ee, but for 3-phenylpropionaldehyde and cinnamaldehyde, it gave only 33% and 27% ee, respectively.



86a: Ar = Ph
86b: Ar = p-MeOC$_6$H$_4$



87



iii. Multicyclic Five-Membered Rings

The bicyclic proline analogue **88** was utilized by Martens and co-workers to prepare a series of bicyclic amino alcohols, such as **89**, for the asymmetric organozinc addition.[62] After various alkyl and aryl substituents at both the nitrogen and hydroxyl carbon of the amino alcohol were screened, compound **89** proved to be the best ligand. It catalyzed the diethylzinc addition to aromatic aldehydes with up to 100% ee (Table 20). However, for the reaction of 2-furaldehyde and heptanal, it gave only 67% and 66% ee's (entries 3 and 6, Table 20). The effects of the structure of the bicyclic amino alcohols on the catalytic properties were systematically studied by preparing ligands **90**−**94**. The results of using these ligands for the diethylzinc addition to aldehydes are summarized in entries 8−12 of Table 20. Both phenyl and alkyl substituents at the α position of the ligand showed high enantioselectivity (94−98% ee, entries 8−10, Table 20). However, in the case of ligand **93**, which contains a rigid cyclic α carbon, there was a dramatic decrease in enantioselectivity (12% ee, entry 11, Table 20). Furthermore, the absolute configuration of the product was also inverted. Interestingly, methylation of the nitrogen atom of **93**, giving **94**, restored the original product configuration as well as the high enantioselectivity (99% ee, entry 12, Table 20).

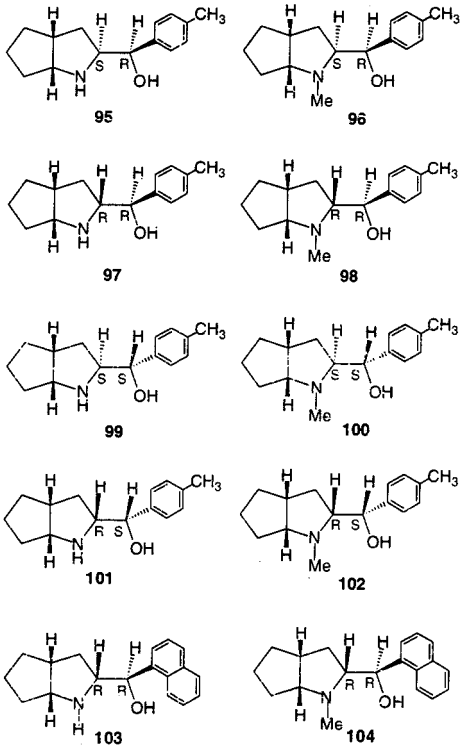
The positive effects of the *N*-methyl group of these bicyclic amino alcohols were further observed when

varying the α and β configurations of the ligands.[62c] Ligands **95**−**104** with various α and β configurations were prepared. Table 21 shows that the configurations of the α and β positions of the ligands have a strong influence on their enantioselectivity. When the configurations at both positions are inverted, the product configuration was also inverted. The highest enantioselectivity (91% ee) was achieved with ligand **98**, which contains an α*R* and β*R* configuration and a *N*-methyl group (entry 4, Table 21). In the case of ligand **104**, the *N*-methyl substitution, however, led to a negative effect on the enantioselectivity. The ee of the product decreased from 75% to 50% for the diethylzinc addition to benzaldehyde by *N*-methylation of **103** to **104** (entries 9 and 10, Table 21).

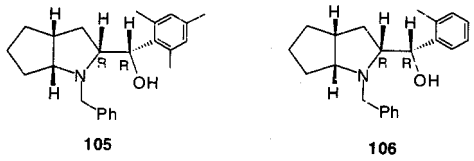
Table 21. Diethylzinc Additions to Benzaldehyde Catalyzed by 95−104[a]

entry	catalyst (mol %)	*T* (°C)	yield (%)	ee (%)	config
1	**95** (10)	24	71	43	*R*
2	**96** (10)	20	78	77	*R*
3	**97** (5)	20	67	8	*S*
4	**98** (5)	21	86	91	*R*
5	**99** (5)	23	74	13	*R*
6	**100** (5)	22	72	54	*S*
7	**101** (10)	22	83	5	*S*
8	**102** (5)	25	69	51	*S*
9	**103** (5)	22	73	75	*R*
10	**104** (5)	20	71	50	*R*

[a] The reactions were carried out in toluene over 16−40 h.



The *N*-benzyl-substituted bicyclic ligands **105** and **106** were studied.[62d] The lithium salts of these ligands, prepared by reaction with ^{n}BuLi, were found to show higher enantioselectivity (86 and 80% ee, respectively) than the ligands themselves (63% and 17% ee, respectively) for the diethylzinc addition to benzaldehyde.

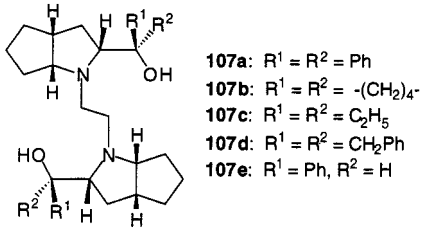


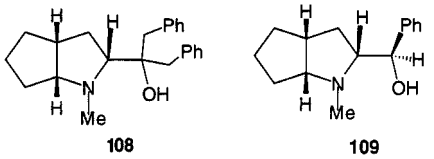
The dimeric forms of the bicyclic amino alcohol ligands **107a**−**e** were prepared.[62e] These compounds were used in the diethylzinc addition to benzaldehyde, and their catalytic properties were compared with their monomeric counterparts **89**, **94**, **108**, and **109** (Table 22). In general, ligands **107** did not show improvement in enantioselectivity over their corresponding monomeric version except in the case of **107a**, which was found to be much better than **89** at low catalyst loading. In the presence of 1 mol % of **107a**, the diethylzinc addition to benzaldehyde proceeded with 88% ee but only 45% ee with the use of 1 mol % of **89** (entries 3 and 4, Table 22). The catalyst loading had a large effect on the enantioselectivity of these catalysts.

Table 22. Diethylzinc Additions to Benzaldehyde Catalyzed by the Dimeric and Monomeric Bicyclic Amino Alcohols[a]

entry	catalyst (mol %)	*T* (°C)	yield (%)	ee (%)	config
1	**107a** (5)	23	73	100	*R*
2	**107a** (2)	21	73	100	*R*
3	**107a** (1)	24	82	88	*R*
4	**89** (1)	20	67	45	*R*
5	**107b** (5)	21	76	90	*R*
6	**107b** (2)	23	57	47	*R*
7	**94** (5)	21	71	99	*R*
8	**107c** (5)	22	68	91	*R*
9	**107c** (2)	22	60	71	*R*
10	**107d** (5)	22	51	54	*R*
11	**108** (10)	21	40	90	*R*
12	**107e** (5)	22	47	65	*R*
13	**107e** (2)	21	59	69	*R*
14	**109** (5)	24	64	68	*R*

[a] The reactions were carried out in toluene solution over 16 h.





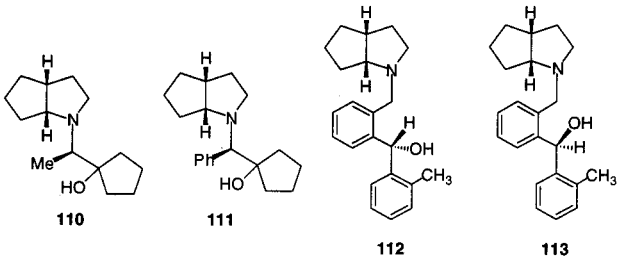
The bicyclic ligands **110**−**113** with various N-functional alkyl groups were also investigated.[62f] The

Table 23. Diethylzinc Additions to Benzaldehyde Catalyzed by 110−113[a]

entry	catalyst (mol %)	*t* (h)	yield (%)	ee (%)	config
1	**110** (1)	72	78	72	*S*
2	**110** (5)	42	93	92	*S*
3	**110** (10)	24	95	96	*S*
4	**111** (5)	40	94	91	*S*
5	**112** (10)		76	90	*S*
6	**113** (10)		75	89	*R*
7	**112-Li** (10)[b]		78	82	*S*

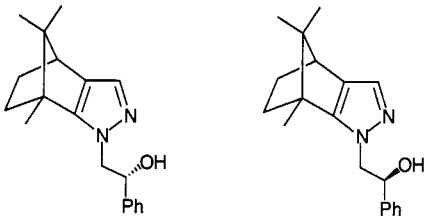
[a] Reactions were carried out at room temperature in toluene. [b] Prepared by reaction of **112** with ^{n}BuLi.

catalytic properties of these compounds for the diethylzinc addition to benzaldehyde are summarized in Table 23. In general, these ligands showed very good enantioselectivity. In the presence of 10 mol % of **111**, the reaction proceeded with 96% ee (entry 3, Table 23). The product configuration obtained by using **113** was opposite to that obtained by using **112**, indicating that the chiral control was provided by the alcohol configuration rather than the bicyclic configuration. The lithium salt of **112** gave lower enantioselectivity.



110 **111** **112** **113**

Kotsuki and co-workers reported that 20 mol % of the tricyclic pyrazole ligand **114** catalyzed the diethylzinc addition to benzaldehyde to give (*R*)-1-phenylpropanol at room temperature with 93% ee.[63] Under the same conditions, **115**, a diastereomer of **114**, catalyzed the reaction to give (*S*)-1-phenylpropanol with the same ee. Thus, the chiral hydroxyl group of these ligands determines the stereochemistry of the reaction instead of the chiral multicyclic structure.



114 **115**

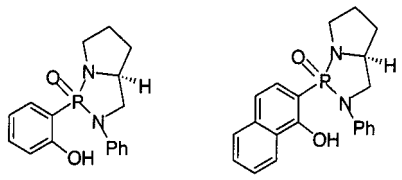
The phosphoramide ligand **116** was prepared by Buono and co-workers.[64a] In the presence of 5 mol % of **116**, the diethylzinc addition to *p*-cyanobenzaldehyde proceeded with over 99% ee (Table 24). As the electron-withdrawing power of the benzaldehyde substituents decreased, their enantioselectivity also decreased. A series of structurally similar ligands were prepared among which the 2-naphthol-derived ligand **117** gave the best results. It catalyzed the

Table 24. Diethylzinc Additions to Aldehyde Catalyzed by 116[a]

entry	aldehyde	yield (%)	ee (%)	config
1	benzaldehyde	98	73	*R*
2	*p*-*N*,*N*-dimethylbenzaldehyde	98	71	*R*
3	*p*-chlorobenzaldehyde	84	86	*R*
4	*p*-cyanobenzaldehyde	91	>99	*R*

[a] The reactions were carried out at 20 °C in THF using 5 mol % of **116** and 2 equiv of diethylzinc over 48 h.

diethylzinc addition to benzaldehyde with 98% ee.[64b] The X-ray structure of **117** showed that the phosphorus center had a *S* configuration.[64c]



116 **117**

iv. Six-Membered Rings

Pericàs and co-workers discovered an excellent ligand, **118**, for the reaction of diethylzinc with aldehydes.[65a] This ligand was easily prepared from the reaction of (*S*)-triphenylethylene oxide (**119**) with piperidine in the presence of lithium perchlorate. It showed high catalytic activity as well as enantioselectivity for a large number of aldehydes. In the presence of 6 mol % of the ligand at 0 °C, benzaldehydes containing various substituents at various positions reacted with diethylzinc in 3 h with over 95% ee (Table 25). For aliphatic aldehydes with

Table 25. Diethylzinc Additions to Aldehydes Catalyzed by 118[a]

entry	aldehyde	*T* (°C)	conv (%)	ee (%)	config
1	benzaldehyde	0	100	98	*S*
2	*o*-chlorobenzaldehyde	0	100	95	*S*
3	*o*-fluorobenzaldehyde	0	99	96	*S*
4	*o*-methylbenzaldehyde	0	99	96	*S*
5	*o*-methoxybenzaldehyde	0	100	97	*S*
6	*m*-fluorobenzaldehyde	0	99	97	*S*
7	*m*-methylbenzaldehyde	0	99	97	*S*
8	*m*-methoxybenzaldehyde	0	99	97	*S*
9	*p*-fluorobenzaldehyde	0	100	98	*S*
10	*p*-methylbenzaldehyde	0	100	98	*S*
11	*p*-methoxybenzaldehyde	0	98	98	*S*
12	1-naphthaldehyde	0	99	>99	*S*
13	2-naphthaldehyde	0	99	98	*S*
14	heptanal	0	100	92	*S*
15	isovaleraldehyde	−20	99	92	*S*
16	3-phenylpropionaldehyde	−20	99	93	*S*
17	cyclohexanecarboxaldehyde	0	99	98	*S*
18	3-cyclohexenecarboxaldehyde	0	99	99	*S*
19	2-ethylbutyraldehyde	0	99	97	*S*
20	cinnamaldehyde	0	88	95	*S*

[a] The reactions were carried out in the presence of 6 mol % of **118** in toluene over 3 h by using 1 M hexane solution of diethylzinc.

α-substituents, ee's were in the range of 95−99%. For aliphatic aldehydes without α-substituents, ee'swere in the range of 92−93%. The reaction of α,*β*-unsaturated aldehydes was not explored except for

Table 26. Diethylzinc Additions to Benzaldehyde Catalyzed by 120a−g[a]

entry	catalyst (mol %)	conv (%)	ee (%)	config
1	**120a** (6)	100	97	*S*
2	**120b** (6)	98	95	*S*
3	**120c** (6)	100	97	*S*
4	**120d** (6)	100	97	*S*
5	**120e** (6)	99	94	*S*
6	**120f** (6)	99	17	*S*
7	**120g** (6)	100	74	*S*

[a] The reaction were conducted in toluene solution at 0 °C over 3 h by using 1 M solution of diethylzinc.

Table 27. Diethylzinc Additions to Aldehydes Catalyzed by 120a,c

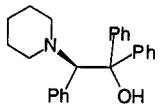
	catalyst **120a** (6 mol %)		catalyst **120c** (6 mol %)	
aldehyde	conv (%)	ee (%)	conv (%)	ee (%)
o-methylbenzaldehyde	99	98	100	98
o-chlorobenzaldehyde	100	95	100	95
o-methoxybenzaldehyde	100	96	100	96
m-methylbenzaldehyde	100	97	98	97
m-fluorobenzaldehyde	100	97	100	96
m-methoxybenzaldehyde	100	96	100	97
p-methylbenzaldehyde	100	97	100	98
p-fluorobenzaldehyde	100	97	100	97
p-methoxybenzaldehyde	100[a]	98	85	97
1-naphthaldehyde	99	96	99	97
2-naphthaldehyde	99	96	99	97
2-furaldehyde	100	96	100	96
2-ethylbutyraldehyde	100	98	100	97
cyclohexanecarboxaldehyde	85	96	84	98
2-methylcinnamaldehyde	95[a]	97	85	96
cinnamaldehyde	99[a]	90	84	90
3-phenylpropionaldehyde	93	94	93	94
isovaleraldehyde	95	94	99	94
heptanal	96	93	99	93
heptanal	99[a]	93	80	91
nonyl aldehyde	96[a]	93	80	89

[a] 10 mol % of **120a** was used.

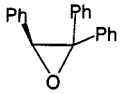
Table 28. Diethylzinc Additions to Benzaldehyde Catalyzed by 122a−k

entry	catalyst	solvent	*T* (°C)	*t* (h)	conv (%)	ee (%)	config
1	**122a**	hexane	r.t.	5	>99	69	*S*
2	**122b**	hexane	r.t.	3	>99	89	*S*
3	**122c**	hexane	r.t.	3	>99	90	*S*
4	**122d**	hexane	r.t.	5	>99	90	*S*
5	**122e**	toluene	r.t.	3	>99	88	*S*
6	**122f**	toluene	r.t.	3	99	91	*S*
7	**122f**	toluene	0	7	>99	92	*S*
8	**122f**	toluene	−18	24	98	95	*S*
9	**122g**	hexane	r.t.	3	>99	87	*S*
10	**122h**	toluene	r.t.	3	>99	87	*S*
11	**122i**	toluene	r.t.	3	>99	92	*S*
12	**122j**	toluene	0	4	>99	97	*S*
13	**122k**	toluene	r.t.	4	>99	84	*S*

cinnamaldehyde, which gave 95% ee (entry 20, Table 25).

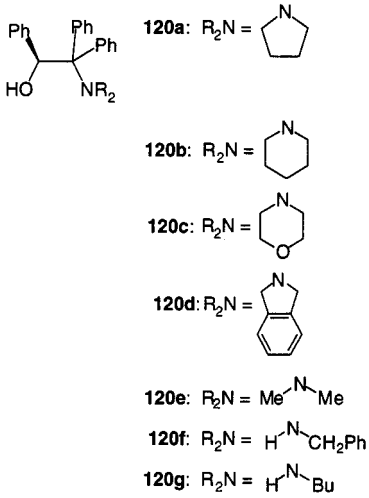


118



119

Compounds **120a−g** were prepared as the analogues of **118**.[65b] These compounds were used to catalyze the reaction of diethylzinc with benzaldehyde. The cyclic amine and acyclic dialkylamine derivatives **120a−e** catalyzed this reaction toward completion within 3 h at 0 °C to give (*S*)-1-phenylpropanol with 94−97% ee (entries 1−5, Table 26). However, the monoalkylamine-substituted ligands **120f,g** showed much lower enantioselectivity (17−74% ee, entries 6 and 7, Table 26). Like **118**, ligands **120a,c** also showed very high enantioselectivity for a broad range of aldehydes (Table 27).

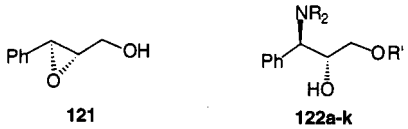


The amino alcohol ligands **122a−k** were prepared from 2,3-epoxypropanol (**121**), and their use in the diethylzinc addition to benzaldehyde was studied (Table 28).[65c,d] Among these ligands, **122f,i,j** were found to show good enantioselectivity (80−97% ee) for the reaction of diethylzinc with a number of aromatic and aliphatic aldehydes (Table 29). The lithium salt of ligand **122k** showed 92% ee for the diethylzinc addition to benzaldehyde, which was higher than the result obtained by using the ligand itself (84% ee, entry 13, Table 28). A quantum mechanics and molecular mechanics study of the reaction catalyzed by **118** was conducted.[65e]

Table 29. Diethylzinc Additions Catalyzed by 122f,i,j[a]

	122f (6 mol %)		**122i** (6 mol %)		**122j** (6 mol %)	
aldehyde	conv (%)	ee (%)	conv (%)	ee (%)	conv (%)	ee (%)
p-methylbenzaldehyde	>99	92	95	95	>99	97
p-fluorobenzaldehyde	>99	93	96	94	>99	97
p-methoxybenzaldehyde	>99	91	72	96	>99	98
o-chlorobenzaldehyde	>99	87	97	87	>99	93
1-naphthaldehyde	99	82	48	80	>99	90
3-phenylpropionaldehyde	>99	86	>99	86	>99	92
isovaleraldehyde	>99	85	>99	80	>99	90

[a] The reactions were carried out in toluene at 0 °C for 4 h.



121 122a-k

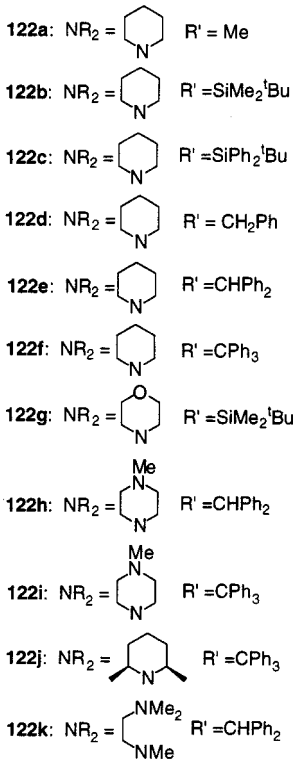
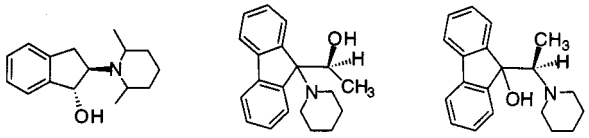


Table 30. Diethylzinc Additions to Aldehyde Catalyzed by 124[a]

entry	aldehyde	conv (%)	ee (%)	config
1	benzaldehyde	99	96	*S*
2	*o*-chlorobenzaldehyde	99	91	*S*
3	*o*-methylbenzaldehyde	99	96	*S*
4	*o*-methoxybenzaldehyde	100	82	*S*
5	*m*-chlorobenzaldehyde	100	97	*S*
6	*m*-methylbenzaldehyde	100	96	*S*
7	*m*-methoxybenzaldehyde	100	96	*S*
8	*p*-fluorobenzaldehyde	100	97	*S*
9	*p*-methylbenzaldehyde	100	97	*S*
10	1-naphthaldehyde	87	90	*S*
11	2-naphthaldehyde	99	96	*S*
12	hexanal	99	91	*S*
13	heptanal	99	91	*S*
14	nonyl aldehyde	85	90	*S*
15	isovaleraldehyde	95	95	*S*
16	3-phenylpropionaldehyde	99	91	*S*
17	cyclohexanecarboxaldehyde	98	98	*S*
18	2-ethylbutyraldehyde	99	94	*S*
19	*E*-α-methylcinnamaldehyde	71	94	*S*

[a] The reactions were carried out at 0 °C in toluene in the presence of 3 mol % of **124** and 2.2 equiv of diethylzinc (1 M in hexane).

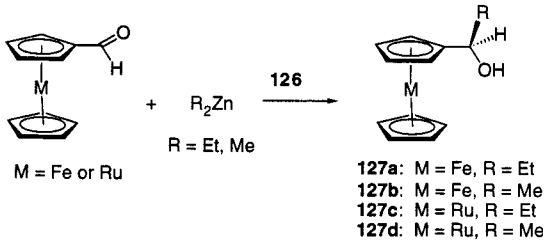
The indane-based amino alcohols such as **123** were studied by the same research group.[66] These compounds showed much lower enantioselectivity. For example, **123** gave 56−80% ee for the reaction of diethylzinc with aromatic and aliphatic aldehydes. Ligand **124** is an amino alcohol ligand derived from fluorene.[67] It showed very high enantioselectivity for the reaction of diethylzinc with a number of aldehydes (Table 30). A large positive nonlinear effect was observed. In the presence of **124** with 46% ee, the reaction of diethylzinc with benzaldehyde gave 96% ee. This was the same as with the use of **124** with 99.9% ee. Compound **125,** a regioisomer of **124**, showed much lower catalytic activity as well as enantioselectivity. It gave (*S*)-1-phenylpropanol with 52% ee for the diethylzinc addition to benzaldehyde. Compounds **124** and **125** were obtained as a mixture from the reaction of piperidine with the corresponding epoxide. This mixture was found to be as good a catalyst as optically pure **124** for the reaction of diethylzinc with a number of aldehydes because of the large nonlinear effect of **124** and its much higher catalytic activity than **125**.



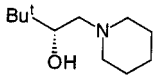
123 124 125

Matsumoto et al. reported the use of the amino alcohol **126** to catalyze the reaction of metallocene-based aldehydes with dialkylzincs to generate alcohols **127a**−**d** (Scheme 10).[68] In the presence of 5 mol

Scheme 10. Dialkylzinc Additions to Metallocene-Based Aldehydes Catalyzed by 126



% of **126**, these reactions proceeded with high enantioselectivity (90−96% ee, Table 31). The dimethylzinc addition was much slower than the diethylzinc addition.



126

Ligands **128a**−**d** derived from (*S*)-leucine were reported by Kawanami et al.[69] They found that **128d**

Table 31. Dialkylzinc Additions to Metallocene-Based Aldehydes Catalyzed by 126

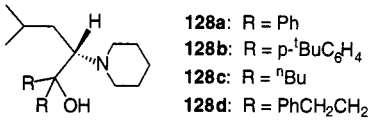
entry	aldehyde [M]	R_2Zn	solvent	*T* (°C)	*t* (d)	product (yield %)	ee (%)
1	Fe	Et_2Zn	toluene/hexane	−5	2	**127a** (96)	>96
2	Fe	Me_2Zn	Et_2O	20	7	**127b** (96)	>99
3	Ru	Et_2Zn	toluene/hexane	−8	5	**127c** (99)	96
4	Ru	Me_2Zn	Et_2O/benzene	20	14	**127d** (84)	90

Table 32. Diethylzinc Additions to Aldehydes Catalyzed by 128d[a]

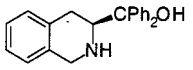
entry	aldehyde	yield (%)	ee (%)	config
1	benzaldehyde	91	97	*R*
2	*p*-chlorobenzaldehyde	76	96	*R*
3	*p*-methylbenzaldehyde	87	89	*R*
4	2-naphthaldehyde	77	97	*R*
5	heptanal	81	88	*R*
6	nonyl aldehyde	88	85	*R*
7	isovaleraldehyde	64	88	*R*
8	cyclohexanecarboxaldehyde	72	95	*R*

[a] The reactions were conducted in hexane solution at 0 °C in the presence of 10 mol % of **128d**.

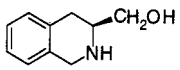
catalyzed highly enantioselective diethylzinc additions to both aromatic and aliphatic aldehydes (85−97% ee, Table 32).



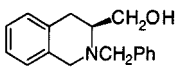
Stingl and Martens used the tetrahydroisoquinoline-derived bicyclic amino alcohols, such as **129**−**131**, to catalyze the reaction of diethylzinc with aromatic aldehydes but with only low enantioselectivity (≤40% ee).[70a] Dai et al. found that ligand **132** showed very high enantioselectivity.[70b] It catalyzed the diethylzinc addition to benzaldehyde with up to 98% ee at room temperature in toluene. Other derivatives of **132** showed 52−85% ee for the reaction. A monocyclic ligand similar to **129**−**132** gave up to 81% ee.[70c]



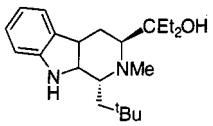
129



130



131



132

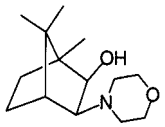
(−)-DAIB (**1**) was the first ligand that showed high enantioselectivity for organozinc additions. However, use of this ligand was limited to the reaction of only certain aromatic aldehydes. Recently, a modified DAIB ligand, **133**, was prepared by Nugent.[71] This compound contains a morpholine substituent and exhibited much more general enantioselectivity. For the reaction of diethylzinc with a number of aromatic as well as aliphatic aldehydes, the ee's were observed in the range of 91−99% (Table 33). However, in the case of sterically bulky aliphatic aldehydes such as trimethylacetaldehyde, it gave a significant amount of reduction byproduct (32%) (entry 10, Table 33). Compound **133** also catalyzed the dimethylzinc addition to *m*-methylbenzaldehyde with 95% ee but over a longer reaction time (entry 11, Table 33). The kinetics of the **133**-catalyzed diethylzinc addition to benzaldehyde was investigated by reaction calorimetry, which revealed

Table 33. Diethylzinc Addition Catalyzed by 133[a]

entry	aldehyde	*T* (°C)	*t* (h)	conv (%)	ee (%)	config
1	benzaldehyde	0	3	98	98	*R*
2	*p*-methylbenzaldehyde	0	3	97	98	*R*
3	*p*-fluorobenzaldehyde	0	3	98	98	*R*
4	3-furaldehyde	0	6	91	97	*R*
5	hexanal	0	3	96	91	*R*
6	isobutyraldehyde	0	3	94	99	*R*
7	cyclohexanecarboxaldehyde	0	3	94	99	*R*
8	2-ethylbutyraldehyde	25	18	92	99	*R*
9	cyclopropanecarboxaldehyde	0	3	91	98	*R*
10	trimethylacetaldehyde	25	24	62	97	*R*
11	*m*-methylbenzaldehyde[b]	25	18	88	95	*R*

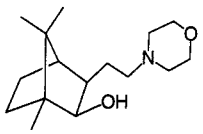
[a] The reactions were carried out in the presence of 5 mol % of **133** in toluene/hexane (1:2) and were quenched by Ac_2O to generate the corresponding acetates. [b] Me_2Zn addition. The reaction was quenched by H_2O rather than Ac_2O to give the corresponding alcohol.

a product inhibition process.[72]

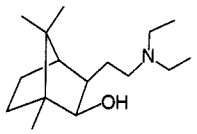


133

Ligand **134**, prepared by Knollmüller et al.,[73] was structurally similar to **133** but with two additional methylene spacers between the morpholine substituent and the isobornenol ring. This 1,4-amino alcohol showed lower enantioselectivity and activity. For the reaction of diethylzinc with benzaldehyde and hexanal, the alcohol products were obtained with 87% and 60% ee, respectively. These products had *S* configurations, opposite to those of the products obtained by using **133**. Compound **135** gave even lower enantioselectivity (78% ee) for the reaction of diethylzinc with benzaldehyde.

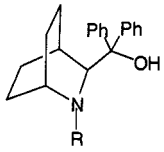


134



135

Isoquinuclidines **136a**−**c** were used by Hongo and co-workers to catalyze the reaction of diethylzinc with aromatic aldehydes.[74] The best result (76% ee) was obtained by using either **136b** or **136c** for the reaction of benzaldehyde with diethylzinc.



136a: R = Me
136b: R = Et
136c: R = Pr

c. Pyridyl and Iminyl Alcohols

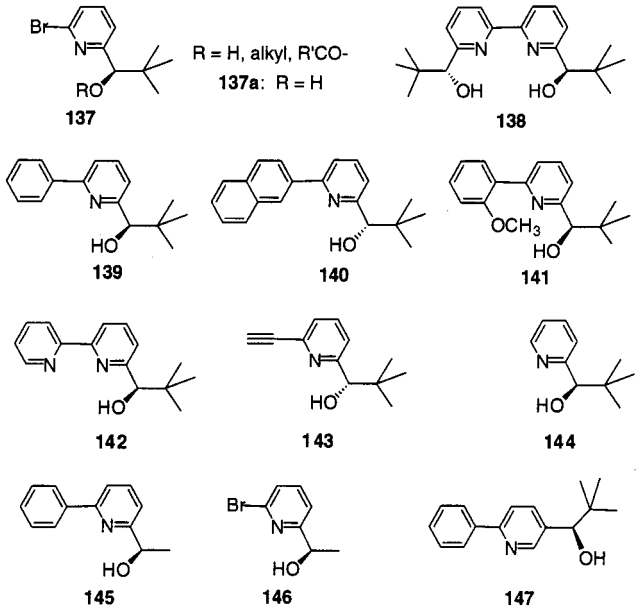
Pyridyl alcohol ligands were studied by Bolm and co-workers.[75] The C_2-symmetric bipyridine ligand **138** was synthesized via dimerization of **137** in the presence of a nickel(0) complex.[75a] A 5 mol % amount

Table 34. Diethylzinc Additions to Aldehydes Catalyzed by 138−147[a]

entry	aldehyde	catalyst (mol %)[c]	*T* (°C)	*t* (h)	yield (%)	ee (%)[b]	config
1	benzaldehyde	**138** (5)	22	0.5	90	91(84)	*R*
2	benzaldehyde	**138** (5)	−25	48	94	97(92)	*R*
3	benzaldehyde	**138** (5)	0	3	83	93(86)	*R*
4	benzaldehyde	**138** (5)[d]	0	3	92	94(88)	*R*
5	*p*-chlorobenzaldehyde	**138** (5)	0	3	65	93(90)	*R*
6	*p*-methoxybenzaldehyde	**138** (5)	0	9.5	96	90(80)	*R*
7	heptanal	**138** (5)	0	3	∼75	∼54(70)	*R*
8	4-pentenal	**138** (5)[d]	0	3	83	(70)	*R*
9	cinnamaldehyde	**138** (5)	0	3	76	28(36)	*R*
10	phenylpropargyl aldehyde	**138** (5)	0	3	88	25(24)	*R*
11	benzaldehyde	**139** (8)	0	3	73	93(88)	*R*
12	benzaldehyde	**140** (5)	0	3	77	95(88)	*S*
13	benzaldehyde	**141** (5)	0	3	51	83(78)	*R*
14	benzaldehyde	**142** (11)	0	3	80	86(78)	*R*
15	benzaldehyde	**143** (5)	0	6	58	82(74)	*S*
16	benzaldehyde	**137a** (10)	0	6	65	(81)	*R*
17	benzaldehyde	**144** (11)	0	6	61	78(74)	*R*
18	benzaldehyde	**145** (10)	0	6	64	5(5)	*R*
19	benzaldehyde	**146** (10)	0	6	24	21(15)	*R*
20	benzaldehyde	**147** (5)	0	3	3	(7)	*R*

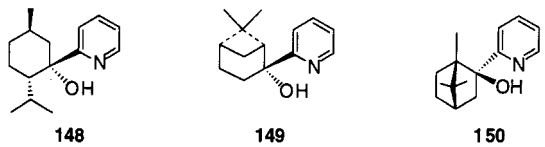
[a] All the reactions were carried out in toluene by using diethylzinc (1 M in hexane) unless indicated otherwise. [b] Based on optical rotation (or MTPA esters). [c] The ee's of the catalysts **138**−**142** were 98%, 90%, 98%, 96%, and 90%, respectively. [d] The reaction was carried out in hexane.

of **138** was used to catalyze diethylzinc additions in toluene solution at 0 °C and found to show good enantioselectivity for aromatic aldehydes (90−97% ee) but much lower for aliphatic and α,*β*-unsaturated aldehydes (entries 1−10, Table 34).[75b,c] Compounds **139**−**142** containing various substituents at the pyridine ring were also prepared by the cross-coupling reactions of **137**. Compounds **139** and **140**



gave 93% and 95% ee, respectively, for the reaction of diethylzinc with benzaldehyde (entries 11 and 12, Table 34). A remarkable nonlinear relationship between the ee of **139** and the ee of the product was observed. For example, **139** with 14% ee generated (*R*)-1-phenylpropanol with 87% ee. A single-crystal X-ray analysis of the zinc complex generated from the reaction of racemic **139** with diethylzinc indicates the formation of a heterodimeric structure. The homodimer from optically pure (*R*)-**139** was found to be less stable. Compounds **141** and **142** containing additional coordinative heteroatoms had lower enantioselectivity (83% and 86% ee, entries 13 and 14, Table 34). Ligands **137a**, **143**, and **144** without aromatic substituents at the 6-position of the pyridine ring showed similar enantioselectivity to each other (74−82% ee, entries 15−17, Table 34). The bulky *tert*-butyl group on the hydroxyl carbon of these ligands was found to be very important since ligands **145** and **146** with less bulky methyl groups gave very low ee (5 and 21% ee, entries 18 and 19, Table 34). In ligand **147**, the hydroxyl group is far away from the pyridine nitrogen, which prevents the formation of a chelate zinc complex. This also led to very low enantioselectivity (7% ee, entry 20, Table 34).

Pyridyl ligands **148**−**150** containing chiral tertiary hydroxyl groups were prepared by Chelucci and Soccolini, which showed much lower enantioselectivity for the diethylzinc addition to benzaldehyde (21−44% ee)[76] than compounds **138**−**142** containing bulky secondary hydroxyls. However, the dimeric struc-



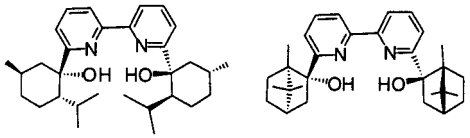
tures of these ligands, **151**−**154**, were reported by Kwong and Lee to have better enantioselectivity (Table 35).[77] For example, ligand **152** gave up to 92% ee for the diethylzinc addition to benzaldehyde (entry 5, Table 35). Ligand **152** was used to catalyze the reaction of other aldehydes with 20−80% ee. Substitution of **148**−**150** at the 6-position of the pyridine ring with a phenyl or pyridyl group gave ligands **155**−**158** which showed improved enantioselectivity (21−78% ee, entries 8−11, Table 35) but still very low compared to the secondary alcohol ligands **138**−**142**. Compound **159** and its analogues, prepared by

Table 35. Diethylzinc Additions to Benzaldehyde Catalyzed by 151−158[a]

entry	catalyst (mol %)	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	**151** (5)	0	3	77	85	*S*
2	**151** (5)	22	0.5	74	81	*S*
3	**152** (5)	0	1	86	95	*R*
4	**152** (2)	22	1	86	91	*R*
5	**152** (5)	22	0.5	78	92	*R*
6	**153** (5)	22	0.5	82	77	*R*
7	**154** (5)	22	0.5	86	79	*R*
8	**155** (5)	22	1.5	b	76	*S*
9	**156** (2)	22	1.5	b	78	*R*
10	**157** (5)	22	1	b	21	*R*
11	**158** (5)	22	3	b	65	*R*

[a] The reactions were carried out in toluene/hexane (1:1.5) by using 1 M solution of diethylzinc. [b] Complete conversion determined by GC.

Collomb and von Zelewsky, catalyzed the reaction of diethylzinc with benzaldehydes with up to 86% ee.[78]



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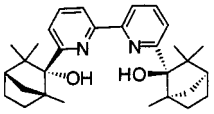
152



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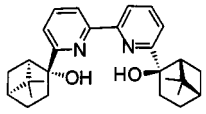

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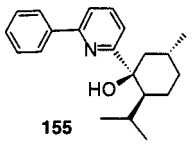

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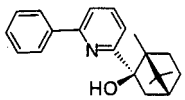

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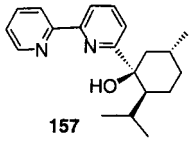

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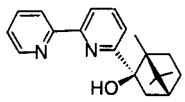

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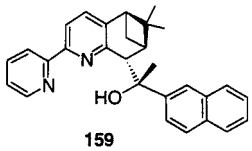
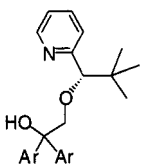


159

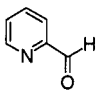
The tridentate pyridyl alcohols **160a**−**c** were studied by Hoshino and co-workers, among which 2 mol % of **160b** catalyzed the diethylzinc addition to benzaldehyde with 93% ee (entries 1 and 2, Table 36).[79a] The reaction took place within 20 min at room



160a: Ar = Ph
160b: Ar = α-naphthyl
160c: Ar = β-naphthyl

temperature in a cosolvent mixture of toluene and hexane. The addition of dimethylzinc to benzaldehyde in the presence of **160b** proceeded in 4 h with 92% ee (entry 3, Table 36). The reaction of aliphatic and α,β-unsaturated aldehydes with diethylzinc gave 70−88% ee (entries 14−17, Table 36). The reaction was faster in hexane than in the toluene/hexane mixture but similar in enantioselectivity. Ligands **160a**−**c** showed much higher enantioselectivity as well as higher activity than the bidentate pyridyl alcohol **144**.[79b] This rate enhancement was attributed to the tridentate bulky structure of **160a**−**c** which could prevent the formation of the less reactive dimeric zinc species probably involved in the use of the bidentate ligand. In the presence of 10 mol % of **160a**−**c**, the diethylzinc addition to pyridinecarboxaldehydes could even be complete within 30 s.

The ee's for the reaction of pyridine-3- and 4-carboxaldehydes with diethylzinc catalyzed by **160b** were 88% and 83%, respectively. The dimethylzinc addition to pyridine-3-carboxaldehyde gave 85% ee. However, a racemic product was obtained for the reaction of pyridine-2-carboxaldehyde (**161**) with diethylzinc under the same conditions. This is probably because **161** can form a bidentate coordination with diethylzinc through its oxygen and nitrogen atoms. This interaction may accelerate the addition of diethylzinc to the carbonyl group without involving the chiral catalyst. With the introduction of a 6-bromo substituent, compound **162** reacted with diethylzinc in the presence of 30 mol % of **160b** enantioselectively (70% ee). The bulky as well as electron-withdrawing bromine atom in **162** might make the chelate coordination of the pyridinecarboxaldehyde with diethylzinc less favorable and allowed catalyst control to be resumed.



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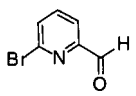
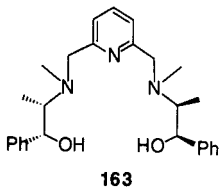
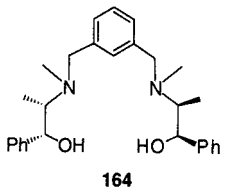


162

Williams and Fromhold studied the C_2-symmetric pyridine-based dimeric amino alcohol ligand **163** in the dialkylzinc addition and compared it with compound **164** containing no pyridine ring.[80] These two ligands were found to have the opposite enantioselectivity to each other. In the presence of 20 mol % of **163**, diethylzinc reacted with aromatic aldehydes to give (*S*)-alcohols, but **164** gave the (*R*)-alcohol products under similar reaction conditions. It was also found that either too much (50 mol %) or too little (<10 mol %) **164** gave reduced enantioselectivity or yield. In most cases, the enantioselectivity of **164** was lower than that of **163**. Compound **163** catalyzed the diethylzinc addition to aromatic aldehydes with up to 90% ee.



163



164

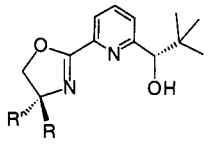
The diastereomeric pyridineoxazoline alcohols **165** and **166** were prepared by Macedo and Moberg to catalyze the reaction of aldehydes with diethylzinc.[81]

Table 36. Diethylzinc Additions to Aldehydes Catalyzed by 160a−c[a]

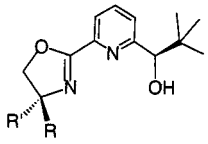
entry	R_2Zn	aldehyde	catalyst (mol %)	solvent	*t* (h)	yield (%)	ee (%)	config
1	Et_2Zn	benzaldehyde	**160b** (2)	b	1.2	96	93	*S*
2	Et_2Zn	benzaldehyde	**160b** (5)	b	0.3	94	93	*S*
3	Me_2Zn	benzaldehyde	**160b** (5)	hexane	4	93	92	*S*
4	Et_2Zn	benzaldehyde	**160a** (5)	b	1	81	96	*S*
5	Et_2Zn	benzaldehyde	**160c** (2)	b	2.3	85	91	*S*
6	Et_2Zn	benzaldehyde	**160c** (5)	b	0.8	94	93	*S*
7	Et_2Zn	*p*-methoxybenzaldehyde	**160b** (2)	b	2	96	90	*S*
8	Et_2Zn	*p*-methylbenzaldehyde	**160b** (2)	b	1.2	96	91	*S*
9	Et_2Zn	*p*-bromobenzaldehyde	**160b** (2)	b	1	97	93	*S*
10	Et_2Zn	*p*-chlorobenzaldehyde	**160b** (2)	b	1	92	91	*S*
11	Et_2Zn	*p*-fluorobenzaldehyde	**160b** (2)	b	0.7	96	95	*S*
12	Et_2Zn	*o*-fluorobenzaldehyde	**160b** (2)	b	0.7	97	89	*S*
13	Et_2Zn	*p*-trifluoromethyl benzaldehyde	**160b** (2)	b	0.5	97	89	*S*
14	Et_2Zn	cinnamaldehyde	**160b** (2)	b	2	93	70	*S*
15	Et_2Zn	3-phenylpropionaldehyde	**160b** (2)	b	2	56	88	*S*
16	Et_2Zn	3-phenylpropionaldehyde	**160b** (2)	hexane	0.2	83	84	*S*
17	Et_2Zn	nonyl aldehyde	**160b** (2)	hexane	0.5	84	80	*S*
18	Et_2Zn	cyclohexanecarboxaldehyde	**160b** (2)	hexane	0.5	88	86	*S*

[a] The reactions were carried out at room temperature by using 1 M hexane solution of diethylzinc or dimethylzinc. [b] Hexane/toluene (1:1).

Among these compounds, **165a** was found to be the most enantioselective catalyst. In the presence of **165a**, the best result obtained was for the reaction of benzaldehyde, which gave (*R*)-1-phenylpropanol with 88% ee and 95% yield at 0 °C in toluene/hexane (1:1). These ligands were also found to be better than compound **144** containing no 6-substituent on the pyridine ring. The product configurations were found to be determined by the chiral hydroxyl carbon of the ligands rather than the chiral center on the oxazoline unit.

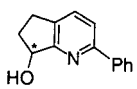


165a: R = ^{i}Pr, R' = H
165b: R = H, R' = Ph

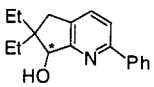


166a: R = ^{i}Pr, R' = H
166b: R = H, R' = Ph

Kang and co-workers reported the use of fused bicyclic pyridyl alcohol ligands **167** and **168** for the diethylzinc addition.[82] It was found that (*S*)-**167** and (*R*)-**168** led to products with the same chirality and similar enantioselectivity. In the presence of 5 mol % of (*S*)-**167** or (*R*)-**168**, diethylzinc reacted with benzaldehyde at room temperature in toluene/hexane (2:1) to give (*R*)-1-phenylpropanol in 48 h with 82% yield and 90% ee or 80% yield and 87% ee. Thus, with the incorporation of the geminal diethyl substituents, ligand (*R*)-**168** exhibited an inverted stereoselectivity from (*R*)-**167**. The enantioselectivity of ligands **167** and **168** for the reaction of diethylzinc with other substituted benzaldehydes and α,*β*-unsaturated aldehydes was low (<60% ee).



(*R*)-**167**
(*S*)-**167**



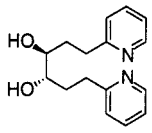
(*R*)-**168**
(*S*)-**168**

The C_2-symmetric ligand **169** was observed to catalyze the reaction of diethylzinc with benzaldehyde with 41% ee.[83] Ligand **170** where the two pyridine groups were closer gave 70% ee for the reaction.[84]

Table 37. Diethylzinc Additions to Aldehydes Catalyzed by 171[a]

entry	aldehyde	*t* (h)	yield (%)	ee (%)	config
1	*p*-chlorobenzaldehyde	5	97	92	*R*
2	*p*-methoxybenzaldehyde	6	96	92	*R*
3	*p*-methylbenzaldehyde	5	98	96	*R*
4	*m*-chlorobenzaldehyde	5	70	90	*R*
5	1-naphthaldehyde	6	94	81	*R*
6	*o*-methoxybenzaldehyde	5	95	88	*R*
7	ferrocenecarboxaldehyde	5	88	98	
8	thiophene-2-carboxaldehyde	5	95	94	*R*
9	cinnamaldehyde	6	99	78	*R*

[a] The reactions were carried out at room temperature in toluene/hexane (4:1) in the presence of 5 mol % of **171**.



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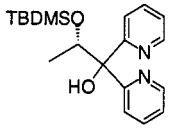
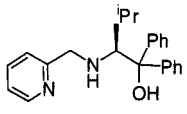


170

Wu et al. reported the use of *N*-(α)-pyridylmethyl amino alcohols to catalyze the reaction of aromatic aldehydes with diethylzinc.[85] They found **171** to be the most enantioselective ligand among those examined, and it gave 78−98% ee for the reaction (Table 37).



171

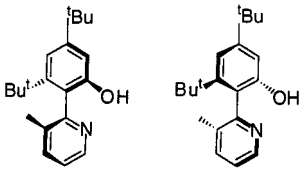
The axially chiral biaryl-based pyridyl alcohols (*R*)- and (*S*)-**172** were obtained in 46% and 49% yield, respectively, by Chan and co-workers from the optical resolution of the diastereomeric camphorsulfonates of the racemic mixture.[86] Compound (*R*)-**172** was used to catalyze the reaction of *para*-substituted

Table 38. Diethylzinc Additions to Benzaldehyde Catalyzed by 180a−p[a]

Entry	Catalyst	R2N	t (h)	Yield (%)	ee (%)	Config
1	**180a**	Me_2N	24	88	86	R
2	**180b**	Et_2N	10	90	81	R
3	**180c**	Bu_2N	10	85	64	R
4	**180d**[b]	$(Me_2NCH_2)_2$	2	98	30	R
5	**180e**	BnMeN	10	86	75	R
6	**180f**	Bn^{i}PrN	10	66	7	R
7	**180g**		10	90	90	R
8	**180h**		10	92	87	R
9	**180i**		10	90	96	R
10	**180j**		10	88	94	R
11	**180k**[b]		2	99	78	R
12	**180l**		10	98	76	R
13	**180m**		10	98	62	R
14	**180n**		10	90	76	R
15	**180o**		10	90	80	R
16	**180p**		10	88	50	R

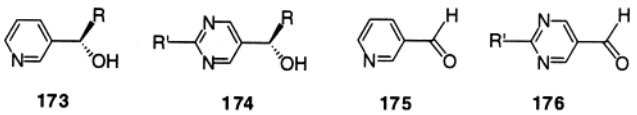
[a] The reactions were carried out at room temperature in the presence of 5 mol % of the catalysts unless indicated otherwise. [b] At 70 °C.

benzaldehydes with diethylzinc. It was found that the enantioselectivity was dependent on the electronic properties of the substituents on the benzene ring. The electron-withdrawing group-substituted benzaldehydes showed higher enantioselectivity than the substrates containing electron-donating groups. The highest enantioselectivity observed was the reaction of *p*-cyanobenzaldehyde, which gave 89% ee at 0 °C in toluene in the presence of 5 mol % of (*S*)-**172**.



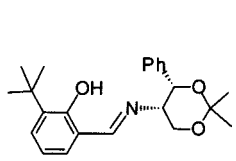
(*R*)-**172** (*S*)-**172**

Soai and co-workers carried out an extensive study on the enantioselective autocatalysis of pyridyl alkanols **173** and pyrimidyl alkanols **174**. These alcohols were observed to catalyze the reaction of their precursor aldehydes, **175** and **176**, with dialkylzincs to generate themselves very efficiently. Compounds **174** demonstrated high enantioselectivity as well as efficient chiral amplification. Since this work was summarized in a recent review article,[87] it is not discussed here in more detail.



173 **174** **175** **176**

The imine alcohol ligand **177** was used by Yamashita and co-workers for diethylzinc additions.[88] In the presence of 5 mol % of **177**, 5 mol % of ^{n}BuLi, 1.0 equiv of Ti(O^{i}Pr)$_4$, and 2.0 equiv of diethylzinc, the reaction of diethylzinc with aromatic aldehydes in toluene/hexane (5:2) at −78 to −35 °C proceeded with 78−85% ee. The chiral salen ligand **178** was used by Cozzi et al. to catalyze the reaction of diethylzinc with aldehydes with up to 77% ee.[89a] An imine alcohol derived from 2-amino-1,2,2-triphenylethanol in combination with Ti(O^{i}Pr)$_4$ showed up to 92% ee for the reaction.[89b]



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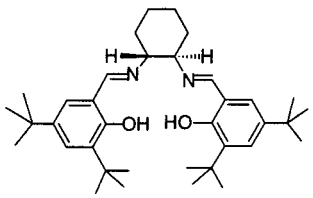
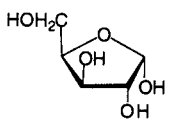


178

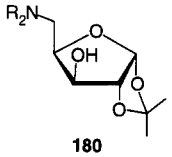
d. Carbohydrate-Based Amino Alcohols

Starting from α-D-xylose (**179**), Cho and Kim synthesized a series of amino alcohol ligands **180** and **181**.[90] These ligands were used to catalyze the diethylzinc addition to benzaldehyde. Among the *N*,*N*-dialkyl-substituted ligands **180a**−**f**, **180a** (R = Me) showed the highest enantioselectivity (86% ee, entry 1, Table 38) and **180f**, containing bulky isopropyl and benzyl groups on nitrogen, gave very low ee (7% ee, entry 6, Table 38). Thus, the ee of the product decreased as the size of the R groups in

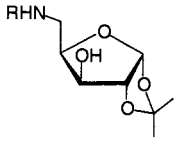
180a−**f** increased (entries 1−6, Table 38). Several of the cyclic amine-based ligands, **180g**−**j**, showed very high enantioselectivity (87−96% ee, entries 7−10, Table 38). The highest ee for the diethylzinc addition to benzaldehyde among all ligands **180** was obtained by using **180i** containing a morpholine substituent as the catalyst, which gave 96% ee (entry 9, Table 38). However, when **180i** was used to catalyze the reaction of diethylzinc with heptanal, it gave only 75% ee. The best ee observed for the reaction of diethylzinc with heptanal was 83% by using **180l** as the catalyst. The monoalkylated ligands **181** gave up to 82% ee for the diethylzinc addition to benzaldehyde.



α-D-xylose, **179**



180



181

Yang and Cho further found that ligand **180i** catalyzed the diisopropylzinc addition to a range of aldehydes with high enantioselectivity (Table 39).[91]

Table 39. Diisopropylzinc Additions to Aldehydes Catalyzed by 180i[a]

entry	aldehyde	*t* (h)	yield (%)	ee (%)	config
1	heptanal	8	88	96	*S*
2	undecannal	9	84	96	*S*
3	3-methylbutanal	9	82	96	*S*
4	3-phenylpropionaldehyde	6	90	96	*S*
5	cyclohexanecarboxaldehyde	8	82	98	*R*
6	cinnamaldehyde	8	80	69	*R*
7	benzaldehyde	4	95	96	*R*
8	*o*-methylbenzaldehyde	6	87	94	*R*
9	*p*-methylbenzaldehyde	8	92	94	*R*
10	*p*-chlorobenzaldehyde	6	90	95	*R*
11	1-naphthaldehyde	12	81	95	*R*
12	ferrocenecarboxaldehyde	4	93	98	*R*

[a] The reactions were carried out at 0 °C in toluene the presence of 10 mol % of **180i**.

Compound **182a** was prepared by Cho and Chun from D-mannitol.[92] In the presence of 10 mol % of **182a** in toluene at 0 °C, the reaction of diethylzinc with aromatic and aliphatic aldehydes gave alcohols with 81−94% ee and 78−93% yield (Table 40). The

Table 40. Diethylzinc Additions to Aldehydes Catalyzed by 182a[a]

entry	aldehyde	*t* (h)	yield (%)	ee (%)	config
1	butyraldehyde	10	88	82	*R*
2	hexanal	10	90	84	*R*
3	heptanal	10	83	85	*R*
4	undecylic aldehyde	12	92	94	*R*
5	3-phenylpropionaldehyde	12	81	90	*R*
6	isovaleraldehyde	8	92	81	*R*
7	cyclohexanecarboxaldehyde	9	78	86	*R*
8	*o*-methylbenzaldehyde	12	87	92	*R*
9	*p*-methylbenzaldehyde	12	83	90	*R*
10	*p*-chlorobenzaldehyde	12	93	89	*R*
11	1-naphthaldehyde	18	82	88	*R*
12	benzaldehyde	12	87	92	*R*

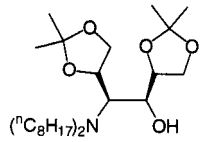
[a] The reactions were carried out at 0 °C in the presence of 10 mol % of **182a**.

Table 41. Diethylzinc Additions to Aldehydes Catalyzed by (*S*)- and (*R*)-186[a]

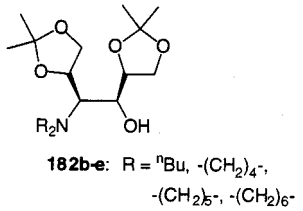
entry	aldehyde	catalyst (mol %)	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	(*S*)-**186** (20)	16		98	*S*
2	benzaldehyde	(*S*)-**186** (10)	16		98	*S*
3	benzaldehyde	(*S*)-**186** (5)	48		94	*S*
4	benzaldehyde	(*S*)-**186** (2)	72		94	*S*
5	benzaldehyde	(*S*)-**186** (10)[b]	16		92	*S*
6	benzaldehyde	(*R*)-**186** (2)	16	95	98	*R*
7	1-naphthaldehyde	(*R*)-**186** (2)	16	98	96	*R*
8	cinnamaldehyde	(*R*)-**186** (2)	16	94	84	*R*
9	heptanal	(*R*)-**186** (2)	16	88	92	*R*

[a] The reactions were carried out at 20 °C in hexane using 1 M hexane solution of diethylzinc unless indicated otherwise. [b] The reaction was carried out in toluene.

enantioselectivity for unhindered linear aliphatic aldehydes was quite good (82−94% ee, entries 1−4, Table 40). Other ligands **182b**−**e** also showed good enantioselectivity for the diethylzinc addition to benzaldehyde (87−90% ee), but their enantioselectivity for the reaction of heptanal with diethylzinc was much lower (70−78% ee).

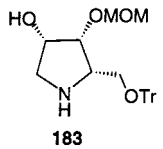


182a



182b-e: R = nBu, -(CH2)4-, -(CH2)5-, -(CH2)6-

The pyrrolidine **183** was prepared from D-ribonolactone by Ikota et al.[93] This compound catalyzed the diethylzinc addition to benzaldehyde with 95% ee and to *p*-chlorobenzaldehyde with 90% ee. Much lower enantioselectivity was observed for the reactions of cinnamaldehyde (79% ee) and heptanal (55% ee). All these reactions produced *R* alcohols. A similar thiol compound **184** was much less enantioselective for the diethylzinc addition to benzaldehyde (41% ee).



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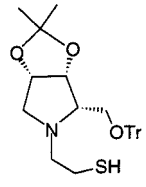
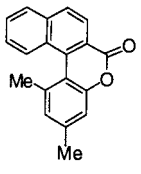


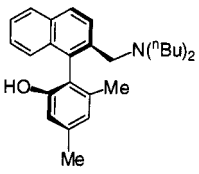
184

e. Axially Chiral Amino Alcohols

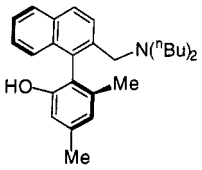
Bringmann and Breuning resolved the atropisomers of **185** by reacting it with (1*R*)-menthol.[94] The two enantiomers were then converted into the enantiomerically pure amino alcohol (*S*)- and (*R*)-**186**. These axially chiral compounds were found to be very good ligands for the reaction of diethylzinc with aldehydes. In the presence of 2 mol % of (*R*)-**186**, the reaction of aromatic aldehydes, α,β-unsaturated aldehydes, and heptanal with diethylzinc proceeded with 84−98% ee and 88−98% yield at 20 °C in hexane (Table 41).



185



(*S*)-**186** (P)



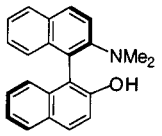
(*R*)-**186** (M)

A series of binaphthyl-based chiral amino alcohols such as (*R*)-**187** were used by Vyskocil et al. for the diethylzinc addition.[95] In the presence of ^{n}BuLi, (*R*)-**187** catalyzed the reaction of aldehydes with diethylzinc with 62−88% ee (Table 42). In the absence of ^{n}BuLi, (*R*)-**187** produced 1-phenylpropanol with 68% ee for the diethylzinc addition to benzaldehyde.

Table 42. Diethylzinc Additions to Aldehydes Catalyzed by (*R*)-187 in the Presence of BuLi[a]

entry	aldehyde	yield (%)	ee (%)	config
1	benzaldehyde	96	88	*R*
2	*p*-methoxybenzaldehyde	95	75	*R*
3	*o*-methoxybenzaldehyde	93	62	*R*
4	*p*-chlorobenzaldehyde	93	83	*R*
5	*o*-chlorobenzaldehyde	93	79	*R*
1	*p*-methylbenzaldehyde	96	82	*R*
2	*o*-methylbenzaldehyde	81	81	*R*
3	*p*-fluorobenzaldehyde	94	79	*R*
4	1-naphthaldehyde	87	79	*R*
4	2-naphthaldehyde	89	83	*R*

[a] The reactions were carried out in toluene/hexane (2:1) at room temperature over 36 h in the presence of 3 mol % of (*R*)-**187** and 5.4 mol % of ^{n}BuLi using 1 M hexane solution of diethylzinc.

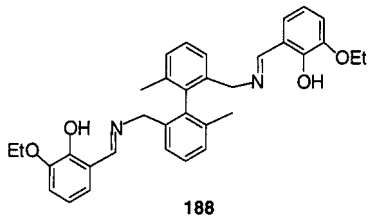


(*R*)-**187**

The cobalt(II) complex of the axially chiral ligand **188** was used by Keller and Rippert to catalyze the diethylzinc addition.[96] A 10 mol % amount of the cobalt(II) complex of **188** was used to catalyze the diethylzinc (2 equiv) addition in toluene at room temperature. Good enantioselectivity was observed for the reaction of aromatic aldehydes (72−93% ee, entries 1−9, Table 43). The *S* (P) isomer of the ligand led to the formation of *R* alcohol products, and the *R* (M) isomer gave the *S* alcohol.

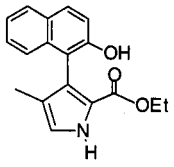
Table 43. Diethylzinc Additions to Aldehydes Catalyzed by the Cobalt(II) Complex of 188

entry	aldehyde	conv (%)	ee (%)
1	benzaldehyde	61	90
2	*p*-chlorobenzaldehyde	82	91
3	*p*-cyanobenzaldehyde	>99	93
4	3,5-dichlorobenzaldehyde	>99	93
5	*p*-methylbenzaldehyde	30	88
6	*o*-methylbenzaldehyde	27	72
7	*p*-methoxybenzaldehyde	14	82
8	1-naphthaldehyde	32	89
9	2-naphthaldehyde	52	89
10	isobutyraldehyde	25	79
11	trimethylacetaldehyde	traces	36

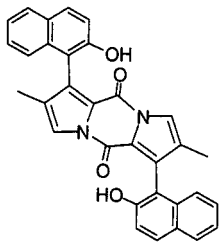


188

Furusho carried out the condensation of the axially chiral pyrrole molecules such as **189** to give diketopyrazines such as **190** and **191**.[97] These compounds were pyrocoll derivatives with two axially chiral elements. The optically resolved **189**−**191** and their derivatives were used to catalyze the diethylzinc addition to aromatic aldehydes with up to 82% ee.



189



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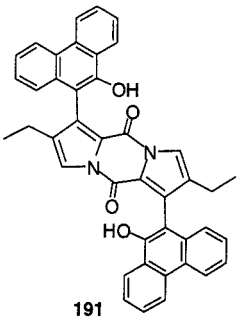
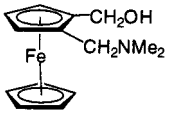


191

f. Ferrocene-Based Amino Alcohols

The planar chirality of substituted ferrocene compounds, their unique bulky structure, and their chemical inertness have attracted the attention of many researchers. A number of ferrocene-based chiral ligands have been developed for asymmetric catalysis. Nicolosi et al. studied the use of the ferrocene-based planar chiral amino alcohol **192** for the reaction of diethylzinc with aldehydes.[98] Among the aromatic aldehydes examined, benzaldehyde gave the best ee. In the presence of 10 mol % of **192**, (*R*)-1-phenylpropanol was obtained with 90% yield and 82% ee at room temperature. For the reaction of aliphatic aldehydes, the best ee (83%) was observed for the diethylzinc addition to cyclohexanecarboxaldehyde.



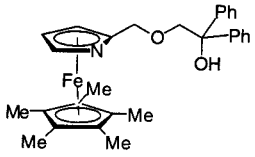
192

Fu and co-workers studied the use of the ferrocene ligand **193** for the dialkylzinc addition to aldehydes.[99] At room temperature, this ligand gave 63−90% ee for the alcohol products (Table 44).

Table 44. Dialkylzinc Additions to Aldehydes Catalyzed by 193

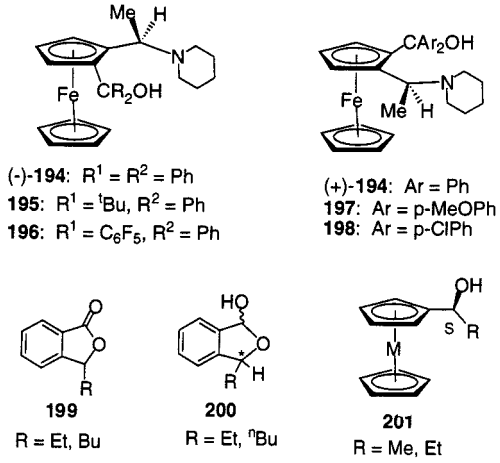
entry	R_2Zn	aldehyde	mol % of **193**	yield (%)	ee (%)	config
1	Et_2Zn	benzaldehyde	3	88	89	*S*
2	Me_2Zn	benzaldehyde	6	82	83	*S*
3	Et_2Zn	*p*-fluorobenzaldehyde	3	91	89	*S*
4	Et_2Zn	*p*-chlorobenzaldehyde	3	94	90	*S*
5	Et_2Zn	*p*-methoxybenzaldehyde	3	94	86	*S*
6	Et_2Zn	heptanal	3	86	63	*S*

[a] The reactions were carried out in toluene at room temperature.



193

The ferrocene-based amino alcohols **194**−**198** containing additional chiral centers besides the planar chirality of the ferrocene unit were studied by Watanabe and co-workers.[100] For example, compound (−)-**194** catalyzed the diethylzinc addition to certain aromatic aldehydes with over 87% ee at room temperature (entries 1−9, Table 45).[100a] Compound **198** was a better catalyst for the reaction of diethylzinc and dibutylzinc with *o*-phthaldehyde, and it allowed the synthesis of 3-ethyl- and 3-*n*-butylphthalides (**199**) by way of **200** with 98% and 94% ee, respectively (entries 14 and 16, Table 45).[100b]



(-)-**194**: $R^1 = R^2 = Ph$
195: $R^1 = {}^tBu$, $R^2 = Ph$
196: $R^1 = C_6F_5$, $R^2 = Ph$

(+)-**194**: Ar = Ph
197: Ar = p-MeOPh
198: Ar = p-ClPh

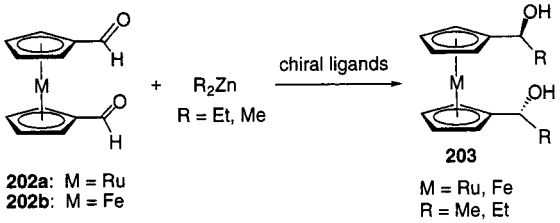
199
R = Et, Bu

200
R = Et, ^{n}Bu

201
R = Me, Et

Watanabe also used (−)-**194**−**196** to catalyze the reaction of ruthenicene-1,1′-dicarboxaldehyde (**202a**) and ferrocene-1,1′-dicarboxaldehyde (**202b**) with diethylzinc and dimethylzinc (Scheme 11).[101] In the presence of 5 mol % of these ligands, the (*S*,*S*)-diol products **203** were produced all with over 99% ee at room temperature. The diastereoselectivity was also very high (∼90% de).

Scheme 11. Dialkylzinc Additions to Metallocence Dicarboxaldehydes Catalyzed by the Ferrocence-Based Amino Alcohols

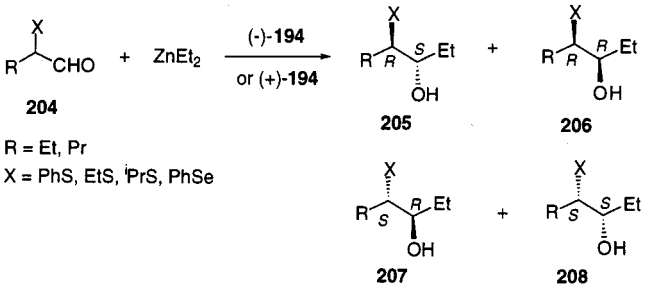


202a: M = Ru
202b: M = Fe

203
M = Ru, Fe
R = Me, Et

Ligands (−)-**194** and (+)-**194** were used by Butsugan and co-workers to catalyze the reaction of diethylzinc with the α-thio and α-seleno-aldehydes **204** (Scheme 12).[102] When (−)-**194** was used, the *R* enantiomer of **204** reacted faster than the *S* enantiomer to give **205** as the major diastereomer (entries 1, 5 and 6, Table 46). Accordingly, when (+)-**194** was used, the *S* enantiomer of **204** reacted faster to give **207** as the major diastereomer (entries 2−4, Table 46). Without the chiral catalyst, **204** reacted with EtMgBr to give the antistereoisomers **205** and **207** as the major products. Thus, the α substituents can control the stereochemistry for the addition of the Grignard reagent.

Scheme 12. Dialkylzinc Additions to α-Thio- and α-Selenoaldehydes Catalyzed by 194



204
R = Et, Pr
X = PhS, EtS, ^{i}PrS, PhSe

205

206

207

208

The structure of the ferrocene ligand **209** contains a fused bicyclic chiral amino alcohol unit. This compound was used by Schlögl and co-workers to catalyze the reaction of various aldehydes with diethylzinc with 66−97% ee (Table 47).[103a] The enantioselectivity of **209** for hexanal, a linear aliphatic

Table 45. Dialkylzinc Additions to Aldehydes Catalyzed by 194−98[a]

entry	R_2Zn	aldehyde	catalyst (mol %)	solvent	*t* (h)	yield (%)	ee (%)	config
1	Me_2Zn	benzaldehyde	(−)-**194** (5)	toluene	10	93	98	*S*
2	Me_2Zn	ferrocenecarboxaldehyde	(−)-**194** (5)	toluene	6	96	97	*c*
3	Me_2Zn	ferrocenecarboxaldehyde	(−)-**194** (2)	toluene	12	96	96	*c*
4	Me_2Zn	ferrocenecarboxaldehyde	(−)-**194** (5)	*b*	4	96	97	*c*
5	Et_2Zn	ruthenicenecarboxaldehyde	(−)-**194** (5)	toluene	1	95	99	*c*
6	Me_2Zn	ruthenicenecarboxaldehyde	(−)-**194** (5)	toluene	12	90	97	*c*
7	Et_2Zn	ruthenicenecarboxaldehyde	(−)-**194** (5)	toluene	2	91	98	*c*
8	Et_2Zn	*o*-phthaldehyde	(−)-**194** (5)	toluene	1	92	87	*S*[d]
9	Et_2Zn	*o*-phthaldehyde	(−)-**194** (5)	hexane	1	95	88	*S*[d]
10	Et_2Zn	*o*-phthaldehyde	(+)-**194** (5)	hexane	1	92	88	*R*[d]
11	Et_2Zn	*o*-phthaldehyde	**197** (5)	hexane	1	86	86	*R*[d]
12	Et_2Zn	*o*-phthaldehyde	**198** (5)	hexane	0.5	85	90	*R*[d]
13	Et_2Zn	*o*-phthaldehyde	(+)-**194** (10)	hexane	3	87	95	*R*[d]
14	Et_2Zn	*o*-phthaldehyde	**198** (10)	hexane	3	88	98	*R*[d]
15	$^nBu_2Zn$	*o*-phthaldehyde	(−)-**194** (5)	hexane	1	50	89	*S*[d]
16	$^nBu_2Zn$	*o*-phthaldehyde	**198** (5)	hexane	3	57	94	*R*[d]

[a] The reactions were carried out at room temperature. [b] Toluene/hexane (1:1). [c] The products were **201**. [d] The products were **200**.

Table 46. Diethylzinc Additions to 204 Catalyzed by 194[a]

	aldehyde				product		ratio
entry	R	X	catalyst (mol %)	yield (%)	**205/206**	**207/208**	**205+206/207+208**
1	Et	PhS	(−)-**194** (25)	49	99:1	46:54	87:13
2	Et	PhS	(+)-**194** (25)	53	35:65	98:2	18:82
3	Et	EtS	(+)-**194** (25)	24	57:43	96:4	14:86
4	Et	^{i}PrS	(+)-**194** (25)	14	41:59	93:7	17:83
5	Pr	PhS	(−)-**194** (25)	38	100:0	45:55	90:10
6	Et	PhSe	(−)-**194** (25)	68	98:2	42:58	67:33

[a] The reactions were carried out in hexane at room temperature.

Table 47. Diethylzinc Additions to Aldehydes Catalyzed by 209[a]

entry	aldehyde	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	25	12	87	83.5	*S*
2	benzaldehyde	40	12	90	83	*S*
3	benzaldehyde	0	12	83	87	*S*
4	*p*-methylbenzaldehyde	25	4.5	93	94	*S*
5	*p*-methoxybenzaldehyde	25	4.5	81	89	*S*
6	*p*-chlorobenzaldehyde	25	4.5	88	82	*S*
7	2-furaldehyde	25	4	84	86	*S*
8	cinnamaldehyde	25	4	86	87	*S*
9	hexanal	25	4	72	74	*S*
10	isobutyraldehyde	25	4	30	97	*S*
11	isovaleraldehyde	25	4	70	85	*S*
12	trimethylacetaldehyde	25	4	68	85	*S*
13	cyclohexylacetaldehyde	25	4	50	66	*S*

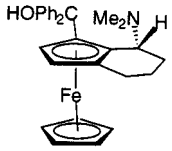
[a] The reactions were carried out in toluene in the presence of 3−5 mol % of **209**.

Table 48. Diethylzinc Additions to Aldehydes Catalyzed by 210[a]

entry	aldehyde	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	0	6	83	93	*R*
2	ferrocenecarboxaldehyde	0	3	93	95	*R*
3	*p*-methoxybenzaldehyde	0	9	93	91	*R*
4	cinnamaldehyde	0	6	89	78	*R*
5	*p*-chlorobenzaldehyde	0	7	94	86	*R*
6	5-(4-chlorophenyl)-2-furaldehyde	0	2	92	91	*R*
7	heptanal	0	26	94	87	*R*

[a] The reactions were carried out in toluene in the presence of 5 mol % of **210**.

aldehyde, was not as good as that for other aldehydes (74% ee, entry 9, Table 47). Low enantioselectivity was observed for other ferrocenyl amino alcohols.[103b]



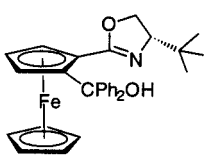
209

Ligand **210** containing a chiral oxazoline unit was reported by Bolm et al. to catalyze the reaction of diethylzinc with aromatic, aliphatic, and α,β-unsaturated aldehydes with 78−95% ee and 83−94% yield at 0 °C in toluene (Table 48).[104] To study the role of planar chirality versus central chirality in the ferrocene ligands, the analogues of **210** were prepared.[104b] These ligands, **211**−**213**, were used to catalyze the reaction of diethylzinc with benzaldehyde, and the results are compared with that of **210** (Table 49). Ligands **210** and **211** have the same central chirality but the opposite planar chirality. This inversion of the planar chirality from **210** to **211** led to a large decrease in both enantioselectivity and catalytic activity. With a 1:1 mixture of **210** and **211**, the addition of diethylzinc to benzaldehyde still proceeded with 95% ee.[104c] Thus, complex **210** controlled the reaction in this mixture. The planar chiral **212** has no central chirality and showed low enantioselectivity. Therefore, in these ferrocene-based ligands, a match of the planar chirality with the central chirality is important for an efficient asymmetric catalysis process. Study of **213** showed that there was no nonlinear effect in the reaction. Interestingly, ligand **214** containing only central chirality still gave high enantioselectivity as well as high catalytic activity.

Table 49. Diethylzinc Additions to Benzaldehydes Catalyzed by 210−214[a]

entry	ligand	*t* (h)	yield (%)	ee (%)	config
1	**210**	6	83	93	*R*
2	**210**	5	99	94	*R*
3	**211**	59	55	35	*R*
4	**212**	20	97	51	*R*
5	**214**	5	85	92	*R*

[a] The reactions were carried out at 0 °C in toluene in the presence of 5 mol % of the ligands.



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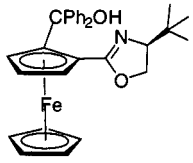

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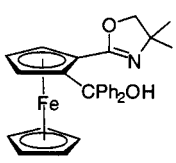

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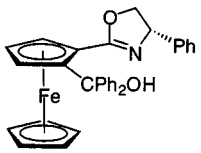

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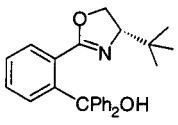


214

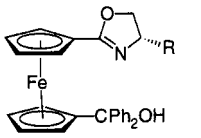
Both of the cyclopentadienyl rings of ferrocene were functionalized by Hou and co-workers to prepare ligands **215a**−**d**.[105] Among these ligands, **215c** was found to have the highest enantioselectivity for the diethylzinc addition to aldehydes. It catalyzed the diethylzinc addition to benzaldehyde with 89% ee and 98% yield at 0 °C in toluene (entry 4, Table 50). It also showed good enantioselectivity for other aromatic aldehydes (85−91% ee) but was not as good

Table 50. Diethylzinc Additions to Aldehydes Catalyzed by 215a−d[a]

entry	aldehyde	catalyst (mol %)	yield (%)	ee (%)	config
1	benzaldehyde	**215a** (5)	98	81	*R*
2	benzaldehyde	**215a** (10)	99	81	*R*
3	benzaldehyde	**215b** (5)	98	72	*R*
4	benzaldehyde	**215c** (5)	98	89	*R*
5	benzaldehyde	**215d** (5)	92	82	*S*
6	*p*-chlorobenzaldehyde	**215c** (5)	95	89	*R*
7	*p*-methoxybenzaldehyde	**215c** (5)	89	87	*R*
8	*p*-bromobenzaldehyde	**215c** (5)	97	91	*R*
9	p−*N*,*N*-dimethylaminobenzaldehyde	**215c** (5)	87	85	*R*
10	*p*-phenylbenzaldehyde	**215c** (5)	98	88	*R*
11	1-naphthaldehyde	**215c** (5)	96	90	*R*
12	*o*-methoxybenzaldehyde	**215c** (5)	94	86	*R*
13	cinnamaldehyde	**215c** (5)	97	64	*R*
14	cyclohexanecarboxaldehyde	**215c** (5)	88	71	*R*

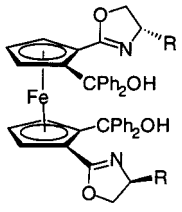
[a] The reactions were carried out in toluene/hexane (1:1) at 0 °C.

for an α,β-unsaturated aldehyde and an aliphatic aldehyde (64% and 71% ee, entries 13 and 14, Table 50). The enantioselectivity of **215c** was comparable to that of **210**, where both functional groups were on the same cyclopentadiene ring.

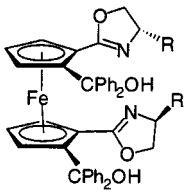


215a: R = ^{i}Pr
215b: R = Bn
215c: R = ^{t}Bu
215d: R = Ph

Ikeda and co-workers studied the use of ligands **216** and **217** for the reaction of diethylzinc with benzaldehyde.[106] In the presence of 10 mol % of **216b** and **217b**, (*R*)-1-phenylpropanol was obtained with 91−93% ee. This indicates that in **217b** probably only the top portion of the ligand is effective in the catalysis because the bottom potion of **217b** has the same planarity and central chirality as **211**, a very inefficient catalyst as shown by Bolm.[104b] Ligands **216a** and **217a** with less bulky isopropyl groups gave low ee (70−83%).

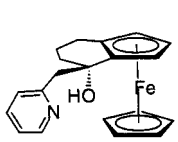


216a: R = ^{i}Pr
216b: R = ^{t}Bu



217a: R = ^{i}Pr
217b: R = ^{t}Bu

Brocard and co-workers studied a series of ferrocene-based ligands, such as **218**, and found that these compounds could only give up to 35% ee for the reaction of diethylzinc with benzaldehyde.[107] They also found that the racemic ferrocenyl aldehyde **219** reacted with diethylzinc in the absence of a catalyst to give **220** with >98% de.[108] When the enantiopure **219** was used, its reaction with diethylzinc gave the enantiopure **220**. This is a highly stereoselective autocatalytic process. The amino alcohol product **220** was used to catalyze the reaction of diethylzinc with benzaldehyde with 62% ee. Compounds **221a−c** also underwent autocatalysis with diethylzinc to give the corresponding secondary alcohols with 68−76% de.[109]



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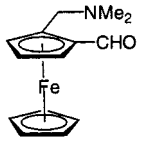

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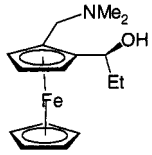

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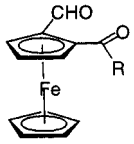


221a: R = Ph
221b: R = Bu
221c: R = Me

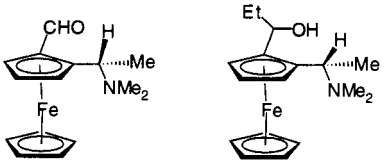
The ferrocene-based amino aldehyde **222** was directly used by Fukuzawa and Kato to catalyze the reaction of diethylzinc with aldehydes.[110] Good enantioselectivity was observed for various aldehydes (80−93% ee, Table 51). It was found that **222** also reacted with diethylzinc to give **223** with >99% de and 80% yield.[111] This is an autocatalytic process.

Table 51. Diethylzinc Additions to Aldehydes Catalyzed by 222[a]

entry	aldehyde	yield (%)	ee (%)	config
1	benzaldehyde	94	91	*R*
2[b]	benzaldehyde	92	87	*S*
3	*p*-methoxybenzaldehyde	97	93	*R*
4	*p*-nitrobenzaldehyde	88	91	
5	1-naphthaldehyde	91	88	*R*
6	ferrocenecarboxaldehyde	90	81	*R*
7	cinnamaldehyde	85	80	*R*
8	3-phenylpropionaldehyde	88	83	*R*
9	valeraldehyde	85	80	*R*
10	isobutyraldehyde	73	81	*R*
11	cyclohexanecarboxaldehyde	87	82	*R*
12	trimethylacetaldehyde	55	80	*R*

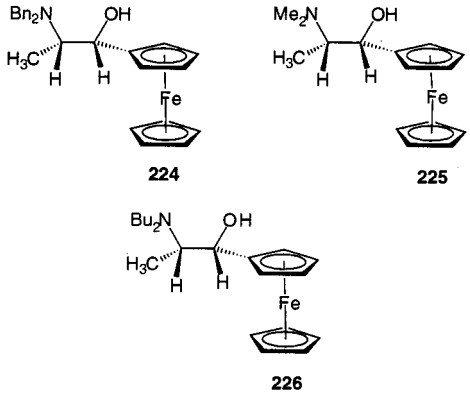
[a] The reactions were carried out in toluene at 0 °C by using 5 mol % of **222**. [b] The enantiomer of **222** was used.

Compound **222** reacted with dimethylzinc with >99% de and 96% yield. The ferrocenyl amino alcohol **223** also cata-lyzed the diethylzinc addition to benzaldehyde with 90% ee.



222 **223**

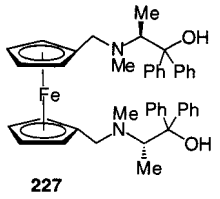
The amino alcohols **224**−**226**, containing a ferrocenyl substituent, were used by Pélinski and co-workers to catalyze the reaction of diethylzinc with benzaldehyde.[112] In the presence of 8 mol % of these ligands, (*R*)-1-phenylpropanol was obtained with 90−95% ee at 20 °C in toluene. The diastereomer of **224** showed lower enantioselectivity (73% ee).



224 **225**

226

The C_2-symmetric ferrocene-based bis(amino alcohol)s such as **227** with various substituents at the nitrogen and oxygen carbons were prepared by Pélinski and co-workers for the catalytic diethylzinc addition.[113] Among these ligands, **227** was found to be the most enantioselective one. It catalyzed the diethylzinc addition to benzaldehyde with 83% ee.



227

g. Amino Alcohols with η^6-Arene–Chromium

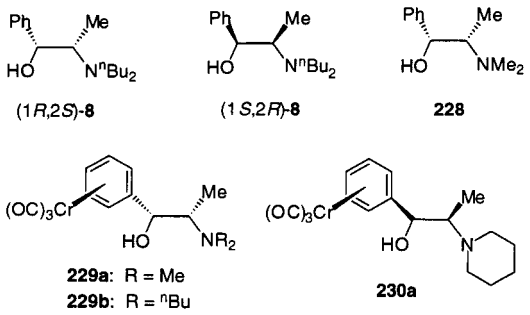
Jones and co-workers reported the conversion of chiral amino alcohols, such as (1*R*,2*S*)-**8** and **228**, to η^6-arene−chromium complexes such as **229a,b** by reaction with $Cr(CO)_6$ in refluxing THF/dibutyl ether (1:10).[114] Compound **229b** showed higher enantioselectivity than (1*R*,2*S*)-**8** for the reaction of diethylzinc with benzaldehyde. It was 94% ee for the use of (1*R*,2*S*)-**8** and 99% ee for the use of **229b** (entries 1 and 2, Table 52).[114a] The increased steric hindrance of **229b** and the electron-withdrawing effect of the $Cr(CO)_3$ moiety were both considered to be responsible for the increased enantioselectivity. Both **229b** and its enantiomer **230b** exhibited excellent enantioselectivity for the reaction of diethylzinc, dimethylzinc, and dibutylzinc with aromatic and α,*β*-unsaturated aldehydes (Table 52).[114b] Their enantioselectivity for aliphatic aldehydes was slightly lower but still much higher than the ligand without the coordination of the chromium. For example, in the presence of 10 mol % of **230b**, dimethylzinc addition to **231** generated alcohol **232** with 85% ee, but only

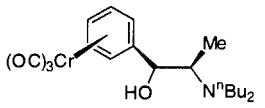
Table 52. Dialkylzinc Additions to Aldehydes Catalyzed by the Chromium-Complexed and -Uncomplexed Amino Alcohols[a]

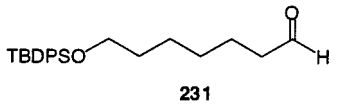
entry	R_2Zn	aldehyde	catalyst	yield (%)	ee (%)	config
1	Et_2Zn	benzaldehyde	**229a**	99	86	*R*
2	Et_2Zn	benzaldehyde	**228**	99	67	*R*
3	Et_2Zn	benzaldehyde	**230a**	99	96	*S*
4	Et_2Zn	benzaldehyde	(1*S*,2*R*)-**8**	99	90	*S*
5	Et_2Zn	benzaldehyde	**229b**	99	99	*R*
6	Et_2Zn	benzaldehyde	(1*R*,2*S*)-**8**	99	94	*R*
7	Et_2Zn	benzaldehyde	**230b**	99	99	*S*
8	Et_2Zn	benzaldehyde	(1*S*,2*R*)-**8**	99	94	*S*
9	Et_2Zn	1-naphthaldehyde	**230b**	98	>99	*S*
10	Et_2Zn	2-naphthaldehyde	**229b**	99	>99	*R*
11	Et_2Zn	*p*-methoxybenzaldehyde	**230b**	99	94	*S*
12	Et_2Zn	phenanthrene-9-carboxaldehyde	**229b**	97	93	*R*
13	Et_2Zn	3-phenylpropionaldehyde	**230b**	89	92	*R*
14	Et_2Zn	3-phenylpropionaldehyde	(1*S*,2*R*)-**8**	90	38	*R*
15	Et_2Zn	3-(4-*tert*-butyldimethylsilylphenyl)propionaldehyde	**230b**	88	85	*R*
16	Me_2Zn	benzaldehyde	**230b**	85	92	*S*
17	Me_2Zn	1-naphthaldehyde	**230b**	95	92	*S*
18	Me_2Zn	2-naphthaldehyde	**230b**	90	94	*S*
19	Me_2Zn	3-phenylpropionaldehyde	**230b**	87	81	*S*
20	Me_2Zn	7-(*tert*-butyldimethylsilyloxy)heptanal	**229b**	82	85	*R*
21	Me_2Zn	4-benzyloxybutyraldehyde	**230b**	86	72	*S*
22	Me_2Zn	5-hexyn-1-al	**229b**	95	64	*R*
23	Bu_2Zn	benzaldehyde	**230b**	75	91	*S*
24	Bu_2Zn	2-naphthaldehyde	**230b**	95	93	*R*

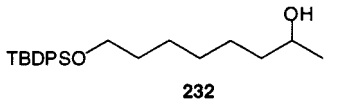
[a] The reactions were carried out in toluene at 0 °C for 12 h in the presence of 10 mol % of the chiral ligands.

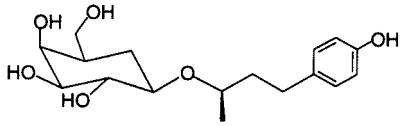
39% ee was observed when the uncomplexed ligand (1*S*,2*R*)-**8** was used. Ligand **230b** was used in the total synthesis of (*R*)-rhododendrin (**233**) and (*S*)-(−)-lasiodiplodin (**234**).[114b,c]

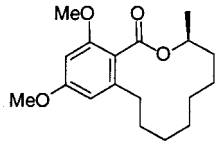










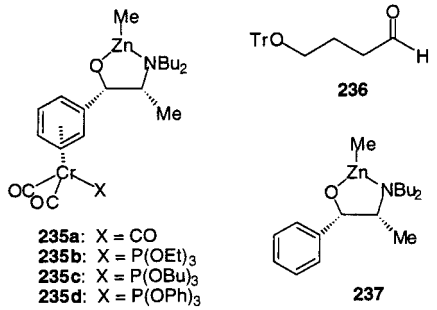


The effect of various chromium ligands in catalyst **235** on the catalytic properties was studied.[115] Complexes **235a**−**d** were used to catalyze the dimethylzinc addition to **236**. As the size of ligand X increased from **235a** to **235d**, the enantioselectivity also increased. Complex **235d** had the bulkiest phosphite group and exhibited the highest enantioselectivity (98% ee, entry 5, Table 53). Compound **237** had no η^6-arene−chromium coordination and gave poor enantioselectivity (59% ee, entry 6, Table 53).

Table 53. Dimethylzinc Additions to 236 Catalyzed by 235a−d and 237[a]

entry	catalyst (mol %)	yield (%)	ee (%)
1	**235a** (10)	94	89
2	**235b** (10)	90	94
3	**235c** (10)	91	95
4	**235d** (10)	82	96
5	**235d** (20)	91	98
6	**237** (10)	91	59

[a] The reactions were carried out at 0 °C for 18 h.

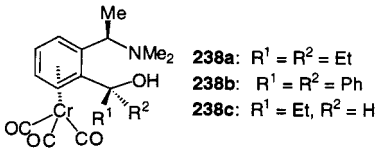


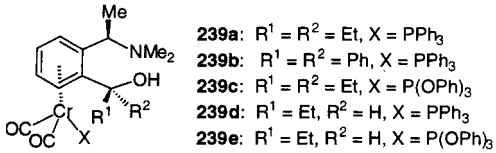
Uemura et al. reported the use of the η^6-arene−chromium complexes such as **238** and **239** for the reaction of diethylzinc with benzaldehyde and observed high enantioselectivity (Table 54).[116] Replacement of a carbonyl ligand in **238** with a more bulky phosphine or phosphate ligand, in general, led to increased enantioselectivity as shown for **239a**−**e**.

Table 54. Diethylzinc Additions to Benzaldehyde Catalyzed by 238 and 239[a]

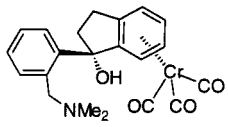
entry	catalyst	yield (%)	ee (%)	config
1	**238a**	89	95	*S*
2	**238b**	83	93	*S*
3	**238c**	87	93	*S*
4	**239a**	99	97	*S*
5	**239b**	99	94	*S*
6	**239c**	96	97	*S*
7	**239d**	97	96	*S*
8	**239e**	96	97	*S*

[a] The reactions were carried out in toluene at 0 °C for 18 h in the presence of 5 mol % of the catalysts.





Chromium complexes **240** and **241** and their uncomplexed ligands **242** and **243** were reported by Brocard and co-workers to catalyze the diethylzinc addition to benzaldehyde.[109] While chromium-complexed ligand **241** showed much higher enantioselectivity (70% ee) than uncomplexed **243** (10% ee), complexed **240** gave a much lower ee (62%) than uncomplexed **242** (99% ee). Therefore, the formation of a chromium−arene complex does not necessarily guarantee an enhancement in enantioselectivity for an amino alcohol ligand.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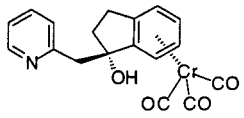
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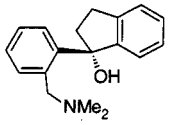
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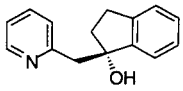
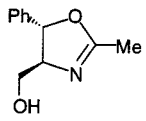

243

h. Oxazolines

Chiral oxazolines can be easily prepared from amino alcohols. These compounds have been used for the asymmetric organozinc addition. The study of ferrocene-based oxazoline ligands has been discussed earlier in section 2.f.

Williams and co-workers used the hydroxylmethyl oxazolines **244**−**246** to catalyze the diethylzinc addition to aromatic aldehydes, which gave 25−67% ee.[117] The C_3-symmetric oxazolinyl ligand **247** was shown by Chan and Zheng to catalyze the reaction of diethylzinc with benzaldehyde with 82% ee and 92% yield.[118] The highest enantioselectivity observed-for this ligand was in the reaction of 9-phenanthrenecarboxaldehdye with diethylzinc (90% ee). The C_2-symmetric ligand **248** gave <20% ee for the reaction of diethylzinc with benzaldehyde.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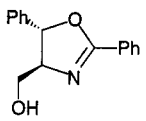
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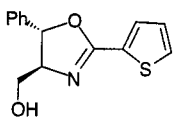
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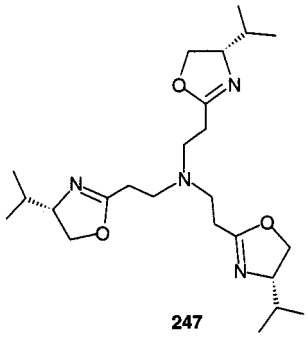
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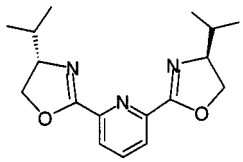
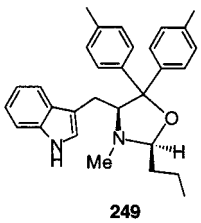

248

The chiral oxazolines such as **249** were prepared by Dai and co-workers from the condensation of abrine-derived amino alcohols with aldehydes.[119] This compound catalyzed the diethylzinc addition to benzaldehyde with 54% ee. Complex **250** was prepared by Prasad and Joshi from the reaction of the amino alcohol **24c** with acetone followed by treatment with diethylzinc.[120] This zinc complex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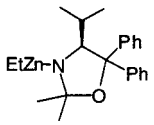
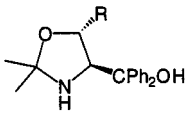

250

Table 55. Diethylzinc Additions to Aldehydes Catalyzed by Complex 250

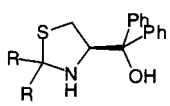
entry	aldehyde	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	4	85	100	*S*
2	*p*-chlorobenzaldehyde	3	86	100	*S*
3	*o*-methylbenzaldehyde	4	75	97	*S*
4	*p*-methylbenzaldehyde	4	79	98	*S*
5	1-naphthaldehyde	8	74	96	*S*
6	2-naphthaldehyde	4	81	100	*S*
7	cyclohexanecarboxaldehyde	8	50	43	*S*

was used to catalyze the diethylzinc addition to aldehydes. In the presence of 10 mol % of **250** at 0 °C in toluene, diethylzinc (2 equiv) reacted with aromatic aldehydes with high enantioselectivity (96−100% ee, Table 55), but the enantioselectivity was low for an aliphatic aldehyde (43% ee, entry 7, Table 55).

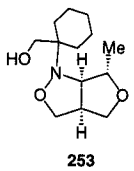
Ligands **251a,b** were found by Falorni et al. to be highly enantioselective for the diethylzinc addition to benzaldehyde (100% and 98% ee, entries 1, 2, 8, and 9, Table 56).[121] However, the enantioselectivity dropped significantly for substituted benzaldehydes (1−83% ee). The enantioselectivity was also much lower for aliphatic aldehydes (79−84% ee, entries 7, 13, and 14, Table 56).


251a: R = H
251b: R = Me

The thiazolidine ligands **252a**−**e**, derived from L-cysteine, were used by Liu and co-workers to catalyze the reaction of diethylzinc with aromatic aldehydes.[122] Among these ligands, **252b** gave the best result. It produced (*S*)-1-phenylpropanol with 81% ee from the reaction of benzaldehyde with diethylzinc at 4 °C for 5 days.


252a: R = H
252b: R = Me
252c: R = Et
252d: R = -$(CH_2)_4$-
252e: R = -$(CH_2)_5$-

A number of bicyclic and tricyclic isoxazolines were prepared by Aurich et al. for the reaction of diethylzinc with aromatic aldehydes, among which ligands **253**−**255** showed good enantioselectivity (Table 57).[123] Up to 95% ee was obtained for the reaction of benzaldehyde with diethylzinc in the presence of **253** (entry 2, Table 57).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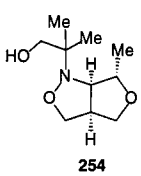
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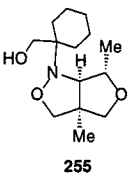

255

Table 56. Diethylzinc Additions to Aldehydes Catalyzed by 251a,b[a]

entry	aldehyde	catalyst (mol %)	*T* (°C)	conv (%)	ee (%)	config
1	benzaldehyde	**251a** (6)	−10	91	100	*S*
2	benzaldehyde	**251a** (6)	20	99	100	*S*
3	*p*-chlorobenzaldehyde	**251a** (6)	−15	64	40	*S*
4	*p*-methoxybenzaldehyde	**251a** (6)	−10	91	78	*S*
5	*p*-methoxybenzaldehyde	**251a** (6)	20	64	57	*S*
6	*o*-methylbenzaldehyde	**251a** (6)	−10	54	72	*S*
7	heptanal	**251a** (6)	20	94	79	*S*
8	benzaldehyde	**251b** (6)	20	98	98	*S*
9	benzaldehyde	**251b** (6)	−10	76	98	*S*
10	*p*-methoxybenzaldehyde	**251b** (6)	−10	46	83	*S*
11	*p*-methoxybenzaldehyde	**251b** (6)	20	95	1	*S*
12	*p*-methylbenzaldehyde	**251b** (6)	35	100	19	*R*
13	heptanal	**251b** (6)	−10	71	84	*S*
14	heptanal	**251b** (6)	20	100	81	*S*

[a] The reactions were carried out in diethyl ether over 14−20 h

Table 57. Diethylzinc Additions to Aromatic Aldehydes Catalyzed by 253−255[a]

entry	catalyst	aldehyde	*t* (h)	yield (%)	ee (%)	config
1	**253**	benzaldehyde	2	100	92	*R*
2[b]	**253**	benzaldehyde	121	80	95	*R*
3	**254**	benzaldehyde	2	100	88	*R*
4	**255**	benzaldehyde	1	100	90	*R*
5	**254**	*p*-methylbenzaldehyde	1.3	100	85	*R*
6	**253**	*p*-methylbenzaldehyde	1	100	90	*R*

[a] The reactions were carried out at 0 °C in the presence of 3 equiv of Et_2Zn, 10 mol % of the ligand in hexane unless indicated otherwise. [b] The reaction was carried out at −55 °C in the presence of 1.5 equiv of Et_2Zn and 20 mol % of the ligand in hexane.

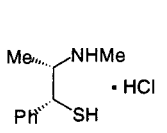
Table 58. Diethylzinc Additions to Benzaldehyde Catalyzed by the Amino Thiol 256 and the Amino Disulfides 257−259[a]

entry	catalyst (mol %)	*t* (h)	conv (%)	ee (%)	config
1	**256** (5)	40	95	80	*R*
2	**257** (5)	40	75	86	*R*
3	**258** (5)	20	96	90	*R*
4	**259**	20	97	89	*R*

[a] The reactions were carried out in toluene at room temperature.

3. Dialkylzinc Additions to Aldehydes Catalyzed by Amino Thiols, Disulfides, and Diselenides

Kellogg and co-workers prepared chiral amino thiols and disulfides from ephedrine for the reaction of diethylzinc with benzaldehyde.[124,125] They found that the *N*-methyl ephedrine thiol HCl salt **256** and *N*-methyl ephedrine disulfides **257**−**259** exhibited good enantioselectivity (80−90% ee, Table 58).



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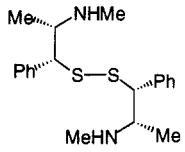

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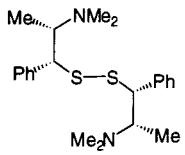

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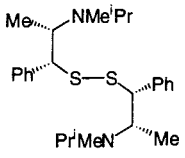
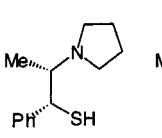


259

The amino thiols **260**−**269** with cyclic and acyclic amino substituents were used by Kang et al. for the diethylzinc addition to aldehydes.[126] For example, in the presence of 5 mol % of **260**, the reaction of diethylzinc with various aldehydes in toluene at 0 °C proceeded with 78−99% ee (entries 1, 9, 20, and 27, Table 59).[126a,b] However, the reaction of hexanal and cinnamaldehyde gave only 62−78% ee. Most of these ligands exhibited good enantioselectivity for 2-naphthaldehyde, cyclohexanecarboxaldehyde, and benzaldehyde but not as good for cinnamaldehyde.



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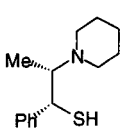

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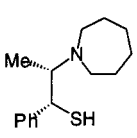

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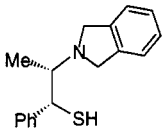

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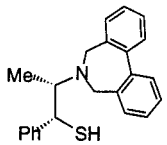

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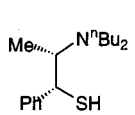

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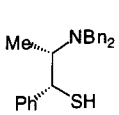

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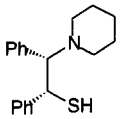

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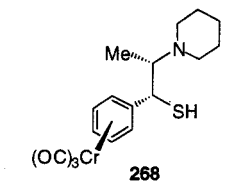

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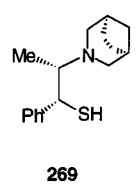


269

The catalytic properties of the amino thiol **270** and its corresponding disulfide **271** were compared.[126c]

Table 59. Diethylzinc Additions to Aldehydes Catalyzed by 260−269[a]

entry	aldehyde	catalyst (mol %)	*T* (°C)	yield (%)	ee (%)	config
1	benzaldehyde	**260** (5)	0		99	*R*
2	benzaldehyde	**261** (5)	0	94	100	*R*
3	benzaldehyde	**262** (5)	0		86	*R*
4	benzaldehyde	**263** (5)	0		97	*R*
5	benzaldehyde	**264** (5)	0		73	*R*
6	benzaldehyde	**265** (5)	0		99	*R*
7	benzaldehyde	**266** (5)	0		72	*R*
8	benzaldehyde	**267** (5)	0		100	*R*
9	cinnamaldehyde	**260** (5)	0		78	*R*
10	cinnamaldehyde	**261** (5)	−50	92	68	*R*
11	cinnamaldehyde	**261** (5)	0	98	77	*R*
12	cinnamaldehyde	**262** (5)	0		74	*R*
13	cinnamaldehyde	**263** (5)	0		72	*R*
14	cinnamaldehyde	**264** (5)	0		66	*R*
15	cinnamaldehyde	**265** (5)	0		81	*R*
16	cinnamaldehyde	**266** (5)	0		72	*R*
17	cinnamaldehyde	**267** (5)	0		79	*R*
18	cinnamaldehyde	**268** (5)	0		69	*R*
19	cinnamaldehyde	**269** (5)	0		75	*R*
20	cyclohexanecarboxaldehyde	**260** (5)	0		99	*R*
21	cyclohexanecarboxaldehyde	**261** (5)	0	97	100	*R*
22	cyclohexanecarboxaldehyde	**262** (5)	0		97	*R*
23	cyclohexanecarboxaldehyde	**263** (5)	0		96	*R*
24	cyclohexanecarboxaldehyde	**264** (5)	0		97	*R*
25	cyclohexanecarboxaldehyde	**265** (5)	0		100	*R*
26	cyclohexanecarboxaldehyde	**266** (5)	0		97	*R*
27	2-naphthaldehyde	**260** (5)	0		99	*R*
28	2-naphthaldehyde	**261** (5)	0	98	99	*R*
29	2-naphthaldehyde	**262** (5)	0		96	*R*
30	2-naphthaldehyde	**263** (5)	0		97	*R*
31	2-naphthaldehyde	**264** (5)	0		96	*R*
32	2-naphthaldehyde	**265** (5)	0		98	*R*
33	2-naphthaldehyde	**266** (5)	0		95	*R*
34	2-naphthaldehyde	**267** (5)	0		100	*R*

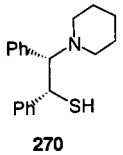
[a] The reactions were carried out in toluene over 12 h using 1 M hexane solution of diethylzinc.

Table 60. Diethylzinc Additions to Aldehyde Catalyzed by 270 and 271[a]

	catalyst **270** (5 mol %)			catalyst **271** (5 mol %)		
aldehyde	*t* (h)	yield (%)	ee (%)	*t* (h)	yield (%)	ee (%)
benzaldehyde	12	90	99	30	92	99
p-chlorobenzaldehyde	12	92	100	28	93	99
o-methoxybenzaldehyde	12	92	99	28	92	98
p-methoxybenzaldehyde	12	91	99	28	91	99
2-naphthaldehyde	12	98	100	28	93	98
ferrocenecarboxaldehyde	12[b]	89	100	18[b]	89	98
trimethylacetaldehyde	12	83	100	24	63	99
cyclohexanecarboxaldehyde	12	87	100	24	92	98
hexanal	12	88	79	20	89	87
cinnamaldehyde	12[b]	88	80	20[b]	93	83

[a] The reactions were carried out in toluene at 0 °C unless indicated otherwise. [b] At room temperature.

Both ligands showed very high enantioselectivity, especially for the reaction of aromatic aldehydes with diethylzinc (98−100% ee, Table 60).



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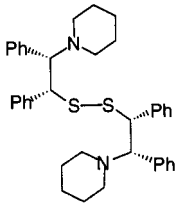


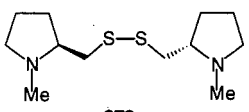
271

Gibson and co-workers found that the amino disulfide **272** prepared from L-proline was effective for the dialkylzinc addition.[127a,b] In the presence of 2.5 mol % of **272**, the reaction of aromatic aldehydes with diethylzinc proceeded with up to 99% ee (Table 61). However, only moderate enantioselectivity was observed for the reaction of α,β-unsaturated and aliphatic aldehydes (67% and 70% ee, entries 5 and 6, Table 61). Another amino disulfide ligand **273** showed much lower enantioselectivity than **272** for the diethylzinc addition to aldehydes.[127c] The amino thiol **274** was found to catalyze the reaction of diethylzinc with aromatic and aliphatic aldehydes with only 8−64% ee.[128]

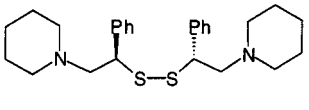
Table 61. Diethylzinc Additions to Aldehydes Catalyzed by 272 and 273[a]

entry	aldehyde	catalyst (mol %)	yield (%)	ee (%)	config
1	benzaldehyde	**272** (2.5)	76	87	*R*
2	benzaldehyde	**272** (1.25)	94	81	*R*
3	*p*-methylbenzaldehyde	**272** (2.5)	83	99	*R*
4	2-naphthaldehyde	**272** (2.5)	88	90	*R*
5	cinnamaldehyde	**272** (2.5)	96	70	*R*
6	3-phenylpropionaldehyde	**272** (2.5)	77	67	*R*
7	benzaldehyde	**273** (2.5)	69	61	*R*
8	*p*-chlorobenzaldehyde	**273** (2.5)	63	61	*R*
9	*p*-methylbenzaldehyde	**273** (2.5)	78	80	*R*
10	2-naphthaldehyde	**273** (2.5)	54	57	*R*
11	cinnamaldehyde	**273** (2.5)	69	40	*R*
12	3-phenylpropionaldehyde	**273** (2.5)	30	39	*R*

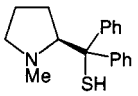
[a] The reactions were carried out in toluene at 0 °C using 1 M hexane solution of diethylzinc. The reaction time was 48−72 h for the use of **272** and 22−48 h for the use of **273**.



272

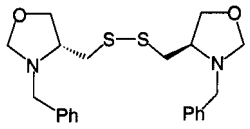


273



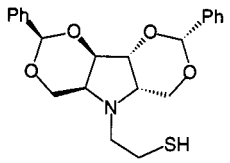
274

Braga et al. reported that the chiral disulfide **275** (1 mol %) catalyzed the reaction of diethylzinc with benzaldehyde and hexanal at 0 °C with over 99% ee (entries 2 and 11, Table 62).[129] For other aldehydes, ee's in the range of 40−92% were observed. The enantioselectivity was greatly reduced when the reactions were carried out at room temperature.



275

The pyrrolidine-based thiol **276**, prepared by Masaki et al., showed much better enantioselectivity than its corresponding amino alcohol **277**.[130] As shown in Table 63, **276** catalyzed the reaction of aromatic aldehydes, aliphatic aldehydes, and cinnamaldehyde with 77−99% ee. However, **277** gave only 42% ee for the reaction of diethylzinc with benzaldehyde.[130b]



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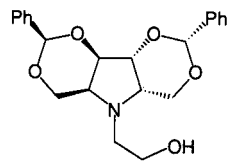
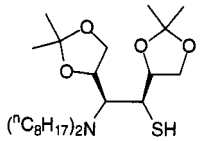


277

Cho et al. reported the use of the D-mannitol-based amino thiol and thioacetate **278** and **279** to catalyze the diethylzinc addition.[92b] They found that **278** was a much better catalyst than **279**. In the presence of 10 mol % of **278**, the reaction of diethylzinc with benzaldehyde and heptanal at 25 °C gave the corresponding *R* alcohols with 82% and 73% ee, respectively. The enantioselectivity of the amino thiol **278** is significantly lower than that of its corresponding amino alcohol **182a**.



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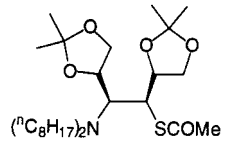


279

The use of the isolated air-stable zinc amino thiolate complex **280** for the alkylzinc addition to aldehydes was studied by van Koten and co-workers.[131] The structure of **280** was established by X-ray analysis. In the presence of 2−4 mol % of **280**, the addition of diethylzinc, dimethylzinc, and diisopropylzinc to aliphatic and aromatic aldehydes gave the corresponding (*S*)-alcohols with 69−99% ee and nearly quantitative yields (Table 64). The dizinc complex **281** generated instantaneously from the reaction of **280** with a dialkylzinc was proposed as the actual catalyst in the reaction. When the isolated **281** was used, the result was identical to the use of

Table 62. Diethylzinc Additions to Aldehyde Catalyzed by 275[a]

entry	aldehyde	catalyst (mol %)	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	2	r.t.	16	98	80	*S*
2	benzaldehyde	2	0	30	81	>99	*S*
3	benzaldehyde	1	0	30	43	76	*S*
4	*p*-methylbenzaldehyde	2	r.t.	16	65	70	*S*
5	*p*-methylbenzaldehyde	2	0	36	71	86	*S*
6	*p*-methoxybenzaldehyde	2	r.t.	16	67	36	*S*
7	*p*-methoxybenzaldehyde	2	0	36	65	70	*S*
8	phenylacetaldehyde	2	r.t.	16	34	55	*S*
9	phenylacetaldehyde	2	0	36	38	92	*S*
10	hexanal	2	r.t.	16	34	36	*S*
11	hexanal	2	0	36	58	>99	*S*
12	decyl aldehyde	2	r.t.	16	56	34	*S*
13	decyl aldehyde	2	0	36	50	40	*S*

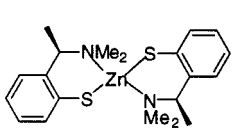
[a] The reactions were carried out in toluene using 1 M hexane solution of diethylzinc.

Table 63. Diethylzinc Additions to Aldehyde Catalyzed by 276[a]

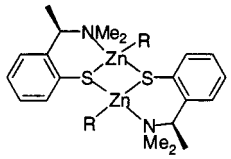
entry	aldehyde	yield (%)	ee (%)	config
1	benzaldehyde	94	96	*S*
2	*p*-methylbenzaldehyde	96	99	*S*
3	*o*-bromobenzaldehyde	89	99	*S*
4	*p*-chlorobenzaldehyde	70	81	*S*
5	*p*-methoxybenzaldehyde	88	82	*S*
6	*o*-methoxybenzaldehyde	93	86	*S*
7	1-naphthaldehyde	85	86	*S*
8	cinnamaldehyde	94	77	*S*
9	3-phenylpropionaldehyde	90	85	*S*
10	nonyl aldehyde	91	88	*S*

[a] The reactions were carried out at 0 °C to room temperature over 20 h in the presence of 6 mol % of **276**.

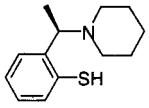
280. The amino thiols **282** and **283** containing cyclic amine substituents showed considerably enhanced rates and enantioselectivity when used for the reaction of diethylzinc with 3-phenylpropionaldehyde. After 1 h, over 80% conversion was observed with 80−82% ee (entries 9 and 10, Table 64).



280



281 R = Et, Me, ^{i}Pr



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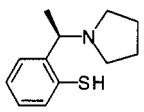
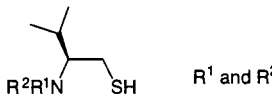


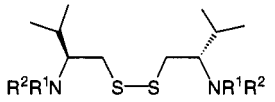
283

The amino thiols and disulfides **284** and **285** derived from L-valine were screened by Anderson et al. for the reaction of diethylzinc with aromatic aldehydes.[132] It was found that ligand **284a** (R^1 = Ph and R^2 = Me) gave the best result with ee's up to 82%.



284

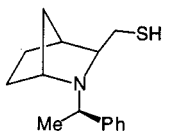
R^1 and R^2: Ph, Me, Bn, -$(CH_2)_5$-, Ts, ^{i}Pr



285

R^1 and R^2: Ph, Me, and Bn

Hongo and co-workers showed that the bicyclic amino thiol **286** was an excellent catalyst for the reaction of diethylzinc with aromatic aldehydes and cyclohexanecarboxaldehyde (94−99% ee, Table 65).[133] However, when **286** was used for the reaction of cinnamaldehyde and octyl aldehyde, the ee's were only 10% and 60%, respectively (entries 5 and 8, Table 65). In the synthesis of (*R*)-3-ethylphalide (**287**) from *o*-bromobenzaldehyde, using **286** led to the product with over 99% ee. The corresponding amino alcohol **288** gave only 22% ee for the reaction of diethylzinc with benzaldehyde.[133b] Compounds containing more bulky hydroxyl groups such as **289** exhibited up to 92% ee for this reaction. Andersson and co-workers studied other ligands that were structurally similar to **288** and **289** for the reaction.[134] They found that **290** gave 75% ee for the diethylzinc addition to benzaldehyde. Ligands in this series with more bulky hydroxyl groups, however, showed much lower enantioselectivity.



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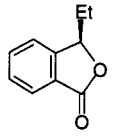

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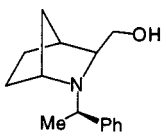

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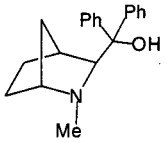

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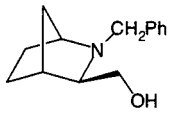


290

The aminothioacetate **291** and **292** were studied by Jin et al.[135] These compounds showed very high

Table 64. Dialkylzinc Additions to Aldehyde Catalyzed by 280, 282, and 283[a]

entry	R_2Zn	aldehyde	catalyst (mol %)	solvent	*t* (h)	yield (%)	ee (%)	config
1	Et_2Zn	benzaldehyde	**280** (2)	toluene	17	99	94	*S*
2	Et_2Zn	*o*-chlorobenzaldehyde	**280** (2)	toluene	17	96	92	*S*
3	Et_2Zn	*p*-chlorobenzaldehyde	**280** (2)	toluene	17	99	97	*S*
4	Et_2Zn	*p*-methoxybenzaldehyde	**280** (2)	toluene	17	94	95	*S*
5	Et_2Zn	*p*-methylbenzaldehyde	**280** (2)	toluene	17	>99	99	*S*
6	Et_2Zn	cinnamaldehyde	**280** (2)	toluene	17	95	75	*S*
7	Et_2Zn	2-furaldehyde	**280** (2)	toluene	17	>99	89	*S*
8	Et_2Zn	3-phenylpropionaldehyde	**280** (2)	toluene	17	98	69	*S*
9	Et_2Zn	3-phenylpropionaldehyde	**282** (4)	toluene	17	>99	82	*S*
10	Et_2Zn	3-phenylpropionaldehyde	**283** (4)	toluene	17	>99	80	*S*
11	Et_2Zn	benzaldehyde	**282** (4)	toluene	17	>99	96	*S*
12	Et_2Zn	benzaldehyde	**283** (4)	toluene	17	93	98	*S*
13	Me_2Zn	benzaldehyde	**280** (2)	toluene	68	88	94	*S*
14	Me_2Zn	benzaldehyde	**282** (4)	toluene	68	97	93	*S*
15	$^iPr_2Zn$	benzaldehyde	**280** (2)	toluene	17	45	80	*S*
16	$^iPr_2Zn$	benzaldehyde	**282** (4)	toluene	17	68	91	*S*
17	Et_2Zn	benzaldehyde	**280** (2)	tBuOMe	17	85	89	*S*
18	Et_2Zn	benzaldehyde	**280** (2)	Et_2O	17	89	83	*S*
19	Et_2Zn	benzaldehyde	**280** (2)	THF	17	9	74	*S*

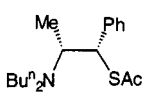
[a] The reactions were carried out at room temperature using 1 M toluene solution of diethylzinc.

Table 65. Diethylzinc Additions to Aldehydes Catalyzed by 286[a]

entry	aldehyde	yield (%)	ee (%)	config
1	benzaldehyde	95	97	*R*
2	2-naphthaldehyde	93	98	*R*
3	*o*-ethoxybenzaldehyde	100	97	*R*
4	*p*-methoxybenzaldehyde	94	94	*R*
5	cinnamaldehyde	100	10	*R*
6	furaldehyde	83	74	*R*
7	cyclohexanecarboxaldehyde	97	>99	*R*
8	octyl aldehyde	87	60	*R*

[a] The reactions were carried out in toluene at 0 °C using 5 mol % of **286** and 1 M hexane solution of diethylzinc.

enantioselectivity for the reaction of diethylzinc with aromatic aldehydes and cyclohexanecarboxaldehyde (98−99% ee, Table 66). The catalytic properties of these two compounds were very similar despite their different nitrogen substituents.



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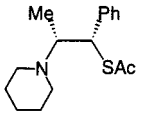
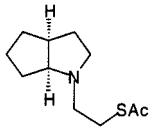


292

Aurich and Soeberdt found that the amino thioacetate **293** and thiol **294** gave 82% and 84% ee, respectively, for the diethylzinc addition to benzaldehyde. Their corresponding alcohol analogues **295** gave only 14−78% ee for the reaction.[136] They later found that the bicyclic amino thioacetate **296** and thiol **297** also showed very good enantioselectivity for the diethylzinc addition to benzaldehyde. Both of them gave (*R*)-1-phenylpropanol with 90% ee and 100% yield. The reaction was carried out at room temperature in toluene in the presence of 5 mol % of **296** or **297**.[62f]



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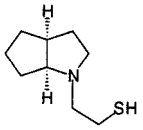

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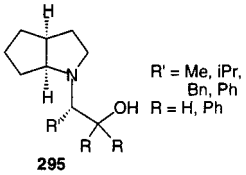

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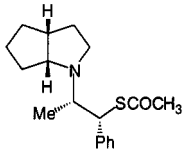

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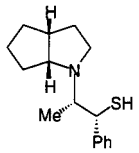
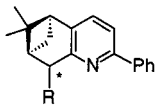


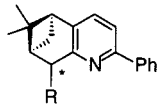
297

The diastereomers of the pyridine-based thiol ligands **298** were reported by Chelucci et al. to catalyze the diethylzinc addition to benzaldehyde with only 5−51% ee.[137] The corresponding alcohol analogues **299** also gave low enantioselectivity (13−62% ee).



298

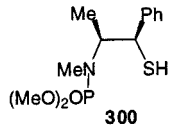
R = SH, CH_2SH



299

R = OH, CH_2OH CPh_2OH, CMe_2OH

The phosphorylated amino thiol **300** was found by Hulst and co-workers to carry out the diethylzinc addition to benzaldehyde with over 98% ee and over 98% yield with or without excess $Ti(O^iPr)_4$.[138] However, a stoichiometric amount of **300** was needed for this reaction. Degradation of **300** during the reaction was observed. A stoichiometric amount of the thiophosphinamide **301** also promoted the reaction in the presence of $Ti(O^iPr)_4$ with 96% ee. In this case, the enantioselectivity became very low (48% ee) without $Ti(O^iPr)_4$. Other ligands, **302a**−**e**, gave 17−87% ee for the diethylzinc addition to benzaldehyde in the presence of $Ti(O^iPr)_4$ and 5−37% ee in the absence of $Ti(O^iPr)_4$. In contrast, the amino thiol **303** showed significantly improved enantioselectivity (from 36% to 89% ee) without addition of $Ti(O^iPr)_4$.



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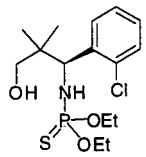

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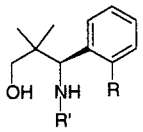
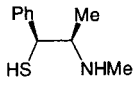


302a: R = H, R' = P(=S)(OEt)$_2$
302b: R = H, R' = P(=O)(OEt)$_2$
302c: R = Cl, R' = P(=O)(OEt)$_2$
302d: R = H, R' = H
302e: R = Cl, R' =H



303

Bolm and co-workers found that the β-hydroxysulfoximines such as **304** catalyzed the diethylzinc addition to aldehydes to give alcohols with up to 88% ee. In this ligand, the chiral center was the sulfur atom instead of the hydroxyl carbon.[139,140] Compound **304** showed a significant nonlinear effect. The ligand

Table 66. Diethylzinc Additions to Aldehydes Catalyzed by 291 and 292[a]

entry	aldehyde	catalyst (mol %)	*t* (h)	yield (%)[b]	ee (%)	config
1	benzaldehyde	**291** (5)	6	100	>99	*S*
2	benzaldehyde	**292** (5)	6	100	>99	*S*
3	*p*-chlorobenzaldehyde	**291** (5)	6	100	>99	*S*
4	*p*-chlorobenzaldehyde	**292** (5)	6	100	>99	*S*
5	*p*-methoxybenzaldehyde	**291** (5)	6	99	99	*S*
6	*p*-methoxybenzaldehyde	**292** (5)	6	99	>99	*S*
7	*o*-methoxybenzaldehyde	**291** (5)	6	100	99	*S*
8	*o*-methoxybenzaldehyde	**292** (5)	6	99	99	*S*
9	2-naphthaldehyde	**291** (5)	6	99	98	*S*
10	2-naphthaldehyde	**292** (5)	6	99	98	*S*
11	cyclohexanecarboxaldehyde	**292** (5)	10	95	>99	*S*

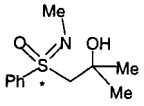
[a] The reactions were carried out in hexane at 0−20 °C. [b] Determined by GC.

Table 67. Diethylzinc Additions to Aldehydes Catalyzed by the Diselenides 305−309[a]

entry	aldehyde	catalyst (mol %)	*T* (°C)	yield (%)[a]	ee (%)	config
1	benzaldehyde	**305a** (1)	r.t.	70	91	*S*
2	benzaldehyde	**305b** (1)	0	48	82	*S*
3	benzaldehyde	**305c** (1)	r.t.	57	91	*S*
4	benzaldehyde	**305d** (1)	r.t.	91	97	*S*
5	benzaldehyde	**305d** (1)	0	97	98	*S*
6	benzaldehyde	**305e** (1)	r.t.	50	4	*S*
7	benzaldehyde	**306** (5)	r.t.	32	8	*R*
8	benzaldehyde	**307** (5)	r.t.	10	15	*S*
9	benzaldehyde	**308** (5)	r.t.	1	8	*R*
10	benzaldehyde	**309** (1)	r.t.	71	92	*R*
11	1-naphthaldehyde	**305d** (1)	0	80	90	
12	*o*-bromobenzaldehyde	**305d** (1)	0	78	91	
13	2-bromo-3-methylbenzaldehyde	**305d** (1)	0	79	92	
14	*m*-trifluoromethyl-benzaldehyde	**305d** (1)	0	98	97	
15	*p*-trifluoromethyl-benzaldehyde	**305d** (1)	0	98	98	
16	*p*-*tert*-butylbenzaldehyde	**305d** (1)	0	67	98	
17	3,5-ditrifluoromethyl-benzaldehyde	**305d** (1)	0	90	98	
18	2,3,4,5-tetrafluoro-benzaldehyde	**305d** (1)	0	95	97	
19	2-bromo-1-cyclopentene-1-carboxaldehyde	**305d** (1)	0	97	98	
20	2-bromo-1-cyclohexene-1-carboxaldehyde	**305d** (1)	0	81	97	

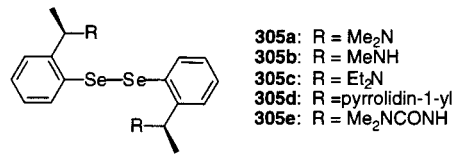
[a] The reactions were carried out in toluene over 12−20 h.

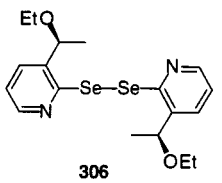
with 23% ee catalyzed the diethylzinc addition to benzaldehyde with 64% ee.



304

Wirth and co-workers studied the diselenides **305**−**309** and found that **305d** gave the best result for the diethylzinc addition to benzaldehyde (98% ee, entry 5, Table 67).[141a,b] In the presence of 1 mol % of **305d**, reaction of diethylzinc with a few aromatic aldehydes and α,β-unsaturated aldehydes proceeded with 90−98% ee (entries 11−20, Table 67). Ligands **305e** and **306**−**308** had very low enantioselectivity (4−15% ee, entries 6−9, Table 67). Other highly enantioselective diselenide ligands were also prepared later.[141c]





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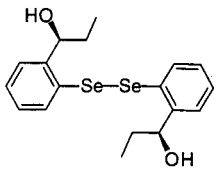

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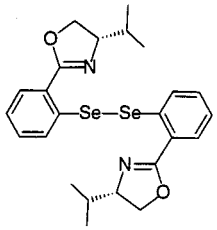
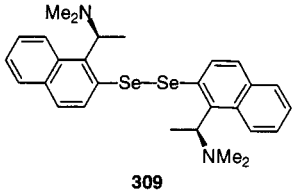


308



309

4. Dialkylzinc Additions to Aldehydes Catalyzed by Amines

Chiral amines containing no hydroxyl or thiol groups but having multiple nitrogen atoms capable of chelate coordination were also found to be effective in the dialkylzinc additions to aldehydes. For example, (*S*)-2-(2′-pyrrolidinyl)pyridine (**310**) was shown by Falorni and co-workers to catalyze the diethylzinc addition with up to 100% ee for aromatic aldehydes (Table 68).[142] Its enantioselectivity for α-unsubsti-

Table 68. Diethylzinc Additions to Aldehyde Catalyzed by 310[a]

entry	aldehyde	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	20	20	100	93	*S*
2	benzaldehyde	−10	18	93	100	*S*
3	*p*-methoxybenzaldehyde	−10	20	60	98	*S*
4	*p*-chlorobenzaldehyde	−10	16	90	100	*S*
5	*p*-methylbenzaldehyde	−10	6	77	92	*S*
6	*o*-methylbenzaldehyde	−10	16	96	100	*S*
7	3-phenylpropionaldehyde	50	6	87	60	*S*
8	3-phenylpropionaldehyde	20	6	89	59	*S*
9	3-phenylpropionaldehyde	−10	40	61	29	*S*
10	cinnamaldehyde	−10	18	98	91	*S*
11	phenylpropargyl aldehyde	−10	18	91	24	*S*
12	heptanal	20	16	89	67	*S*
13	heptanal	−10	40	56	40	*S*
14	cyclohexanecarboxaldehyde	−10	16	77	90	*S*
15	2-furaldehyde	−10	8	93	33	*S*
16	ferrocenecarboxaldehyde	−10	20	50	54	*S*

[a] The reactions were carried out in diethyl ether using 6 mol % of **310** and 1 M hexane solution of diethylzinc.

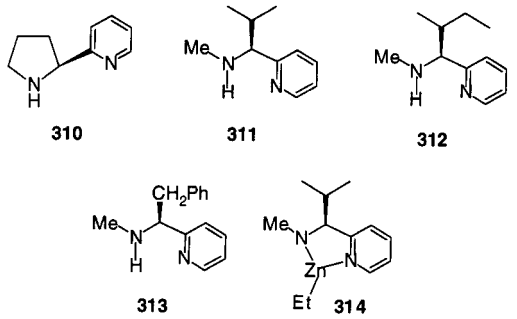
tuted aliphatic aldehydes and phenyl propargyl aldehyde was low (24−67% ee, entries 8, 11, and 12, Table 68). Other ligands such as **311**−**313** gave 90−98% ee for the reaction of diethylzinc with benzaldehyde.[142b] When **311** was treated with 1 equiv of diethylzinc, its ^{1}H NMR spectrum showed the disappearance of the N−H signal, indicating the formation of **314**. Addition of 1 equiv of benzaldehyde to **314** did not lead to an ethyl migration product.

Table 69. Dialkylzinc Additions to Aldehydes Catalyzed by 315 and 316a−d[a]

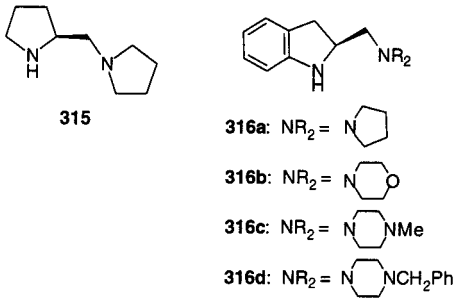
entry	aldehyde	R_2Zn	catalyst	solvent	*T* (°C)	yield (%)	ee (%)
1	benzaldehyde	Et_2Zn	**315**	*b*	r.t.	80	80
2	benzaldehyde	Et_2Zn	**316a**	*c*	0	89	91
3	benzaldehyde	Et_2Zn	**316b**	*c*	0	82	93
4	benzaldehyde	Et_2Zn	**316c**	*c*	0	85	95
5	benzaldehyde	Et_2Zn	**316d**	*c*	0	74	90
6	*p*-methoxybenzaldehyde	Et_2Zn	**316c**	*c*	0	80	74
7	*o*-methoxybenzaldehyde	Et_2Zn	**316c**	*c*	0	71	91
8	*p*-chlorobenzaldehyde	Et_2Zn	**316c**	*c*	0	91	93
9	cinnamaldehyde	Et_2Zn	**316c**	*c*	0	80	59
10	3-phenylpropionaldehyde	Et_2Zn	**316c**	*c*	0	67	66
11	heptanal	Et_2Zn	**316c**	*c*	0	71	60
12	cyclohexanecarboxaldehyde	Et_2Zn	**316c**	*c*	0	70	97
13	benzaldehyde	Me_2Zn	**316c**	*c*	r.t.	84	96
14	benzaldehyde	$^iPr_2Zn$	**316c**	*c*	r.t.	80	87

[a] The reactions were carried out over 15 h using 15 mol % of the ligands. The benzaldehyde addition products had *S* configuration. [b] Cyclohexane/hexane (3:4). [c] Cyclohexane/hexane (2.7:6).

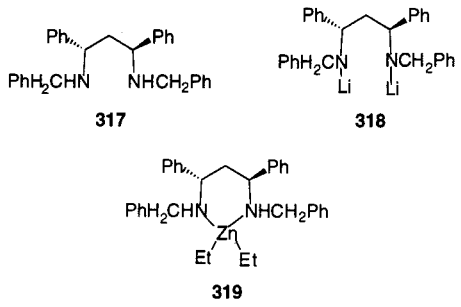
The ^1H NMR study revealed that there was a tight coordination of the aldehyde to the zinc center. Another equivalent of diethylzinc was needed for the alkyl addition to aldehyde to occur. This is similar to what was observed in the amino alcohol catalysts.



The use of the chiral diamines and triamines **315**[143] and **316a−d**[144] in the reaction of dialkylzincs with aldehydes were studied by Asami and co-workers. It was found that the triamine ligand **316c** exhibited the best enantioselectivity for the diethylzinc addition to benzaldehyde (95% ee, entry 4, Table 69). This compound was used to catalyze the reaction of various aldehydes with diethylzinc, dimethylzinc, and diisopropylzinc. Its enantioselectivity for aromatic aldehydes and cyclohexanecarboxaldehyde (74−97% ee) was much higher than that for cinnamaldehyde and linear aliphatic aldehydes (59−66% ee) (Table 69).



Salvadori and co-workers studied the chiral diamine **317** and its lithium salt **318** for the reaction of diethylzinc with benzaldehyde.[145] Both compounds gave incomplete conversion and a significant amount of benzyl alcohol side product. The enantioselectivity was low (13−15% ee). They found that when **317** was treated with diethylzinc, there was no deprotonation of the secondary amine groups. The zinc complex **319** was probably produced. This compound was found to directly react with 1 equiv of an aldehyde unlike zinc complexes **2** and **314** which did not react with aldehydes without an additional dialkylzinc. Further addition of diethylzinc to **319** did not affect its ^1H NMR spectrum.



The chiral piperazines **320** and **321** were used by Fuji et al. for the reaction of diethylzinc with benzaldehyde,[146a] but all of them gave very low enantioselectivity (<50% ee) as well as low yield (<60%) even with the addition of ^{n}BuLi. The solution structure of the dilithiumamide/diethylzinc complex of a chiral piperazine was studied.[146b,c] The derivatives of Troger's base, **322** and **323**, were used to catalyze the reaction of diethylzinc with aromatic aldehydes by Harmata and Kahraman.[147] Among these ligands, compound **323** was found to show the highest enantioselectivity (67−86% ee).

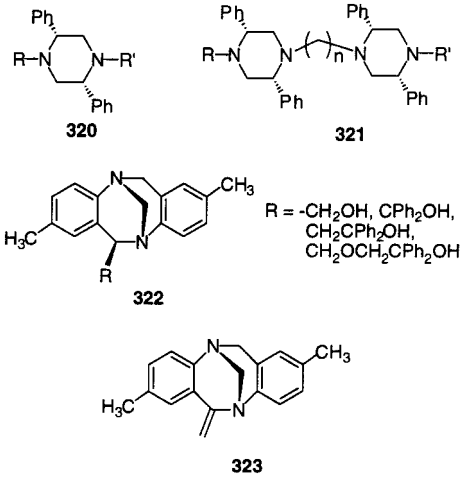


Table 70. Diethylzinc Additions to Aldehydes Catalyzed by the Titanium Complexes 325 and 326[a]

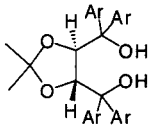
entry	aldehyde	catalyst (mol %)	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	**325b** (20)	−25	30	76	98.6	*S*
2	benzaldehyde	**326a** (10)	−75 to r.t.	15 to 24	75	99	*S*
3	3-phenylpropionaldehyde	**325b** (20)	−22	15	87	>98	*S*
4	3-phenylpropionaldehyde	**326a** (10)	−75 to r.t.	15 to 24	85	82	*S*
5	cinnamaldehyde	**325b** (20)	−27	24	87	91	*S*
6	cinnamaldehyde	**326a** (10)	−75 to r.t.	15 to 24	89	96	*S*
7	cyclohexanecarboxaldehyde	**325b** (20)	−27	30	77	99	*S*
8	cyclohexanecarboxaldehyde	**326a** (10)	−75 to r.t.	15 to 24	67	82	*S*
9	heptanal	**325b** (20)	−28	50	70	97	*S*
10	heptanal	**326a** (10)	−75 to r.t.	15 to 24	75	92	*S*
11	phenylpropargyl aldehyde	**325b** (20)	−27	22	83	>99	*S*
12	crotonaldehyde	**325b** (20)	−76 to −27	20	56	>98	*S*
13	1-cyclopentene-1-carboxaldehyde	**325b** (20)	−29	20	79	98	*S*
14	terephthalaldehyde[b]	**325b** (20)	−76 to −23	42	79	>99% de 98% ee	*S,S*
15	isophthalaldehyde[b]	**325b** (20)	−76 to −25	50	95	93% de 99% ee	*S,S*

[a] The reactions were carried out in the presence of 1.2−1.8 equiv of Et_2Zn and 1.2 equiv of $Ti(O^iPr)_4$ in toluene unless indicated otherwise. [b] 2.4 equiv of Et_2Zn and 2.4 equiv of $Ti(O^iPr)_4$ were used.

5. Dialkylzinc Additions to Aldehydes Catalyzed by Diols

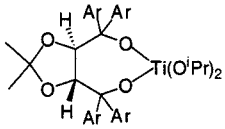
a. TADDOLs and Related Alcohols

All of the ligands discussed so far for the catalytic asymmetric dialkylzinc addition contain nitrogen atoms. Compounds without nitrogen atoms have also been widely used in the asymmetric catalysis. For example, α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs) such as **324a,b** are a family of chiral diols derived from optically active tataric acid. Seebach and co-workers carried out an extensive study on using the titanium complexes of TADDOLs such as **325** and **326** for the asymmetric organozinc addition.[148] They found that in the presence of 20 mol % of **325** or 10 mol % of **326** and an excess amount of $Ti(O^iPr)_4$ (1.2−2.4 equiv), additions of dialkylzinc reagents to aromatic and aliphatic aldehydes were highly enantioselective (82−99% ee) in toluene at −76 to −20 °C (Table 70). The spirotitanates **326** were air stable. They were converted to **325** when treated with 1 equiv of $Ti(O^iPr)_4$ in toluene. The sterically bulkier complex **325b** was a more effective catalyst than **325a**, especially for aliphatic, olefinic, and acetylenic aldehydes. The enantioselectivity of **325b** with respect to its optical purity was found to be linear.[148b] Ligand **325b** was also used to catalyze the reactions of propargyl aldehydes with a homoallyl zinc reagent to generate highly functionalized alcohols with 90−96% ee.[148e]

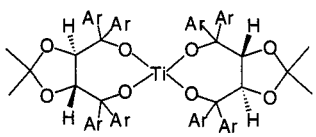


TADDOL

324a: Ar = Ph
324b: Ar = 2-Naphthyl



325a: Ar = Ph
325b: Ar = 2-Naphthyl



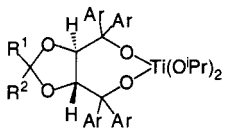
326a: Ar = Ph
326b: Ar = 2-Naphthyl

Table 71. Diethylzinc Additions to Benzaldehyde Catalyzed by the TADDOL Complexes 325a−o[a]

entry	catalyst (mol %)	*t* (h)	yield (%)	ee (%)	config
1	**325a** (2)	24	100	68	*S*
2	**325a** (5)	16	100	90	*S*
3	**325a** (20)	21	99	98	*S*
4	**325b** (20)	1.5	90	96	*S*
5	**325c** (20)	48	95	94	*S*
6	**325d** (5)	18	90	92	*S*
7	**325e** (20)	20	90	28	*S*
8	**325f** (20)	30	98	94	*S*
9	**325 g** (20)	17	100	94	*S*
10	**325h** (20)	17	90	94	*S*
11	**325i** (20)	14	97	96	*S*
12	**325j** (20)	19	100	96	*S*
13	**325k** (20)	22	81	96	*S*
14	**325l** (20)	18	87	98	*S*
15	**325m** (20)	14	94	94	*S*
16	**325n** (20)	16	97	96	*S*
17	**325o** (20)	14	98	94	*S*

[a] The reactions were carried out in toluene at −20 to −25 °C in the presence of 1.2 equiv $Ti(O^iPr)_4$.

Many TADDOL derivatives, e.g., **325a**−**o**, were prepared from tartrate esters and aryl Grignard reagents.[148c] It was found that varying the aryl groups as well as the protecting acetal groups on TADDOL had little effect on the enantioselectivity for the diethylzinc addition to benzaldehydes. In



325a: $R^1 = R^2$ = Me, Ar = Ph
325b: $R^1 = R^2$ = Me, Ar = 2-naphthyl
325c: $R^1 = R^2$ = Me, Ar = 4-MeO-Ph
325d: $R^1 = R^2$ = Me, Ar = 4-Ph-Ph
325e: $R^1 = R^2$ = Me, Ar = 1-naphthyl
325f: $R^1 = R^2 = -(CH_2)_5-$, Ar = Ph
325g: $R^1 = R^2$ = H, Ar = Ph
325h: $R^1 = R^2$ = H, Ar = 4-Me_2N-Ph
325i: R^1 = Me, R^2 = H, Ar = Ph
325j: R^1 = ^{t}Bu, R^2 = H, Ar = Ph
325k: R^1 = ^{t}Bu, R^2 = H, Ar = 2-naphthyl
325l: R^1 = Ph, R^2 = H, Ar = Ph
325m: R^1 = 1-naphthyl, R^2 = H, Ar = Ph
325n: R^1 = 2-naphthyl, R^2 = H, Ar = Ph
325o: R^1 = Ph, R^2 = Me, Ar = Ph

general, over 90% ee was observed with 0.02−0.2 equiv of the chiral titanates and excess $Ti(O^iPr)_4$ (Table 71). The study found that the role of excess $Ti(O^iPr)_4$ was to remove the product alkoxides from the titanium TADDOLate complexes by ligand ex-

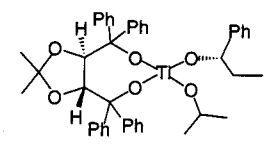
Table 72. Diethylzinc Additions to *p*-Methoxybenzaldehyde Catalyzed by 325a,l and 327−330[a]

entry	catalyst (mol %)	$Ti(O^iPr)_4$ (mol %)	*t* (h)	yield (%)	ee (%)	config
1	**325a** (140)		40	69[b]	42	*S*
2	**325a** (20)	120	15	95	96	*S*
3	**325a** (4)	120	40	98	84	*S*
4	**325l** (140)		40	76[b]	42	*S*
5	**325l** (20)	120	15	98	94	*S*
6	**327** (140)		40	63[b]	66	*S*
7	**327** (20)	120	15	98	96	*S*
8	**327** (20)		40	27[c]	24	*S*
9	**328** (140)		40	73[b]	42	*S*
10	**328** (20)	120	15	98	92	*S*
11	**329** (140)		40	52[b,c]	34	*S*
12	**329** (20)	120	15	96	94	*S*
13	**330** (140)		40	45[b,c]	0	*S*
14	**330** (20)	120	15	98	94	*S*

[a] The reactions were carried out in the presence of 1.8 equiv of diethylzinc in toluene at −25 °C. [b] By ^1H NMR analysis of the crude product. 1-(4′-methoxyphenyl)propan-1-one was identified as a byproduct. [c] Unreacted 4-methoxybenzaldehyde in the crude product was detected by ^1H NMR.

change. The rate enhancement of the titanium TADDOLate complexes over $Ti(O^iPr)_4$ was attributed to the bulkiness of the TADDOLate ligand, which increases the ligand exchange rate and facilitates the catalytic alkyl additions. Ligand **325e** containing 1-naphthyl substituent rather than 2-naphthyl showed much lower enantioselectivity than **325b** (entry 7, Table 71).

Chiral alkoxy groups, (*R*)- and (*S*)-1-phenylpropyloxy, were introduced to replace the isopropoxy groups of the TADDOL complexes to generate **327**−**330**.[148c] It was found that in the presence of excess $Ti(O^iPr)_4$, the enantioselectivity of these complexes is essentially the same as the corresponding complexes **325a,l** that do not have the nonchelating chiral alkoxyls, and the chiral 1-phenylpropoxy groups of these complexes played little role in the asymmetric induction (Table 72).



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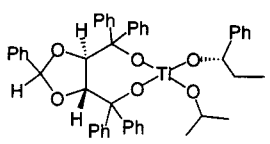

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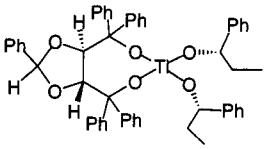

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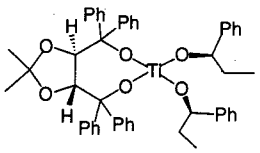


330

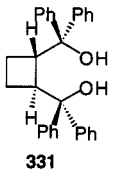
Other analogues of TADDOL, **331**−**339** and **324c**−**j**, were also prepared.[148f] In compounds **331**−**339**, the dioxolane ring of TADDOL was replaced with carbocycles including cyclobutane, cyclopentane, cyclohexene, cyclohexane, bicyclo[2,2,1]heptene, bicyclo-[2,2,1]heptane, bicyclo[2,2,2]octene, and bicyclo[2,2,2]-octane moieties. By analyzing the structures of these molecules with X-ray crystallography and molecular mechanics and studying their uses in the asymmetric

Table 73. Diethylzinc Additions to Benzaldehyde Catalyzed by 331−339 and 324a−j[a]

entry	ligand	yield (%)	ee (%)	config
1	**331**	79	88	*R*
2	**333**	53	22	*S*
3	**334**	79	10	*S*
4	**335a**	99	60	*R*
5	**335b**	73	6	*S*
6	**336**	90	70	*R*
7	**337**	42	70	*R*
8	**338a**	91	70	*R*
9	**338b**	71	2	*S*
10	**338c**	37	0	
11	**339**	60	68	*R*
12	**324a**	99	98	*S*
13	**324c**[a]	95	34	*S*
14	**324d**	94	14	*S*
15	**324e**[a]	99	8	*R*
16	**324f**	94	94	*S*
17	**324g**	97	0	
18	**324h**	98	8	*S*
19	**324i**	85	40	*S*
20	**324j**	98	28	*R*

[a] The reactions were carried out in the presence of 1.8 equiv of diethylzinc, 0.2 equiv ligand-titanium complex and 1.2 equiv of $Ti(O^iPr)_4$ in toluene at −25 °C. [b] 65% ee of the ligand was used.

organozinc addition, it was found that a better selectivity was achieved with a smaller torsion angle between the chelating oxygen atom and the ortho carbon atom of the axial phenyl group and the higher "degree of perpendicularity" of the axial phenyl group. Among all these ligands, the TADDOL derivatives **324a,f** showed the highest enantioselectivity (98% and 94% ee, entries 12 and 16, Table 73) and other ligands much lower. The low enantioselectivity of many of these ligands was attributed to the combination of the low facial bias of their titanium complexes and the competition of $Ti(O^iPr)_4$ in catalysis.



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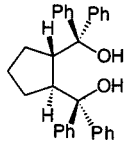

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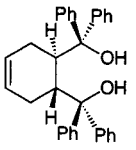

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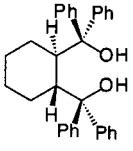

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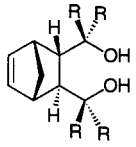
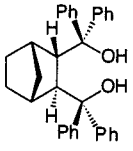


335a: R = Ph
335b: R = Me



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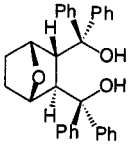

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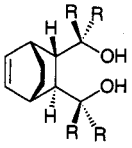
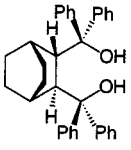


338a: R = Ph
338b: R = Me
338c: R = H



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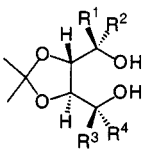


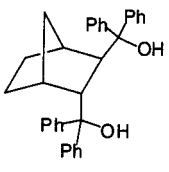
324a: $R^1 = R^2 = R^3 = R^4$ = Ph
324b: $R^1 = R^2 = R^3 = R^4$ = 2-naphthyl
324c: $R^1 = R^4$ = Ph, $R^2 = R^3$ = Me
324d: $R^1 = R^3$ = Ph, $R^2 = R^4$ = Me
324e: $R^1 = R^4$ = Me, $R^2 = R^3$ = Ph
324f: $R^1 = R^3$ = Ph, $R^2 = R^4$ = 1-naphthyl
324g: $R^1 = R^2 = R^3 = R^4$ = Me
324h: $R^1 = R^2 = R^3 = R^4 = CH_2Ph$
324i: $R^1 = R^2 = R^3 = R^4$ = cyclohexyl
324j: $R^1 = R^2$ = H, $R^3 = R^4$ = Ph

Table 74. Diethylzinc Additions to Aldehydes Catalyzed by the Chiral Diols 340−342[a]

entry	aldehyde	ligand (mol %)	solvent	*T* (°C)	yield (%)	ee (%)	config
1	benzaldehyde	**340** (10)	hexane	−78 to −20	95	90	*S*
2	benzaldehyde	**340** (20)	hexane	−78 to −20	95	95	*S*
3	benzaldehyde	**340** (20)	Et_2O	−78 to −20	90	98	*S*
4	benzaldehyde	**336** (20)	Et_2O	−78 to −20	50	93	*R*
5	benzaldehyde	**336** (20)	hexane	−78 to −20	76	91	*R*
6	*p*-methoxybenzaldehyde	**340** (20)	hexane	−78 to −20	97	91	*S*
7	*p*-methoxybenzaldehyde	**340** (20)	Et_2O	−78 to −20	48	91	*S*
8	*p*-chlorobenzaldehyde	**340** (20)	hexane	−78 to −20	96	92	*S*
9	*p*-chlorobenzaldehyde	**340** (20)	Et_2O	−78 to −20	55	92	*S*
10	*o*-chlorobenzaldehyde	**340** (20)	hexane	−78 to −20	94	33	*S*
11	*o*-methoxybenzaldehyde	**340** (20)	hexane	−78 to −20	95	63	*S*
12	phenylacetaldehyde	**340** (20)	hexane	−78 to −20	44	28	*S*
13	cinnamaldehyde	**340** (20)	hexane	−78 to −20	98	80	*S*
14	cinnamaldehyde	**340** (20)	Et_2O	−78 to −20	66	83	*S*
15	3-methyl-2-butenal	**340** (20)	hexane	−78 to −20	81	40	*S*
16	*trans*-2-methyl-2-butenal	**340** (20)	hexane	−78 to −20	86	85	*S*
17	benzaldehyde	**341b** (20)	hexane	−30	93[b]	64	*S*
18	benzaldehyde	**341b** (20)	hexane	−78	100	82	*S*
19	*p*-chlorobenzaldehyde	**341b** (20)	hexane	−78	95	80	*S*
20	*p*-methoxybenzaldehyde	**341b** (20)	hexane	−78	83	82	*S*
21	benzaldehyde	**342b** (20)	hexane	−30	100	40	*S*
22	benzaldehyde	**341a** (20)	hexane	−30	100	0	
23	benzaldehyde	**342a** (20)	hexane	−30	100	0	

[a] The reactions were carried out in the presence of 1.2−1.4 equiv of $Ti(O^iPr)_4$ using 1 M hexane solution of diethylzinc. [b] Conversion.

The chiral diols **340**−**342** were used by Wandrey and co-workers to catalyze the reactions of various aldehydes with diethylzinc in the presence of $Ti(O^iPr)_4$.[149] Compound **340** was the enantiomer of **336**. They both showed high enantioselectivity for the diethylzinc addition to benzaldehyde in hexane or Et_2O but gave the opposite enantiomeric product (90−95% ee, entries 1−5, Table 74).[149a] Compound **340** exhibited high enantioselectivity for *para*-substituted benzaldehydes and cinnamaldehyde but not as good for *ortho*-substituted benzaldehydes and an aliphatic aldehyde (entries 6−14, Table 74). The study of **341a,b** and **342a,b** demonstrates that the bulky hydroxyl carbon centers are essential for the chiral induction.[149b] Without the substituents at the hydroxyl carbons, compounds **341a** and **342a** showed no enantioselectivity at all. The enantioselectivity of **341b** was significantly lower than that of **340** but much higher than that of **342b**.



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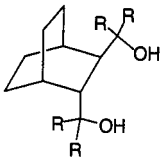
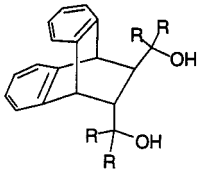
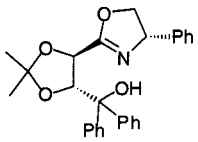


341a: R = H
341b: R = Ph



342a: R = H
342b: R = Ph

The TADDOL-derived oxazoline ligand **343** was found by Seebach et al. to catalyze the reaction of diethylzinc with benzaldehyde without the addition of a titanium complex.[150] In the presence of 2 mol % of **343**, the reaction proceeded with 84% ee at −20 °C in toluene. Other derivatives of TADDOL were prepared by Qian et al.[151] In their study, compounds **344a**−**d** catalyzed the reaction of diethylzinc with aromatic aldehydes with 43−88% ee in the absence of a titanium complex. In all cases, the enantioselectivity of **344c,d** was opposite to that of **344b**. The secondary amine **344b** led to the *R* alcohol products, whereas the tertiary amines **344c,d** gave *S* products. The primary amine **344a** reacted with an aldehyde to generate an imine, which was inefficient both in chemical selectivity and enantioselectivity.



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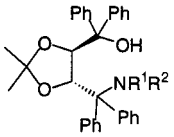
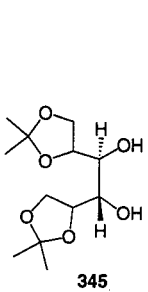


344a: $R^1 = R^2 = H$
344b: $R^1 = H$, $R^2 = Me$
344c: $R^1 = R^2 = Me$
344d: $R^1 = H$, $R^2 = Bn$

You et al. reported the bistitanium complex **346** from the reaction of the D-mannitol derivative **345** with 1 equiv of $Ti(O^iPr)_4$.[152] The structure of **346** was established by an X-ray analysis. The isolated **346** (10 mol %) catalyzed the reaction of *p*-methoxybenzaldehyde with diethylzinc with 50% ee and 42% yield. When this reaction was carried out with the addition of 0.8 equiv of $Ti(O^iPr)_4$, it gave 85% ee and 100% yield. Apparently, a catalytically more active as well as more selective species was generated from the reaction of **346** with $Ti(O^iPr)_4$. The diol **345** alone did not catalyze the diethylzinc addition. Mixing 20 mol % of **345** with 0.6−1.5 equiv of $Ti(O^iPr)_4$ catalyzed the diethylzinc addition to aromatic aldehydes with up to 86% ee. Compound **347**, also prepared from D-mannitol, in combination with $Ti(O^iPr)_4$ catalyzed the diethylzinc addition to benzaldehyde with 41% ee. β-Cyclodextrin and its alkylated derivatives were used by Fornasier and co-workers for the reaction of diethylzinc with aromatic aldehydes.[153] However, a low yield (0−49%) and low enantioselectivity (0−20% ee) were observed.



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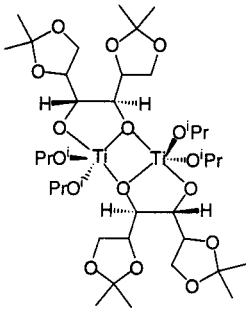

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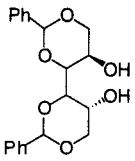
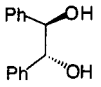


347

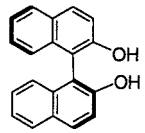
Prasad and Joshi reported the use of a chelate zinc dialkoxide complex, prepared by treatment of **348** with 1 equiv of diethylzinc in toluene at 80 °C for 0.5 h, to catalyze the reaction of diethylzinc with aromatic aldehydes.[154] In the presence of the zinc complex, diethylzinc reacted with a few *para*-substituted benzaldehydes with 69−89% ee. However, the reaction of *ortho*-substituted benzaldehydes proceeded with very low yields (<50%).



348

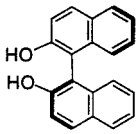
b. BINOL-Based Ligands

1,1′-Bi-2-naphthol (BINOL), (*S*)- or (*R*)-**349**, and its derivatives are axially chiral diols that have found extensive applications in asymmetric catalysis and others.[155] In 1997, two research groups, Nakai[156a] and Chan,[156b,c] independently reported the use of a titanium complex of (*S*)-**349** for the diethylzinc addition to aldehydes. It was found that the ratio of (*S*)-**349** and $Ti(O^iPr)_4$ had great effect on the enantioselectivity. A ratio of 1:7 [(*S*)-**349**/$Ti(O^iPr)_4$] gave the best result in methylene chloride and a ratio of 1:12 in toluene. In the presence of 20 mol % of (*S*)-**349** and 1.4 equiv of $Ti(O^iPr)_4$, the addition of diethylzinc to aromatic aldehydes, aliphatic aldehydes, and α,β-unsaturated aldehydes proceeded with up to 92% ee (Tables 75[156a] and 76[156b,c]). The enantioselectivity for the reaction of benzaldehyde was slightly better in CH_2Cl_2 than in toluene. All of the alcohol products generated from (*S*)-**349** had a *S* configuration. The x-ray structures of the complexes generated by treatment of BINOL with various amount of $Ti(O^iPr)_4$ were obtained by Walsh and coworkers.[156d]



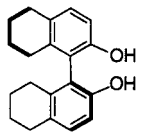
(*S*)-**349**

BINOL



(*R*)-**349**

When (*S*)-**349** was partially hydrogenated to (*S*)-**350**, a significant improvement in enantioselectivity was observed in many cases.[156c] With the use of excess $Ti(O^iPr)_4$, (*S*)-**350** catalyzed the diethylzinc addition to aromatic aldehydes with 85−99% ee (data in parentheses of Table 76). The enhanced enantioselectivity from (*S*)-**349** to (*S*)-**350** probably resulted from the increased steric interaction between the two tetrahydronaphthyl rings in (*S*)-**350**, which made the rotation around the pivotal 1,1′-bond more restricted.



(*S*)-**350**

The BINOL derivatives (*R*)-**351a**−**e** containing amide functional groups at the 3,3′-positions were found by Katsuki and co-workers to be efficient catalysts for the diethylzinc addition without the use of a titanium complex.[157a,b] The reactions in polar solvents such as THF gave higher enantioselectivity as well as better chemical yield than those in nonpolar solvents such as toluene. Among these BINOL ligands, (*R*)-**351b,c** were the most enantioselective ones for the reaction of various aldehydes. Participation of the amide carbonyl groups in the coordination to the zinc centers of the intermediate in situ generated from the reaction of the ligands with diethylzinc was believed to be important for the high enantioselectivity. In the presence of 10 mol % of (*R*)-**351b** or (*R*)-**351c**, aromatic aldehydes, cyclohexanecarboxaldehydes, cinnamaldehyde, and phenylpropargyl aldehyde reacted with diethylzinc with 91−99% ee (Table 77). BINOLs containing 3,3′-oxazoline substituents were found by Ohta and coworkers to catalyze the diethylzinc addition to aldehydes with

Table 75. Diethylzinc Additions to Aldehydes Catalyzed by (*S*)-349 in Toluene[a]

entry	aldehyde	ligand (mol %)	$Ti(O^iPr)_4$ (equiv)	*T* (°C)	*t* (h)	yield (%)	ee (%)[a]
1	benzaldehyde	20	0.8	−30	20	89	85
2	benzaldehyde	20	1.2	0	1	97	85
3	benzaldehyde	10	1.2	0	1	>98	85
4	nonyl aldehyde	20	1.2	0	3	90	81
5	nonyl aldehyde	20	1.2	−30	40	94	86
6	cyclohexanecarboxaldehyde	10	1.2	0	3	51	79
7	cyclohexanecarboxaldehyde	20	1.2	−30	40	75	85
8	cinnamaldehyde	10	1.2	0	1	>98	78
9	cinnamaldehyde	20	1.2	0	1	97	82
10	trimethylsilylpropargylaldehyde	20	1.2j	0	1	>98	56
11	trimethylsilylpropargylaldehyde	20	1.2	−30	20	>98	26
12	*tert*-butyldimethylsilylpropargylaldehyde	10	1.2	0	1	>98	62
13	*tert*-butyldimethylsilylpropargylaldehyde	20	1.2	0	1	>98	79

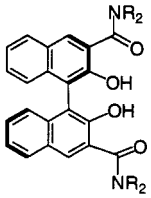
[a] 1 M hexane solution of diethylzinc was used.

Table 76. Diethylzinc Additions to Aldehydes Catalyzed by (*S*)-349 and (*S*)-350 in CH_2Cl_2

entry	aldehyde	$Ti(O^iPr)_4$ (equiv)	yield (%)	ee (%)[a,b]
1	benzaldehyde	2.8	99 (conv)	89
2	benzaldehyde	0.28	17	92
3	benzaldehyde	1.4	100	92 (99)
4	1-naphthaldehyde	1.4	100	94
5	2-naphthaldehyde	1.4	100	81
6	*m*-methoxybenzaldehyde	1.4	100	94 (96)
7	*m*-chlorobenzladehyde	1.4	99	88 (96)
8	*m*-nitrobenzaldehyde	1.4	100	70 (88)
9	*p*-fluorobenzaldehyde	1.4	100	86 (97)
10	*p*-chlorobenzaldehyde	1.4	86	88 (97)
11	*p*-methylbenzaldehyde	1.4	99	88 (91)
12	*p*-methoxybenzaldehyde	1.4	100	79 (97)
13	*o*-fluorobenzaldehyde	1.4	100	73 (94)
14	*o*-chlorobenzaldehyde	1.4	100	69 (92)
15	*o*-bromobenzaldehyde	1.4	99	59 (85)

[a] The reactions were carried out at 0 °C over 5 h using 20 mol % of (*S*)-**349**. [b] The data in the parentheses are from experiments using (*S*)-**350** as the ligand.

up to 64% ee.[157c] With the addition of $Ti(O^iPr)_4$, ee's up to 81% were obtained.



(*R*)-**351a**: R = Et
(*R*)-**351b**: R = ^{n}Bu
(*R*)-**351c**: R = ^{i}Pr
(*R*)-**351d**: R = cyclohexyl
(*R*)-**351e**: R = Me

Pu and co-workers discovered that another 3,3′-substituted BINOL ligand, (*R*)-**352**, was highly enantioselective for the diethylzinc and dimethylzinc additions to aldehydes without the use of a titanium complex.[158] This compound catalyzed the reaction of diethylzinc with many types of aldehydes including *ortho*-, *para*-, or *meta*-substituted benzaldehydes, linear or branched aliphatic aldehydes, and aryl- or alkyl-substituted α,β-unsaturated aldehyde with 91−99% ee. The data in Table 78 demonstrates that (*R*)-

Table 77. Diethylzinc Additions to Aldehydes Catalyzed by (*R*)-351a−e[a]

entry	aldehyde	catalyst (mol %)	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	phenylpropargyl aldehyde	(*R*)-**351a** (10)	0	6	92	78	*R*
2	phenylpropargyl aldehyde	(*R*)-**351b** (10)	0	15	68	84	*R*
3	phenylpropargyl aldehyde	(*R*)-**351c** (10)	−23	24	56	92	*R*
4	phenylpropargyl aldehyde	(*R*)-**351c** (10)	0	6	77	88	*R*
5	phenylpropargyl aldehyde	(*R*)-**351c** (10)	−23	24	90	92	*R*
6	phenylpropargyl aldehyde	(*R*)-**351d** (10)	0	6	56	80	*R*
7	phenylpropargyl aldehyde	(*R*)-**351e** (10)	0	15	82	79	*R*
8	benzaldehyde	(*R*)-**351b** (10)	0	24	88	99	*R*
9	benzaldehyde	(*R*)-**351b** (2)	0	72	63	98	*R*
10	benzaldehyde	(*R*)-**351c** (10)	0	24	82	97	*R*
11	*p*-chlorobenzaldehyde	(*R*)-**351b** (10)	0	24	88	97	*R*
12	*p*-methoxybenzaldehyde	(*R*)-**351b** (10)	0	24	85	94	*R*
13	*o*-fluorobenzaldehyde	(*R*)-**351b** (10)	0	24	86	95	*R*
14	cyclohexanecarboxaldehyde	(*R*)-**351c** (10)	0	24	51	98	*R*
15	*trans*-4-*tert*-butylcyclohexanecarboxaldehyde	(*R*)-**351c** (10)	0	48	51	98	
16	cinnamaldehyde	(*R*)-**351b** (10)	−23	24	53	91	*R*

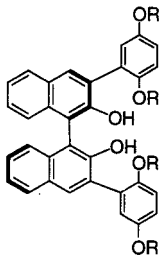
[a] The reactions were carried out in THF using 1 M hexane solution of diethylzinc.

Table 78. Diethylzinc Additions to Aldehydes Catalyzed by (*R*)-352[a]

entry	R_2Zn	aldehyde	*t* (h)	yield (%)	ee (%)	config
1	Et_2Zn	benzaldehyde	4	95	>99	*R*
2	Et_2Zn	*p*-methylbenzaldehyde	4	91	98	*R*
3	Et_2Zn	*p*-methoxybenzaldehyde	6	92	97	*R*
4	Et_2Zn	*p*-chlorobenzaldehyde	4	96	>99[a]	*R*
5	Et_2Zn	*m*-chlorobenzaldehyde	4	97	98	*R*
6	Et_2Zn	*m*-methoxybenzaldehyde	6	95	99	*R*
7	Et_2Zn	*o*-fluorobenzaldehyde	4	93	94	*R*
8	Et_2Zn	*o*-methoxybenzaldehyde	8	90	94	*R*
9	Et_2Zn	1-naphthaldehyde	6	92	>99	*R*
10	Et_2Zn	2-naphthaldehyde	5	94	99	*R*
11	Et_2Zn	2-furaldehyde	6	90	91	*R*
12	Et_2Zn	hexanal	40	89	98	*R*
13	Et_2Zn	heptanal	24	86	98	*R*
14	Et_2Zn	nonyl aldehyde	45	91	98	*R*
15	Et_2Zn	cyclohexanecarboxaldehyde	40	90	98	*R*
16	Et_2Zn	3-isovaleraldehyde	30	73	98	*R*
17	Et_2Zn	cinnamaldehyde	24	91	92	*R*
18	Et_2Zn	2-methylcinnamaldehyde	27	86	98	*R*
19	Et_2Zn	2-butenal	18	66	91[b]	*R*
20	Et_2Zn	3-methyl-2-butenal	40	62	93[b,c]	*R*
21	Et_2Zn	*trans*-2-methyl-2-butenal	18	64	97	*R*
22	Et_2Zn	2-butyl-2-propenal	18	90	98	*R*
23	Et_2Zn	phenylpropargyl aldehyde	15	90	93[d]	*R*
24	Me_2Zn	benzaldehyde	96	90	90	*R*
25	Me_2Zn	2-naphthaldehyde	96	86	92	*R*
26	Me_2Zn	octyl aldehyde	165	62	88	*R*

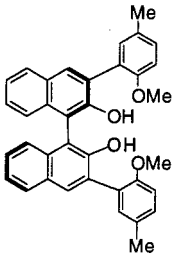
[a] All the reactions were carried out at 0 °C in toluene in the presence of 5 mol % of (*R*)-**352** unless otherwise indicated. [b] Et_2O was used as the solvent. [c] A 0.3 equiv amount of catalyst was used at −40 °C. [d] A 0.2 equiv amount of catalyst was used. The reaction was carried out in THF at −10 °C and the aldehyde was distilled before use.

352 is the most generally enantioselective catalyst for the diethylzinc addition to aldehydes, especially to α,β-unsaturated aldehydes. Compound (*R*)-**352** also catalyzed the dimethylzinc addition to aldehydes with high enantioselectivity (88−92% ee, entries 24−26, Table 78)[159] but with a much lower rate than the reaction with diethylzinc. Ligand (*R*)-**353** was also prepared, which catalyzed the diethylzinc addition to benzaldehyde with 98% ee at room temperature.



(*R*)-**352**

R = $^{n}C_6H_{13}$



(*R*)-**353**

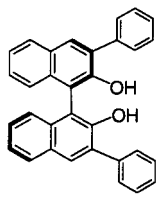
Mikami and co-workers developed a combinatorial method for catalyst screening by coupling nonchiral stationary phase HPLC with CD detection.[160] Using this method, they discovered that a 1:1 mixture of (*R*)-**354** and **355** catalyzed the diethylzinc addition to benzaldehyde with up to 99% ee (entry 1, Table 79). Compound (*R*)-**354** alone was not effective for the

Table 79. Diethylzinc Additions to Aldehydes Catalyzed by (*R*)-354 and 355[a]

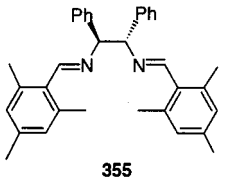
entry	aldehyde	yield (%)	ee (%)	config
1	benzaldehyde	100	99	*S*
2	*p*-methoxybenzaldehyde	100	99	
3	*m*-methoxybenzaldehyde	100	96	
4	*p*-chlorobenzaldehyde	99	99	*S*
5	*p*-tertiarybutylbenzaldehyde	100	99	
6	2-naphthaldehyde	100	94	*S*
7	1-naphthaldehyde	93	92	*S*

[a] All the reactions were carried out at −78 °C for 4 h and −20 °C for 1 h in hexane in the presence of 10 mol % of (*S*)-**354** and **355**.

reaction. The (*R*)-**354**+**355** catalyst system also showed high enantioselectivity for the reaction of other aromatic aldehydes (92−99% ee, Table 79).

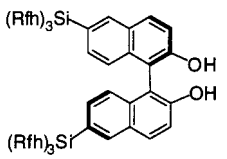


(*R*)-**354**



355

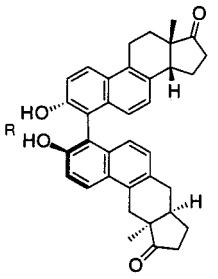
The BINOL ligand (*R*)-**356** containing 6,6′-fluorinated alkyl substituents was synthesized by Curran and co-workers for an organic (toluene) and fluorous (FC-72) biphasic catalysis.[161] Because the partition coefficient of the titanium complex of (*R*)-**356** in FC-72 was much higher than that in toluene (49:1), the complex was easily recovered from the reaction mixture. The titanium complex, prepared from the reaction of (*R*)-**356** with Ti(O^{i}Pr)$_4$, was used to catalyze the reaction of benzaldehyde with diethylzinc, which showed 83% ee for the first run. The reused titanium complex showed higher than 80% ee, even at the fifth-run reaction.



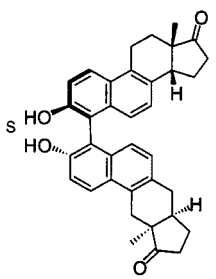
(*R*)-**356**

Rfh = -$CH_2CH_2C_6F_{13}$

The use of the steroid-derived BINOL ligands **357**−**359** in the asymmetric organozinc addition was studied by Dimitrov and co-workers.[162a] They found that these ligands in the presence of excess Ti(O^{i}Pr)$_4$ catalyzed the diethylzinc addition to aromatic aldehydes in toluene at −20 °C with 49−86% ee. Ligand **359** containing no carbonyl group gave lower enantioselectivity than **357** and **358**. Chan and coworkers prepared a quinoline-derived BINOL which catalyzed the diethylzinc addition to aromatic aldehydes in the presence of Ti(O^{i}Pr)$_4$ with up to 89% ee.[162b]



357



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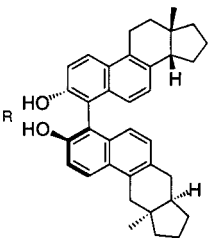
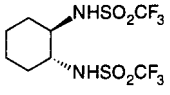


359

6. Dialkylzinc Additions to Aldehydes and Ketones Catalyzed by Titanium Sulfonamide and Phosphoramide Complexes

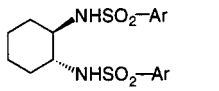
Extensive studies on the use of the C_2-symmetric bistriflamide **360** in the catalytic asymmetric organozinc addition have been conducted since the original work of Ohno and co-workers.[163] In the presence of titanium complexes such as Ti(O^{i}Pr)$_4$, **360** can catalyze the reaction of a variety of alkylzincs as well as functionalized alkylzincs with many aldehydes with excellent enantioselectivity as demonstrated by Ohno, Knochel, and others. Since the work on **360** has been summarized in two reviews by Knochel et al.,[163d,e] it will not be discussed here.



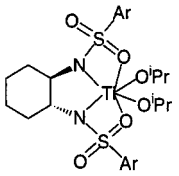
360

Walsh and co-workers prepared the titanium complexes of ligands **361** by reacting them with Ti(NMe)$_2$(O^{i}Pr)$_2$.[164] No reaction was observed when **361a** was treated with 5 equiv of Ti(O^{i}Pr)$_4$. The X-ray struc-

tures of the titanium complexes **362a** and **362d** were solved. It was shown that the two sulfonyl groups of the ligand also coordinated to the titanium center through the oxygen atoms to form a hexacoordinated complex. Both the isolated titanium complexes and the mixture of **361** + $Ti(O^iPr)_4$ catalyzed the diethylzinc addition to benzaldehydes with similar enantioselectivity (up to 97% ee). Ligands **361** first reacted with diethylzinc, which then reacted with $Ti(O^iPr)_4$ to generate the catalytically active titanium sulfonamide complexes.

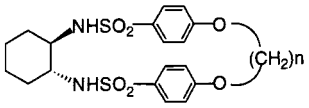


361a: Ar = p-MePh
361b: Ar = 1-naphthyl
361c: Ar = 2,5-Me_2Ph
361d: Ar = 2,4,6-Me_3Ph

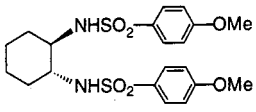


362a: Ar = p-MePh
362b: Ar = 1-naphthyl
362c: Ar = 2,5-Me_2Ph
362d: Ar = 2,4,6-Me_3Ph

The enantioselectivity of **361a** was compared with that of **361d** for the diethylzinc addition to benzaldehyde in the presence of $Ti(O^iPr)_4$.[165] Although **361a** gave (*S*)-1-phenylpropanol with 97% ee, the more bulky aryl-substituted ligand **361d** gave only 3% ee. This dramatic difference in enantioselectivity indicates that the catalytic sites for the titanium complexes of **361a** and **361d** should have very different steric environments. To probe the relationship between the catalyst conformation and the enantioselectivity, Walsh and co-workers prepared ligands **363a**−**f** containing a cyclic disulfonamide structure with various ring sizes. They found that the small ring ligand **363a** showed 10% ee for the diethylzinc addition to benzaldehyde, but the large ring ligand **363f** gave 89% ee. Thus, as the ring became larger, the ligands behaved more like the acyclic ligand **364** which gave 98% ee for the reaction.

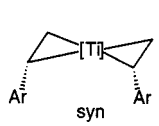


363a: n = 6 **363d**: n = 12
363b: n = 9 **363e**: n = 18
363c: n = 10 **363f**: n = 22



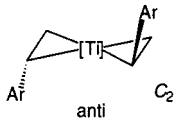
364

A seven-coordinated titanium complex was proposed as the intermediate for the reaction catalyzed by the sulfonamide ligands in combination with $Ti(O^iPr)_4$. That is, the titanium center is bonded to the bis(sulfonamide) (4), two alkoxide groups (2), and the aldehyde carbonyl (1). In this intermediate, the small ring ligand such as **363a** might adopt a syn conformation (**365**) where the two aryl groups are on the same side of the coordination plane of the titanium center. This is not a favorable conformation for the asymmetric induction because there are two different coordination faces, the top and bottom faces of **365**, for the alkyl addition to take place. These two sterically inequivalent faces led to the low enantioselectivity of **363a**. However, for the large ring ligand **363f** and the acyclic ligands **361a** and **364**, their diaryl groups might adopt an anti conformation (**366**) with respect to the titanium center. This is a more favorable C_2-symmetric structure for the asymmetric catalysis, leading to the observed high enantioselectivity. The low enantioselectivity of **361d** may also be attributed to a possible syn conformation in its titanium complex.



syn

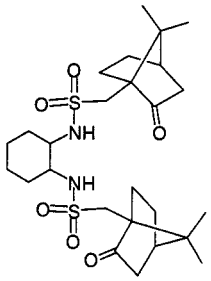
365



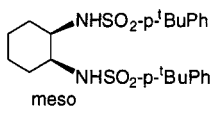
anti

366

In a related study, Balsells and Walsh found that when technical-grade 1,2-diaminocyclohexane, containing a mixture of racemic trans and meso cis isomers, was bound to (1*S*)-(+)-10-camphorsulfonyl groups, the resulting sulfonamide **367** catalyzed the diethylzinc addition to benzaldehyde in the presence of $Ti(O^iPr)_4$ with good enantioselectivity (80% ee).[166] This remarkable chiral induction was explained by a diastereoselective self-inhibiting mechanism of the titanium complex of **367**. That is, there was a positive nonlinear effect due to an intramolecular inhibition involving the coordination of the camphor carbonyl group to the titanium center. The less effective diastereomeric catalysts formed more stable carbonyl-coordinated complexes and allowed the more effective catalyst to control the reaction process. They also studied the use of achiral sulfonamide titanium complexes in the presence of a chiral alkoxy group to catalyze the reaction of diethylzinc with *p*-methylbenzaldehyde.[167] The meso compound **368** in the presence of chiral titanium alkoxide **369** was found to catalyze the reaction to give (*R*)-1-(*p*-methylphenyl)propanol with 84% ee. In this process, the titanium complex of **368** should exist in two enantiomeric conformations **370** and **371**. The chiral alkoxy ligands made these two conformations diastereomeric, thus energetically inequivalent and also different in catalytic efficiency. One of the two conformations might have controlled the catalytic process, leading to the observed high enantioselectivity.

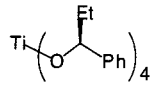


367
a mixture of stereoisomers

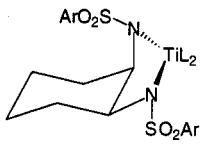


meso

368



369



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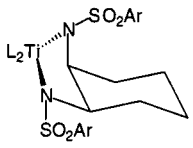


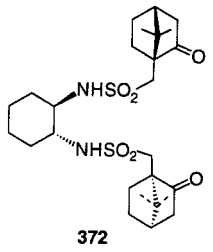
371

The titanium complexes of the optically pure chiral disulfonamides **372**[168] and **373a**−**c**[169] showed very good enantioselectivity for the reaction of diethylzinc with aldehydes. Hwang and Uang found that in the presence of 20 mol % of **372** and 1.4 equiv of $Ti(O^iPr)_4$, the enantioselectivity was in the range of 59−90% ee (Table 80).[168] The titanium complexes of **373a**−**c** were found by Paquette and Zhou to have much higher enantioselectivity probably because of their more rigid bidentate structure.[169] In the presence of 1 mol % of **373a**−**c** and 0.6−1.2 equiv of $Ti(O^iPr)_4$, the reaction of diethylzinc with aromatic and aliphatic aldehydes proceeded with 81−98% ee (Table 81). Lower enantioselectivity was observed for the reaction of cinnamaldehyde (72% ee, entries 9 and 10, Table 81).

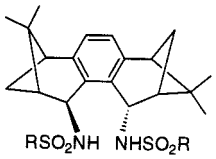
Table 80. Diethylzinc Additions to Aldehydes Catalyzed by 372[a]

entry	aldehyde	*t* (h)	yield (%)[a]	ee (%)	config
1	benzaldehyde	12	99	81	*S*
2	*p*-methoxybenzaldehyde	14	91	87	*S*
3	*p*-chlorobenzaldehyde	12	95	77	*S*
4	*o*-methoxybenzaldehyde	16	95	59	*S*
5	2-naphthaldehyde	14	99	90	*S*
6	cinnamaldehyde	12	93	88	*S*
7	3-phenylpropionaldehyde	12	94	76	*S*

[a] The reactions were carried out in hexane at −20 °C using (20 mol % of **372** and 1.4 equiv $Ti(O^iPr)_4$.

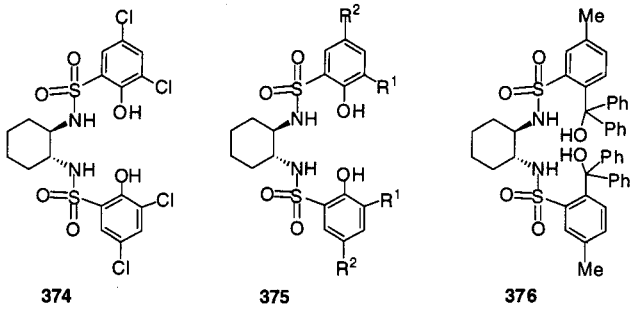


372



373a: R = Me
373b: R = p-Me-C_6H_4
373c: R = CF_3

The sulfonamide ligand **374** containing phenol functions was prepared by Zhang and co-workers.[170] In the presence of 7 equiv of $Ti(O^iPr)_4$ and 20 mol % of **374** at −23 °C in hexane, diethylzinc additions to various aldehydes were investigated. The reaction of certain aromatic aldehydes, α,β-unsaturated aldehydes, and cyclohexanecarboxaldehyde showed up to 99% ee (Table 82). However, the enantioselectivity was quite low for substrates such as crotonaldehyde and valeraldehyde (22% and 11% ee, entries 21 and 27, Table 82). ^1H NMR spectroscopic analysis indicated that a monomeric titanate species was produced during the catalytic process. Zhang, Walsh, and co-workers prepared a series of sulfonamide ligands, **375**, for the diethylzinc addition to benzaldehyde in the presence of $Ti(O^iPr)_4$.[171] They found that ligands with substituents $R^1 = R^2 =$ F, Cl, or Br catalyzed the reaction with 91%, 99%, and 92% ee, respectively. Other ligands gave less than 75% ee. Compound **376** catalyzed the diethylzinc addition to benzaldehyde with 92% ee in the presence of 1.2 equiv of $Ti(O^iPr)_4$.[172]



374 **375** **376**

R^1, R^2: F, Cl, Br, Me, Et, ^{i}Pr, p-BrPh

Ligands **360**, **374**, and **377** in the presence of $Ti(O^iPr)_4$ were used by Takemoto et al. to catalyze the reaction of dimethylzinc with the meso (diene)Fe(CO_3) complex **69** to generate **70c** (see Scheme 8).[54] The enantioselectivity of **360** (96% ee) was much higher than that of **374** (87% ee) and **371** (54% ee). Yus and co-workers studied the camphordisulfonamides such as **378** for the reaction of diethylzinc with benzaldehyde.[173] This compound combined with $Ti(O^iPr)_4$ catalyzed the reaction with 64% ee (entry 1, Table 83). The endo isomer **379** gave only 12% ee for the reaction. In the presence of $Ti(O^iPr)_4$, **378** showed

Table 81. Diethylzinc Additions to Aldehydes Catalyzed by 373a−c[a]

entry	aldehyde	ligand	$Ti(O^iPr)_4$ (equiv)	yield (%)[a]	ee (%)	config
1	benzaldehyde	**373a**	1.2	93	98	*R*
2	benzaldehyde	**373b**	1.2	93	89	*R*
3	benzaldehyde	**373c**	1.2	90	95	*R*
4	*p*-fluorobenzaldehyde	**373a**	1.2	97	81	*R*
5	*p*-fluorobenzaldehyde	**373b**	1.2	83	81	*R*
6	*p*-fluorobenzaldehyde	**373c**	1.2	83	86	*R*
7	hexanal	**373a**	0.6	87	98	*R*
8	hexanal	**373b**	0.6	77	92	*R*
9	cinnamaldehyde	**373a**	0.6	81	72	*R*
10	cinnamaldehyde	**373b**	0.6	90	72	*R*
11	3-phenylpropionaldehyde	**373a**	0.6	86	97	*R*
12	3-phenylpropionaldehyde	**373b**	0.6	74	96	*R*
13	cyclohexanecarboxaldehyde	**373a**	1.2	65	96	*R*
14	cyclohexanecarboxaldehyde	**373b**	1.2	64	88	*R*
15	(*S*)-(−)-perillaldehyde	**373a**	1.2	75	82 (de)	
16	(*S*)-(−)-perillaldehyde	**373b**	1.2	83	81 (de)	

[a] The reactions were carried out in toluene at −40 °C over 16 h in the presence of 1 mol % of the ligands.

Table 82. Diethylzinc Additions to Aldehydes Catalyzed by 374 in the Presence of $Ti(O^iPr)_4$[a]

entry	aldehyde	mol %of **374**	yield (%)	ee (%)	config
1	benzaldehyde	20	99	99	*S*
2	benzaldehyde	10	98	99	*S*
3	*o*-methylbenzaldehyde	20	87	97	*S*
4	*p*-methylbenzaldehyde	20	93	93	*S*
5	*o*-methoxybenzaldehyde	20	100	75	*S*
6	*o*-methoxybenzaldehyde	10	67	42	*S*
7	*p*-methoxybenzaldehyde	20	80	95	*S*
8	*p*-methoxybenzaldehyde	10	61	30	*S*
9	*o*-chlorobenzaldehyde	20	100	83	*S*
10	*o*-chlorobenzaldehyde	10	83	84	*S*
11	1-naphthaldehyde	20	99	98	*S*
12	2-methoxy-1-naphthaldehyde	20	60	3	*R*
13	2-naphthaldehyde	20	100	95	*S*
14	2-furaldehyde	20	67	90	*S*
15	2-methylpropenal	20	84	95	*S*
16	2-ethylpropenal	20	99	94	*S*
17	2-*tert*-butylpropenal	20	99	97	*S*
18	2-methyl-3-phenyl-2-propenal	20	95	96	*S*
19	4-(2-propenyl)−1-cyclohexenecarboxaldehyde	20	100	89	*S*
20	*trans*-2-methyl-2-butenal	20	73	57	*S*
21	crotonaldehyde	20	69	22	*S*
22	3-methyl-2-butenal	20	75	2	*S*
23	cinnamaldehyde	20	100	75	*S*
24	cyclohexanecarboxaldehyde	20	69	95	*S*
25	phenylacetaldehyde	20	81	51	*S*
26	trimethylacetaldehyde	20	81	51	*S*
27	valeraldehyde	20	96	11	*S*

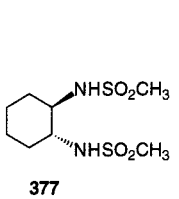
[a] The reactions were carried out in hexane at −23 °C over 4 h in the presence of 1.4 equiv $Ti(O^iPr)_4$.

Table 83. Diethylzinc Additions to Aldehydes Catalyzed by 378 in the Presence of $Ti(O^iPr)_4$[a]

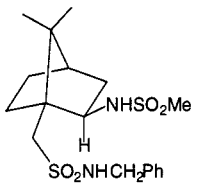
entry	aldehyde	ee (%)
1	benzaldehyde	64
2	*p*-chlorobenzaldehyde	44
3	*p*-methoxybenzaldehyde	20
4	heptanal	96
5	3-phenylpropionaldehyde	94
6	cyclohexanecarboxaldehyde	92
7	crotonaldehyde	12
8	cinnamaldehyde	14
9	phenylpropargylaldehyde	38

[a] The reactions were carried out in the presence of 20 mol % of **378**, 1.3 equiv of $Ti(O^iPr)_4$ at −20 °C over 2 h in over 95% yield.

much higher enantioselectivity for aliphatic aldehydes (92−96% ee, entries 4−6, Table 83) than for aromatic aldehydes and α,β-unsaturated aldehydes.



377



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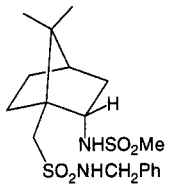
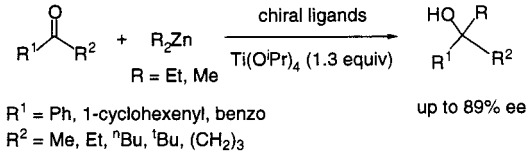


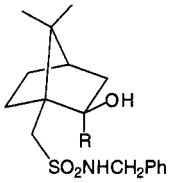
379

Using the camphorsulfonamide alcohols such as **380a**, **381,** and **382**, Ramón and Yus achieved the first catalytic dialkylzinc addition to ketones (Scheme 13).[174] These reactions generated chiral tertiary alcohols with up to 89% ee (Table 84). The sterically bulkier **381** showed a faster reaction rate than **380a**.

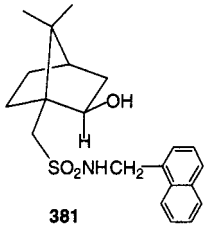
Scheme 13. Catalytic Asymmetric Dialkylzinc Additions to Ketones



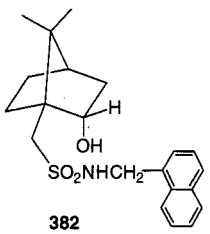
Addition of CaH_2 improved the enantioselectivity. They also found that **380a,b** in the presence of $Ti(O^iPr)_4$ and various additives catalyzed the diethylzinc addition to benzaldehyde with ≤72% ee.[175]



380a: R = H
380b: R = Me

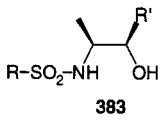


381



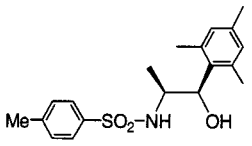
382

Katsuki and co-workers prepared a series of sulfonamide alcohols **383**.[176] Although these ligands could not directly catalyze the reaction of diethylzinc with benzaldehyde as tested with **383a**, when treated with excess $Ti(O^iPr)_4$, they catalyzed the reaction of diethylzinc with benzaldehyde with 6−84% ee in toluene at 0 °C. Ligands **384a,b** catalyzed the reaction with 81% and 83% ee, respectively, under the same conditions. Ligand **385** showed no enantioselectivity at all, while **386** gave only 34% ee. When the solvent was changed from toluene to CH_2Cl_2, the enantioselectivity of **384a,b** was greatly improved. As shown in Table 85, **384b** catalyzed the reaction of diethylzinc with a few aldehydes in the presence of $Ti(O^iPr)_4$ with 90−97% ee. In these reactions, CaH_2 was added to increase the yield of the alcohol products, which, however, did not effect the enantioselectivity.

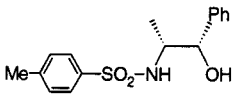


383

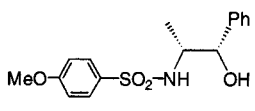
R = p-MePh, Me, CF_3, C_6F_5, p-MeOPh, 2,4,6-trimethylphenyl
R' = H, 2,4,6-trimethylphenyl



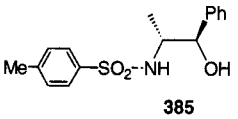
383a



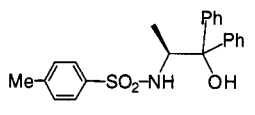
384a



384b



385



386

In contrast to Katsuki's result above, Cho and Chun found that the sulfonamide alcohols **387** were able to catalyze the diethylzinc addition to benzaldehyde with good yield in most cases without using $Ti(O^iPr)_4$.[177] It is not clear why there is such a big

Table 84. Diethylzinc Additions to Ketones Catalyzed by 380a, 381, and 382 in the Presence of Ti(O^{i}Pr)$_4$[a]

entry	R_2Zn	ligand	ketone	T (°C)	t (d)	yield (%)	ee (%)	config
1	Et_2Zn	**380a**	PhCOMe	25	2	56	77	*S*
2	Et_2Zn	**380a**	PhCOMe	60	0.1	58	72	*S*
3	Et_2Zn	**380a**	PhCOMe	4	5	60	84	*S*
4	Et_2Zn	**380a**	PhCOMe	−15	12	11	82	*S*
5	Et_2Zn	**380a**[c]	PhCOMe	25	1	89	80	*S*
6	Et_2Zn	**381**	PhCOMe	4	4	85	82	*S*
7[b]	Et_2Zn	**381**	PhCOMe	4	4	71	86	*S*
8[b]	Et_2Zn	**382**	PhCOMe	4	4	4	34	
9[b]	Me_2Zn	**381**	PhCOEt	4	14	89	89	*R*
10[b]	Me_2Zn	**381**	PhCO^{n}Bu	4	17	95	83	*R*
11[b]	Et_2Zn	**381**	PhCO^{n}Bu	4	6	78	86	*R*
12[b]	Me_2Zn	**381**	PhCO^{t}Bu	60	2	3	0	
13[b]	Et_2Zn	**381**	α-tetralone	4	14	25	89	
14[b]	Et_2Zn	**381**	*d*	4	6	36	51	

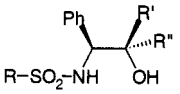
[a] The reactions were carried out in the presence of 20 mol % of the ligands and 1.3 equiv Ti(O^{i}Pr)$_4$ unless indicated otherwise. [b] 40 mol % of CaH_2 was added. [c] A stoichiometric amount of **380a** was used. [d] 1-Cyclohexenylmethyl ketone

Table 85. Diethylzinc Additions to Aldehydes Catalyzed by 384b in the Presence of Ti(O^{i}Pr)$_4$ and CaH_2[a]

entry	aldehyde	yield (%)	ee (%)	config
1	benzaldehyde	99	97	*S*
2	cinnamaldehyde	95	90	*S*
3	*p*-methoxybenzaldehyde	98	94	*S*
4	cyclohexanecarboxaldehyde	77	90	*S*

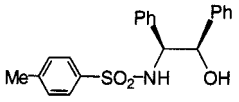
[a] The reactions were carried out in the presence of 20 mol % of **384b**, 1.2 equiv Ti(O^{i}Pr)$_4$ and 0.5 equiv of CaH_2 at 0 °C over 24 h using 1 M hexane solution of diethylzinc.

difference in the catalytic activity between **383** and **387**. Compound **387a** gave up to 83% ee for the reaction. It also showed 10−76% ee for the reaction of other aromatic and aliphatic aldehydes.



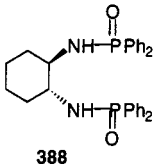
387

R = Me, CF_3, p-MePh, p-MeOPh, 2,4,6-triisopropylphenyl, 2,4-dinitrophenyl
R' = Ph, H; R" = Ph, H

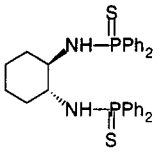


387a

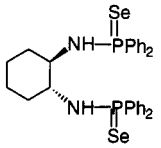
The phosphoramide **388** and the thiophosphoramide **389** were prepared by Shi and Sui.[178a] In the presence of 1.4 equiv of Ti(O^{i}Pr)$_4$, **388** catalyzed the reaction of diethylzinc with aldehydes with up to 83% ee but **389** only gave ≤50% ee. 1,1′-Binaphthyl-2,2′-diamine-derived sulfonamides and phosphoramides in the presence of Ti(O^{i}Pr)$_4$ catalyzed the diethylzinc addition to aldehydes with ≤64% ee.[178b] The diphenylselenophosphoramides **390**−**392** were also studied.[179] Among these ligands, **390** showed the highest enantioselectivity. It catalyzed the diethylzinc addition to benzaldehyde in the presence of Ti(O^{i}Pr)$_4$ with 61% ee.



388



389



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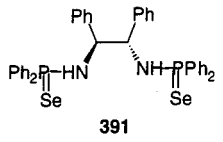
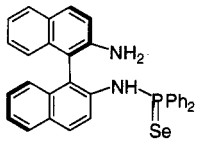
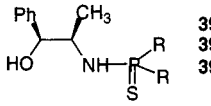


391



(*R*)-**392**

The thiophosphoramidate ligands **393a**−**c** in combination with Ti(O^{i}Pr)$_4$ were used by Soai and coworkers to catalyze the diethylzinc addition to aldehydes.[180] In the presence of 15 mol % of **393a** and 0.8 equiv of Ti(O^{i}Pr)$_4$, the reaction of aromatic aldehydes and α,β-unsaturated aldehydes with diethylzinc produced chiral alcohols with 90−97% ee and good yield (Table 86). The reaction of dimethylzinc with benzaldehyde gave (*S*)-1-phenylethanol with 95% ee and 52% yield (entry 3, Table 86). Compounds **393b,c** gave slightly lower ee's (88% and 74%, respectively) for the reaction of diethylzinc with benzaldehyde (entries 6 and 7, Table 86).



393a: R = OMe
393b: R = OEt
393c: R = Me

Compound **393a** in combination with Ti(O^{i}Pr)$_4$ was used to catalyze the reaction of isophthaldehyde (**15b**) and phthaldehyde (**394**) with diethylzinc (see Scheme 5).[22] In the presence of **393a** (0.3 equiv) and Ti(O^i-

Table 86. Dialkylzinc Additions to Aldehydes Catalyzed by 393a−c[a]

entry	R_2Zn	aldehyde	catalyst (mol %)	T (°C)	t (h)	yield (%)	ee (%)	config
1	Et_2Zn	benzaldehyde	**393a** (15)	−50	2.3	93	95	*S*
2	Et_2Zn	benzaldehyde	**393a** (15)	−30	2.9	80	97	*S*
3	Me_2Zn	benzaldehyde	**393a** (15)	−30 to 0	3.8	52	95	*S*
4	Et_2Zn	*o*-methoxybenzaldehyde	**393a** (15)	−50 to 0	5	82	95	*S*
5	Et_2Zn	cinnamaldehyde	**393a** (15)	−50	2.2	75	90	*S*
6	Et_2Zn	benzaldehyde	**393b** (15)	−35 to −20	1.3	97	88	*S*
7	Et_2Zn	benzaldehyde	**393c** (15)	−35 to −20	3	98	74	*S*

[a] The reactions were carried out in toluene in the presence of 0.8 equiv Ti(O^{i}Pr)$_4$.

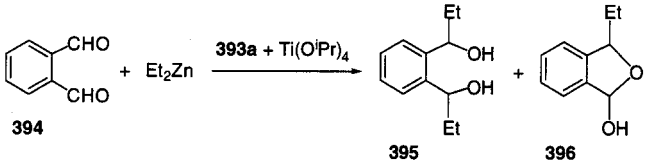
Table 87. Dicyclopropylzinc Additions to Aldehydes in the Presence of 397 and Ti(O^{i}Pr)$_4$[a]

entry	aldehyde	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	2	93.1	96	*R*
2	*p*-methoxybenzaldehyde	3	98.9	97	
3	*p*-chlorobenzaldehyde	2	85.0	91	
4	1-naphthaldehyde	2	88.6	96	
5	cinnamaldehyde	1.5	94.1	64	

[a] The reactions were carried out in toluene at −30 °C in the presence of 1.2 equiv of Ti(O^{i}Pr)$_4$ and 15 mol % of **397**.

Pr)$_4$ (1.6 equiv), isophthaldehyde reacted with diethylzinc at 0 °C in toluene/hexane (1:1) to give the diol **16b** with >99% ee and 94% yield. The DL/meso ratio was 92:8. Under the same conditions, **394** reacted with diethylzinc to give the diol **395** and the hemiacetal **396** (Scheme 14). Compound **395** was obtained

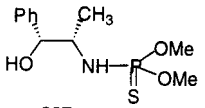
Scheme 14. Diethylzinc Addition to Phthaldehyde Catalyzed by 393a and Ti(O^{i}Pr)$_4$



394 395 396

as the major product with 92% ee and 64% yield. The DL/meso ratio was 9:91 with the meso diol dominating. The hemiacetal **396** was obtained as a minor product in 21% yield.

In the presence of Ti(O^{i}Pr)$_4$, ligand **397**, the enantiomer of **393a**, was used to catalyze the reaction of aldehydes with dicyclopropylzinc.[181] As shown in Table 87, ee's up to 97% were obtained for the dicyclopropylzinc additions to aromatic aldehydes in the presence of 15 mol % of **397** and 1.2 equiv of Ti(O^{i}Pr)$_4$. The enantioselectivity for the addition to cinnamaldehyde was low (64% ee, entry 5, Table 87).



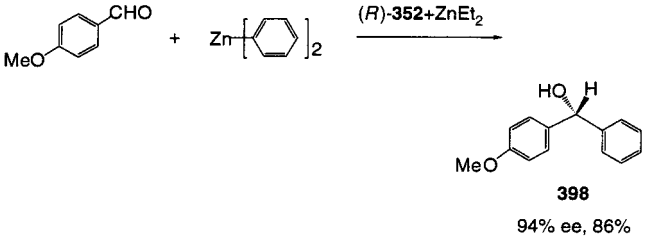
397

7. Aryl-, Vinyl-, and Alkynylzinc Additions to Aldehydes and Ketones

a. Arylzinc Addition

Unlike the dialkylzinc addition which proceeds extremely slowly in the absence of a catalyst, the diphenylzinc addition to aldehydes can take place smoothly even without a catalyst. This background

Scheme 15. Asymmetric Addition of Diphenylzinc to *p*-Methoxybenzaldehyde Catalyzed by (*R*)-352

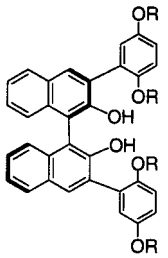


398

94% ee, 86%

reaction makes it more challenging to develop enantioselective catalysts for the arylzinc additions. Only recently, highly enantioselective catalysts for diphenylzinc addition to aldehydes were obtained.

In 1999, Huang and Pu found that the chiral binaphthyl ligand (*R*)-**352**, a highly enantioselective catalyst for dialkylzinc additions,[158,159] was also highly enantioselective for the diphenylzinc addition to aldehydes.[182] For example, the reaction of propionaldehyde with diphenylzinc at 0 °C in toluene in the presence of 10 mol % (*R*)-**352** produced (*S*)-1-phenylpropanol with 87% ee. The diphenylzinc addition to aldehydes are summarized in Table 88. The reaction of diphenylzinc with arylaldehydes allowed the synthesis of chiral diarylcarbinols that were difficult to prepare by asymmetric catalysis. Entry 2 in Table 88 shows that at 0 °C the diphenylzinc addition to *p*-methoxybenzaldehyde can proceed even without a catalyst. Because of the competitive background reaction, a low ee was observed when a 5 mol % of (*R*)-**352** was used (entry 3, Table 88). When a larger amount of (*R*)-**352** was pretreated with diethylzinc, the resulting chiral zinc complex catalyzed the reaction of diphenylzinc with *p*-methoxybenzaldehyde to generate (*R*)-*p*-methoxyphenyl phenyl carbinol (**398**) with up to 93% ee and 84% yield at −30 °C in toluene (entry 5, Table 88) (Scheme 15).



(*R*)-352

R = ^{n}C$_6$H$_{13}$

Table 88. Diphenylzinc Additions to Aldehydes Catalyzed by (*R*)-352[a]

entry	aldehyde (mM)	(*R*)-**352** or + additive (mol %)	solvent	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1[b]	propionaldehyde (100)	10	toluene	0	20	90	87	*S*
2	*p*-methoxybenzaldehyde (50)	0	toluene	0	10	61	0	
3[c]	*p*-methoxybenzaldehyde (50)	5	toluene	0	10	76	54	*R*
4	*p*-methoxybenzaldehyde (50)	5 + 10Et$_2$Zn	toluene	0	10	87	77	*R*
5	*p*-methoxybenzaldehyde (50)	20 + 40Et$_2$Zn	toluene	−30	24	84	93	*R*
6	*p*-chlorobenzaldehyde (50)	20 + 40Et$_2$Zn	Et$_2$O	r.t.	10	70	57	*R*
7	*p*-chlorobenzaldehyde (5)	20 + 40Et$_2$Zn	Et$_2$O	r.t.	10	86	94	*R*
8	2-naphthaldehyde (5)	20 + 40Et$_2$Zn	THF	−10	96	66	87	*R*
9	cinnamaldehyde (5)	20 + 40Et$_2$Zn	CH$_2$Cl$_2$	r.t.	28	98	50	*S*
10	cinnamaldehyde (5)	20 + 80Et$_2$Zn +40MeOH	CH$_2$Cl$_2$	r.t.	22	92	77	*S*
11	cinnamaldehyde (5)	20 + 80Et$_2$Zn + 40MeOH	CH$_2$Cl$_2$	reflux	10	94	83	*S*

[a] 1 equiv of Ph$_2$Zn was used unless indicated otherwise. [b] 1.2 equiv of Ph$_2$Zn was used. [c] 2 equiv of Ph$_2$Zn was used.

Table 89. Reaction of Cinnamaldehyde with Diphenylzinc in the Presence of the Ligands 352 and 399−404[a]

entry	ligand	yield (%)	ee (%)	config
1	(*R*)-**352**	88	50	*S*
2	(*S*)-**399**	90	73	*R*
3	(*S*)-**400**	88	81	*R*
4	(*S*)-**401**	88	70	*R*
5	(*S*)-**402**	92	87	*R*
6	(*S*)-**404**	90	81	*R*

[a] The reaction was carried out under nitrogen at room temperature in CH_2Cl_2 in the presence of 20 mol % of the chiral ligand and 40 mol % of Et_2Zn. The concentration of aldehyde was 5 mM. The reaction was quenched in 5 h.

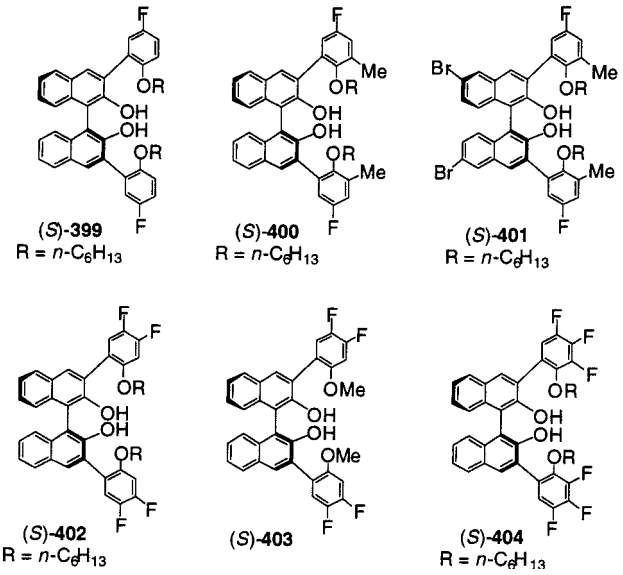
Table 90. Synthesis of Chiral Diarylcarbinols by the Diphenylzinc Addition to Aryl Aldehydes Catalyzed by (*S*)-402[a]

entry	aldehyde	yield (%)	ee (%)	config
1	cinnamaldehyde	92	87	*R*
2	4-chlorobenzaldehyde	92	95	*S*
3	2-methylbenzaldehyde	87	91	*S*
4	2-naphthaldehyde	90	88	*S*
5	3-pyridinecarboxaldehyde	86	80	(+)
6	3-pyridinecarboxaldehyde[b]	90	70	(+)
7	3-pyridinecarboxaldehyde[c]	89	86	(+)

[a] The reaction was carried out under nitrogen at room temperature in CH_2Cl_2 in the presence of 20 mol % of (*S*)-**402** and 40 mol % of Et_2Zn unless otherwise indicated. The concentration of aldehyde was 5 mM. The reaction was quenched in 5 h. [b] (*S*)-**403** was used in place of (*S*)-**402**. [c] Et_3B-pretreated aldehyde was used.

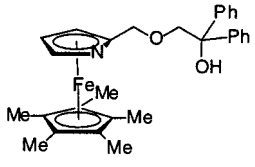
The factors that influence the enantioselectivity of these reactions are summarized as follows. (1) Pretreatment of the chiral ligand (*R*)-**352** with diethylzinc generally increased the enantioselectivity. (2) Reducing the concentration of the substrates in the reaction led to dramatically increased enantioselectivity (entries 6 and 7, Table 88). (3) In the case of the α,β-unsaturated aldehyde, addition of methanol might have modified the structure of the catalyst formed from the reaction of (*R*)-**352** with diethylzinc, leading to a much improved enantioselectivity (entries 10 and 11, Table 88). *Higher* temperature in methylene chloride solution actually led to higher ee for the reaction of diphenylzinc with *trans*-cinnamaldehyde (entry 11, Table 88).

The structure of (*R*)-**352** was modified by introducing multiple electron-withdrawing fluorine and bromine atoms to give (*S*)-**399**−(*S*)-**404**.[183] These ligands were used to catalyze the diphenylzinc addition to cinnamaldehyde. It was found that the reactions proceeded with significantly improved enantioselectivity over (*R*)-**352** at room temperature without using methanol additive (Table 89). In these reactions, each ligand was first treated with 2 equiv of diethylzinc in methylene chloride, and then a 20 mol % amount of the in situ generated zinc complex was used to catalyze the diphenylzinc addition to cinnamaldehyde. As shown in Table 89, the introduction of the electron-withdrawing substituents imparted positive effects on the catalysis. Ligand (*S*)-**402** had the highest enantioselectivity among the ligands tested (87% ee, entry 5, Table 89). The electron-withdrawing groups in this ligand might have increased the Lewis acidity of the corresponding zinc complex and made the background reaction less competitive. As for ligand (*S*)-**404**, though more electron-deficient, its fluorine atoms ortho to the alkoxy groups might perturb the catalyst structure by participation in the coordination to the zinc center with the adjacent alkoxy group, leading to a lower enantioselectivity than (*S*)-**402** (entries 6 and 5, Table 89).



Ligand (*S*)-**402** was used to catalyze the reaction of various aryl aldehydes with diphenylzinc for the synthesis of optically active diarylcarbinols.[183] These results are summarized in Table 90. Unlike (*R*)-**352** which required a longer reaction time, in some cases ≤0 °C and also very different reaction conditions for different substrates in order to achieve high enantioselectivity, (*S*)-**402** catalyzed the reaction of various aryl aldehydes with diphenylzinc at room temperature in methylene chloride in 5 h with high enantioselectivity. For example, the reaction of 2-naphthaldehyde catalyzed by (*R*)-**352** took 4 days at −10 °C with incomplete conversion and 66% isolated yield. However, in the presence of (*S*)-**402**, this reaction was completed in 5 h at room temperature with 90% isolated yield (entry 4, Table 90). When the nitrogen of 3-pyridinecarboxaldehyde was protected with triethylborane, its reaction with diphenylzinc in the presence of (*S*)-**402** gave 86% ee and 89% yield (entry 7, Table 90).

Earlier, Dosa and Fu found that the ferrocene-based ligand **405** catalyzed the diphenylzinc addition to 4-chlorobenzaldehyde but with only 57% ee.[184]



405

Ligands **210** and **213** were used for the dialkylzinc additions to aldehydes.[104] Bolm and Muñiz also reported the use of these ligands for the diphenylzinc addition to aldehydes.[185] In the presence of 5−10 mol

% of **210**, diphenylzinc added to *p*-chlorobenzaldehyde and ferrocenecarboxaldehyde with 90% and >96% ee, respectively (entries 4 and 6, Table 91). However, for

Table 91. Diphenylzinc Additions to Aldehydes Catalyzed by 210 and 213[a]

entry	aldehyde	catalyst (mol %)	*T* (°C)	*t* (h)	yield (%)	ee (%)	config
1	*p*-chlorobenzaldehyde	**210** (3)	0	12	99	64	*R*
2	*p*-chlorobenzaldehyde	**210** (5)	0	15	99	82	*R*
3	*p*-chlorobenzaldehyde	**210** (10)	0	14	99	88	*R*
4	*p*-chlorobenzaldehyde	**210** (10)	−20	11	92	90	*R*
5	*p*-chlorobenzaldehyde	**213** (10)	0	13	99	88	*R*
6	ferrocenecarboxaldehyde	**210** (5)	0	11	89	>96	*R*
7	*o*-bromobenzaldehyde	**210** (5)	0	14	98	31	*R*
8	1-naphthaldehyde	**210** (5)	0	14	99	28	*R*
9	acetaldehyde	**210** (5)	0	15	94	75	*S*
10	3-phenylpropionaldehyde	**210** (5)	0	10	91	50	*S*
11	trimethylacetaldehyde	**210** (5)	0	16	99	56	*S*
12	2-pyridinecarboxaldehyde	**210** (5)	0	12	98	3	*R*

[a] The reactions were carried out in toluene.

the reaction of other aromatic or aliphatic aldehydes, the enantioselectivity was quite low (3−75% ee, entries 7−12, Table 91).

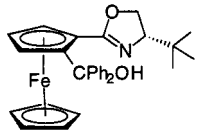
Later, Bolm et al. reported that with the use of a 1:2 mixture of diphenylzinc and diethylzinc, the enantioselectivity of ligand **210** for the diphenylzinc addition to *p*-chlorobenzaldehyde was significantly increased to 99% ee (entry 2, Table 92).[186] Using a

Table 92. Diphenylzinc Additions to Aldehydes Catalyzed by 210 with the Addition of Diethylzinc[a]

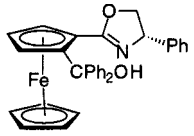
entry	aldehyde	yield (%)	ee (%)	config
1	*p*-chlorobenzaldehyde	86	97	*R*
2	*p*-chlorobenzaldehyde	94	99[b]	*R*
3	*p*-methoxybenzaldehyde	82	98	*R*
4	*m*-methoxybenzaldehyde	99	96	*R*
5	*p*-methylbenzaldehyde	86	98	*R*
6	*p*-phenylbenzaldehyde	98	97	*R*
7	2-naphthaldehyde	70	96	*R*
8	*o*-bromobenzaldehyde	64	91	*R*
9	2-furaldehyde	99	95	*R*
10	cinnamaldehyde	97	90	*S*
11	trimethylacetaldehyde	68	94	*S*
12	phenylacetaldehydehyde	82	83	*S*
13	isobutyraldehyde	75	91	*S*

[a] The reactions were carried out at 10 °C in toluene in the presence of 10 mol % of **210** and a mixture of Ph_2Zn (0.65 equiv) and Et_2Zn (1.3 equiv) unless indicated otherwise. [b] At 0 °C. 40 mol % of **210** was used.

similar procedure, **210** catalyzed the reaction of diphenylzinc with a range of aldehydes with very high enantioselectivity. This improved enantioselectivity with the addition of diethylzinc for the diphenylzinc addition to aldehydes is similar to what was observed earlier by Pu in the use of (*R*)-**352** and (*S*)-**402**.[182,183]



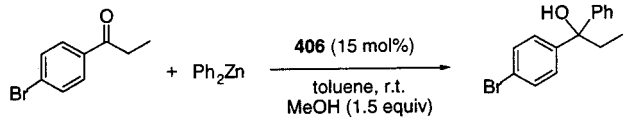
210



213

In 1998, Dosa and Fu discovered that diphenylzinc could also add to ketones to generate chiral tertiary alcohols in the presence of (+)-DAIB (**406**), the enantiomer of ligand **1** (Scheme 16).[184] In this reac-

Scheme 16. Catalytic Asymmetric Diphenylzinc Addition to Ketone



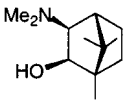
tion, the addition of excess methanol resulted in enhanced enantioselectivity as well as improved product yield. Up to 91% ee for the diphenylzinc addition to ketones was obtained by using 15 mol % of **406** as the catalyst (entry 4, Table 93). A

Table 93. Diphenylzinc Additions to Ketones Catalyzed by 406[a]

entry	ketones	yield (%)	ee (%)
1	2′-acetonaphthone[b]	26	64 (+)
2	2′-acetonaphthone	58	72 (+)
3	4′-bromoacetophenone	53	80 (−)
4	3′-bromoacetophenone	91	91 (−)
5	ethyl 2-naphthyl ketone	79	86 (−)
6	ethyl 4′-bromophenyl ketone	83	90 (−)
7	3-methylbutanone	63	60 (+)
8	methyl cyclohexyl ketone	76	75 (+)
9	2-pentanone[c]	74	36

[a] The reactions were carried out in toluene at room temperature in the presence of 15 mol % of **406** and 1.5 equiv of methanol over 48 h unless indicated otherwise. [b] Without methanol. [c] At 0 °C.

nonlinear relationship between the enantiopurity of the catalyst and that of the product was observed. This enantioselective catalytic diphenylzinc addition to ketones allowed the synthesis of chiral tertiary alcohols that were difficult to produce by asymmetric catalysis.



406
(+)-DAIB

b. Vinylzinc Addition

Vinylzinc addition can afford the synthetically very useful allyl alcohols. Generally, two methods were used to generate vinylzinc reagents, one involving the reaction of $ZnCl_2$ with vinyl Grignard reagents and another involving the reaction of alkyne with borane followed by boron−zinc exchange. Earlier, Oppolzer and Radinov used a catalytic amount of **407** or a stoichiometric amount of the lithium salt of **408** to carry out the reaction of either divinylzinc or vinylzinc bromide to aldehydes with up to 97% ee.[187] In these reactions, the divinylzinc was prepared from the reaction of vinyl Grignard reagent with $ZnCl_2$ and the alkenylzinc bromide was made from the reaction of alkenyllithium with $ZnBr_2$. In 1992, the same authors reported the preparation of alkenylzinc reagents for the asymmetric addition to aldehydes

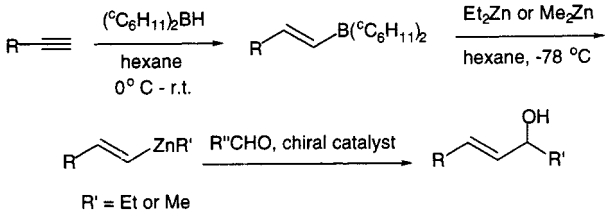
Table 94. Vinylzinc Additions to Aldehydes Catalyzed by 1[a]

entry	R of alkyne	R_2Zn	aldehyde	yield (%)	ee (%)
1	Bu	Me_2Zn	benzaldehyde	87	96
2	C_6H_{13}	Et_2Zn	benzaldehyde	77	92
3	C_6H_{13}	Me_2Zn	benzaldehyde	85	94
4	C_6H_{13}	Et_2Zn	propionaldehyde	91	84
5[b]	C_6H_{13}	Et_2Zn	propionaldehyde	86	86
6	C_6H_{13}	Et_2Zn	valeraldehyde	86	85
7	C_6H_{13}	Me_2Zn	valeraldehyde	85	80
8	C_6H_{13}	Et_2Zn	isovaleraldehyde	78	85
9	C_6H_{13}	Et_2Zn	cyclohexanecarboxaldehyde	70	91
10	C_6H_{13}	Et_2Zn	trimethylacetaldehyde	28	73
11	$^cC_6H_{11}$	Me_2Zn	benzaldehyde	83	95
12	$^cC_6H_{11}$	Et_2Zn	cyclohexanecarboxaldehyde	67	80
13	tBu	Me_2Zn	benzaldehyde	90	98
14	tBu	Et_2Zn	valeraldehyde	94	79
15	tBu	Me_2Zn	valeraldehyde	95	74

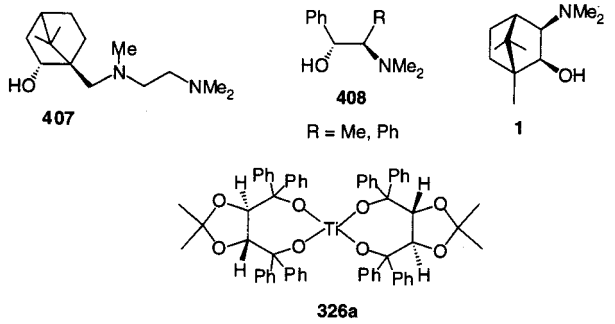
[a] The additions to aldehydes were carried out in hexane at 0 °C in the presence of 1 mol % of **1** unless indicated otherwise. Me_2Zn was a 2 M toluene solution. [b] 5 mol % of **1** was used.

by reaction of alkyne with borane followed by boron−zinc exchange (Scheme 17).[188] By using the amino

Scheme 17. Hydoboration, B−Zn Exchange, and Asymmetric Addition to Aldehydes



alcohol **1**, good enantioselectivity was achieved for certain aromatic and aliphatic aldehydes (73−98% ee, Table 94). The titanium TADDOLate **326a** was used by Seebach et al. to catalyze the reaction of divinylzinc with benzaldehyde to give 84% ee.[189]



Soai et al. used the amino alcohol (*S*)-**65** to catalyze the reaction of the vinylethylzinc **409** with cinnamaldehyde with 77% ee.[190] The zinc reagent was prepared from the boron−zinc exchange reaction. Soai also prepared diisopropenylzinc by reaction of isopropenylbromide with Li and $ZnBr_2$ in diethyl ether under ultrasonic conditions at 0 °C followed by extraction and sublimation.[191] The amino alcohols (*S*)-**65** and **410a**−**c** (5−20 mol %) were used to catalyze the reaction of diisopropenylzinc (3 equiv) with benzaldehydes to generate the allyl alcohol **411** with 80−90% ee (Scheme 18). Ligands (*S*)-**65** and **410a** were found to be the best among these compounds and were used to catalyze the reaction

Scheme 18. Diisopropenylzinc Additions to Benzaldehyde Catalyzed by Amino Alcohols

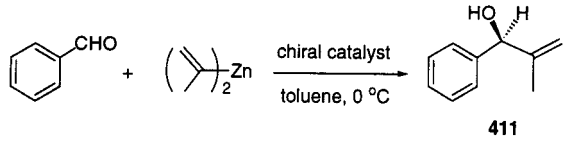
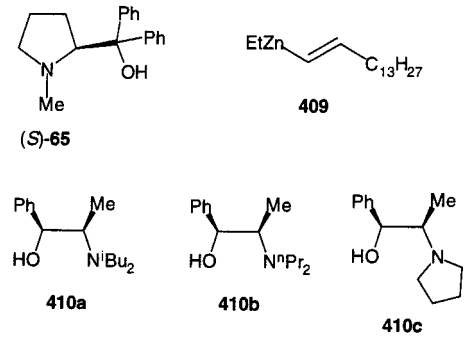


Table 95. Diisopropenylzinc Additions to Benzaldehyde Catalyzed by (*S*)-65 and 410a[a]

entry	aldehyde	catalyst	*t* (h)	yield (%)	ee (%)	config
1	benzaldehyde	(*S*)-**65**	2	91	89	*S*
2[b]	benzaldehyde	**410a**	2	73	88	*S*
3[c]	*p*-chlorobenzaldehyde	(*S*)-**65**	3	67	87	*S*
4	*p*-chlorobenzaldehyde	**410a**	2	84	89	*S*
5	*p*-methoxybenzaldehyde	(*S*)-**65**	3	50	82	*S*
6	*p*-methoxybenzaldehyde	**410a**	2	68	92	*S*
7	1-naphthaldehyde	**410a**	2	85	79	*S*
8	cinnamaldehyde	**410a**	2	75	73	*S*
9	3-phenylpropionaldehyde	**410a**	2	81	73	*S*

[a] The reactions were carried out in toluene at 0 °C in the presence of 5 mol % of the catalysts and 3 equiv of diisopropenylzinc unless indicated otherwise. [b] The reaction was performed at −10 °C. [c] Hexane was used as the solvent.

of other aldehydes with 73−92% ee (Table 95). Bis-(1,2-dimethyl-1-propenyl)zinc was also prepared and reacted with benzaldehyde in the presence of **410a** to give the corresponding allylic alcohol product with 69% ee.



Wipf and Xu developed a method to prepare vinylzinc reagents by treatment of terminal alkynes

Table 96. Vinylzinc Additions to Aldehydes Catalyzed by 412[a]

entry	R of alkyne	aldehyde	yield (%)	ee (%)	config
1	*n*-C_4H_9	*p*-chlorobenzaldehyde	83	97	*S*
2[b]	*n*-C_4H_9	*p*-trifluoromethylbenzaldehyde	71	93	*S*
3[c]	*n*-C_4H_9	*p*-methoxybenzaldehyde	75	63	*S*
4	*n*-C_4H_9	*m*-methoxybenzaldehyde	79	99	*S*
5	*n*-C_4H_9	cyclohexanecarboxaldehyde	63	74	*R*
6	*n*-C_4H_9	3-phenylpropionaldehyde	71	64	*R*
7	*n*-C_4H_9	benzaldehyde	80	95	*S*
8	$(CH_3)_3C$	benzaldehyde	73	83	*S*
9	*b*	benzaldehyde	66	99	*S*
10	TIPSOC(O)CH_2CH_2[c]	benzaldehyde	67	92	*S*

[a] The additions to aldehydes were carried out in toluene at −30 °C in the presence of 10 mol % of **412**. [b] An internal alkyne, 3-hexyne, was used. [c] TIPS = triisopropylsilyl.

Scheme 20. Alkynylzincs and Their Catalytic Additions to Aldehydes

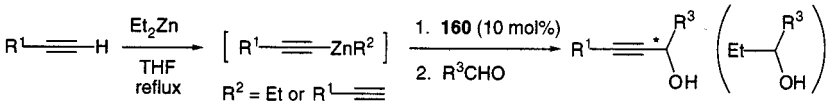


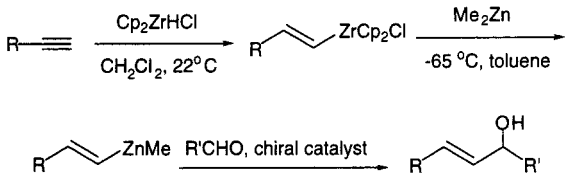
Table 97. Alkynylzinc Additions to Aldehydes Catalyzed by 160a−c[a]

entry	R^1	R^2	R^3	catalyst	*T* (°C)	*t* (h)	yield[b](%)	ee (%)	config
1	Ph	Et	Ph	**160a**	r.t.	7	82	66	*R*
2	Ph	PhCC	Ph	**160b**	r.t.	7	88	63	*R*
3	Ph	Et	Ph	**160b**	r.t.	7	93	81	*R*
4	Ph	Et	Ph	**160b**	0	15	64	90	*R*
5	Ph	Et	Ph	**160c**	r.t.	7	87	81	*R*
6	Ph	Et	$^nC_8H_{17}$	**160b**	0	4	65	83	
7	Ph	Et	cyclohexyl	**160b**	0	10	88	91	
8	Ph	Et	^{t}Bu	**160b**	0	10	61	95	
9	$^nC_6H_{13}$	$^nC_6H_{13CC}$	Ph	**160b**	r.t.	18	90	38	
10	$^nC_6H_{13}$	Et	Ph	**160b**	r.t.	2	41(52)	78	
11	$^nC_6H_{13}$	Et	Ph	**160b**	0	24	33(23)	71	
12	$^nC_6H_{13}$	Et	$^nC_8H_{17}$	**160b**	r.t.	1	62(22)	73	
13	$^nC_6H_{13}$	Et	$^nC_8H_{17}$	**160b**	0	17	31(23)	62	
14	$^nC_6H_{13}$	Et	cyclohexyl	**160b**	r.t.	3	79(18)	82	
15	$^nC_6H_{13}$	Et	^{t}Bu	**160b**	r.t.	3	67(b)	87	
16	Ph_3Si	Et	cyclohexyl	**160b**	r.t.	5	55	91	

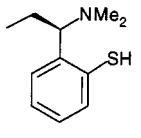
[a] A 10 mol % of the catalysts was used. [b] Yields in the parenthesis were those of the ethylated products. [c] Not isolated because the product was volatile.

with Cp_2ZrHCl followed by exchanging with Me_2Zn (Scheme 19).[192] Later, Wipf and Ribe discovered that

Scheme 19. Hydrozirconation, Zr−Zn Exchange, and Asymmetric Addition to Aldehydes



the vinylzinc reagents underwent highly enantioselective additions (up to 99% ee) to aldehydes in the presence of the amino thiol **412** (Scheme 19) (Table 96).[193] Other amino alcohols or amino thiols were also examined but gave lower enantioselectivity.

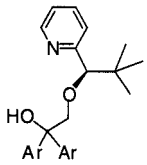


412

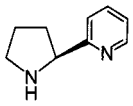
c. Alkynylzinc Addition

Alkynylzinc additions to aldehydes will allow the synthesis of propargyl alcohols that are synthetically very useful. Ishizaki and Hoshino found that ligands **160a−c** were effective for the addition of alkynylzinc reagents to aldehydes.[194] In this process, either a dialkynylzinc or an ethylalkynlzinc was generated from the reaction of a terminal alkyne (1 or 2 equiv) with diethylzinc in refluxing THF solution (Scheme 20). In the presence of 10 mol % of **160b**, addition of bis(2-phenylethynyl)zinc to benzaldehyde at room temperature gave (*R*)-1,3-diphenylpropanol with 63% ee (entry 2, Table 97). Using ethyl(2-phenylethynyl)-zinc at 0 °C gave the product with 90% ee (entry 4, Table 97). Up to 95% ee was achieved for the reaction of ethyl(2-phenylethynyl)zinc with trimethylacetaldehyde (entry 8, Table 97). However, the use of ethyl(1-octynyl)zinc led to a mixture of alcohols generated from both octynyl and ethyl additions (entries 10−15, Table 97). Falorni and co-workers showed that **310** catalyzed the addition of $(^nBuCC)_2Zn$ to benzaldehyde in ether at 20 °C over 15 h to give the corresponding (*S*)-propargyl alcohol with 16%

ee and 87% yield.[142]

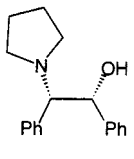


160a: Ar = Ph
160b: Ar = α-naphthyl
160c: Ar = β-naphthyl

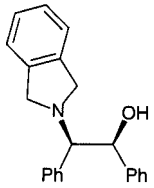


310

Li et al. reported the use of the amino alcohols **413**, **414**, and their derivatives to catalyze the reaction of terminal alkynes with aromatic aldehydes. In the presence of 10 mol % of these ligands and 1.2 equiv of dimethylzinc, the reactions proceeded with up to 85% ee and 65−94% yield at −20 to −30 °C.[195] The authors observed that in the absence of a ligand, there was no reaction between phenylacetylene and dimethylzinc at room temperature. Addition of **413** led to the formation of a zinc acetylide and a zinc−ligand complex. In these reactions, the methyl addition was almost completely suppressed.



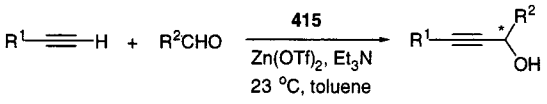
413



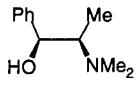
414

Carreira and co-workers used a stoichiometric amount of *N*-methylephedrine **415** and $Zn(OTf)_2$ to carry out the reaction of terminal alkynes with a variety of aromatic or aliphatic aldehydes containing α-substituents.[196,197] Very high enantioselectivity was achieved (92−99% ee) (Scheme 21) (Table 98). This

Scheme 21. Amino Alcohol-Promoted Alkynylzinc Addition to Aldehydes



reaction could even be carried out in air using reagent-grade toluene. The addition of 2-methyl-3-butyn-2-ol to a wide range of aldehydes was observed to show high enantioselectivity.[196b]



415

8. Macromolecules in Organozinc Additions

The use of polymer-based catalysts is very attractive for asymmetric catalysis because it allows easy recovery and reuse of the often quite expensive chiral catalysts.[198] Polymer-based chiral catalysts also make it possible to carry out the asymmetric reactions in a flow system for continuous production. In addition, the site isolation in macromolecules may enhance the catalyst activity and lifetime since it prevents the aggregation of the catalytically active species. Three types of polymer-based chiral catalysts have been investigated in the asymmetric organozinc additions: (1) polymers anchored with chiral catalysts, (2) main chain chiral polymer catalysts, and (3) dendritic chiral catalysts. The study of these macromolecular catalysts is discussed below.

Table 98. Alkynylzinc Additions to Aldehydes Promoted by 415[a]

entry	alkyne R^1	aldehyde	*t* (h)	yield (%)	ee (%)
1	Ph	cyclohexanecarboxaldehyde	1	99	96
2	$Ph(CH_2)_2$	cyclohexanecarboxaldehyde	4	98	99
3	$Ph(CH_2)_2$	isobutyraldehyde	2	90	99
4	Ph	isobutyraldehyde	2	95	90
5	$Ph(CH_2)_2$	cinnamaldehyde	20	39	80
6	$Ph(CH_2)_2$	trimethylacetaldehyde	2	84	99
7	Ph	trimethylacetaldehyde	2	99	94
8	$Ph(CH_2)_2$	benzaldehyde	20	52	96
9	Ph	benzaldehyde	20	53	94
10	Me_3Si	cyclohexanecarboxaldehyde	2	93	98
11	$Ph(CH_2)_2$	3,3-dimethylbutyraldehyde	2	72	99
12	Ph	*tert*-butylacetaldehyde	2	90	97
13	Me_3SiCH_2	cyclohexanecarboxaldehyde	4	84	98
14	$TBDMSOCH_2$	cyclohexanecarboxaldehyde	5	83	98
15	$(EtO)_2CH$	cyclohexanecarboxaldehyde	8	90	98
16	CH_2=C(Me)	cyclohexanecarboxaldehyde	3	94	98
17	$Me_2C(OH)$	isobutyraldehyde	4	97	98

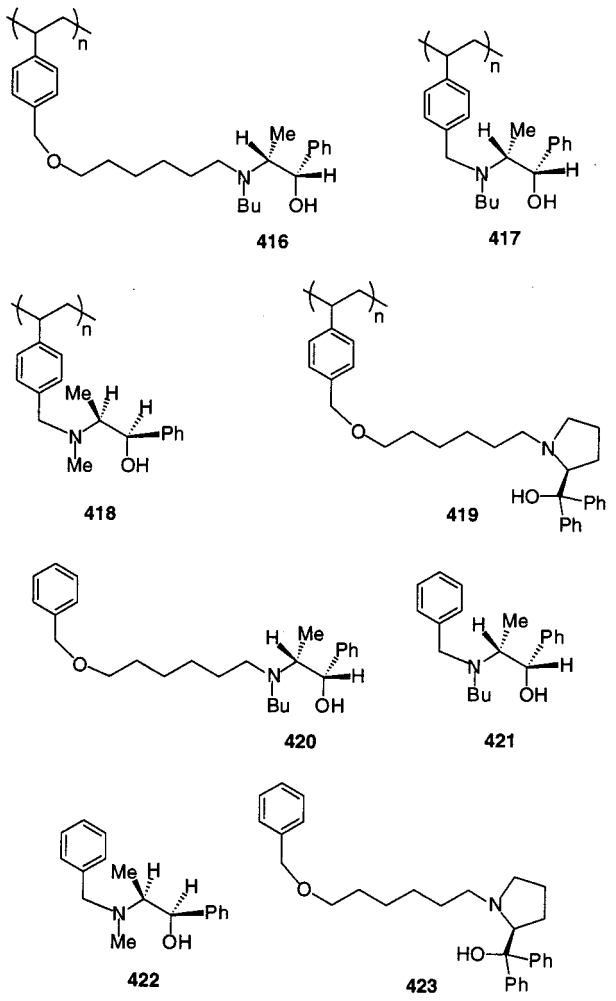
[a] The reactions were carried out using 1.1 equiv $Zn(OTf)_2$, 1.2 equiv **415** and 1.2 equiv Et_3N in toluene (0.3 M) at 23 °C.

a. Polymers Anchored with Chiral Ligands

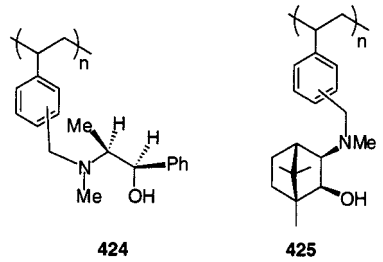
Fréchet, Itsuno, and Soai pioneered the use of polymer-anchored chiral catalysts for the asymmetric organozinc addition to aldehydes.[3,198a−c] The earlier work in this area has been summarized in the review article of Soai and Niwa.[3] In most cases, the enantioselectivity of the polymer-supported catalysts was lower than the corresponding monomer catalyst.

Recently, Watanabe and Soai studied the use of the polystyrene-supported ligands **416**−**419** for the reaction of diethylzinc with aldehydes.[199] These polymers showed 82%, 17%, 89%, and 61% ee, respectively, for the reaction of diethylzinc with benzaldehyde. The enantioselectivity of the polymers was lower compared to that of their corresponding monomers **420**−**423**, which gave 99%, 89%, 92%, and 81% ee, respectively. For the reaction of aliphatic aldehydes, polymer **416** gave the highest enantioselectivity among the amino alcohol-based polymers. It catalyzed the reaction of diethylzinc with nonyl aldehyde with 71% ee. Its monomer ligand **420** gave 73% ee. The reactions using these polymers were carried out in hexane, which allowed the polymer ligands to be easily recycled by simple filtration, and the recovered polymers showed the same enantioselectivity as the

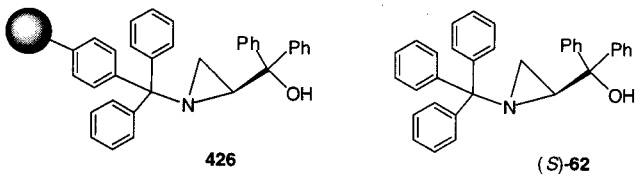
original polymers.



Polymers **424** and **425** were studied in a benchtop flow system by Hodge and co-workers.[200a] This reaction system allowed a convenient extended usage of the polystyrene-chiral catalysts. However, after a certain reaction period, a drop of the enantioselectivity was observed due to gradual chemical degradation of the catalytic sites. For example, when **425** was used in the benchtop flow system for the reaction of diethylzinc with benzaldehyde, (*S*)-1-phenylpropanol was produced initially with 95% yield and >94% ee. After being used for ca. 275 h, the chemical yield decreased to 50−60% and the ee to 81−84%. It was also observed that a higher ee of the product was obtained by using the polystyrene-supported ephedrine ligand **424** in a flow system than by using the monomeric (1*R*,2*S*)-*N*-benzylephedrine under typical reaction conditions. The increase in ee was probably because the flow system produced a high molar ratio of the catalyst versus diethylzinc and the substrate. In addition, the flow system could also continuously remove the initial alkoxide reaction product that might act as a catalyst to give product with low ee. The influence of the polymer support on the catalytic properties of these catalysts was studied in detail. Highly enantioselective (up to 97% ee) polymer catalysts were obtained for the reaction of diethylzinc with benzaldehyde.[200b]



The polymer-supported *N*-tritylaziridinyldiphenylmethanol **426** was used by Zwanenburg and coworkers to catalyze the reaction of diethylzinc with aldehydes.[201] The enantioselectivity of the polymer was very close to that of the corresponding monomer catalyst (*S*)-**62**. The enantioselectivity of **426** was very high for aromatic aldehydes and cyclohexanecarboxaldehyde (95−97% ee, entries 1−4, Table 99) but much lower for aliphatic aldehydes (81% and 77% ee, entries 5 and 6, Table 99).



Pericàs and co-workers attached a highly enantioselective amino alcohol ligand to Barlos' cross-linked polystyrene resin.[202] The resulting polymer-supported ligand **427** showed high enantioselectivity for the diethylzinc addition to both aromatic and aliphatic aldehydes (86−95% ee, Table 100). After the reaction, **427** was easily recovered with no loss of enantioselectivity. The enantioselectivity of **427** was only slightly lower than that of the monomer **122j**. Liu and Ellamn carried out a solid-phase synthesis of chiral amino alcohol ligands.[203] They found that the

Table 99. Diethylzinc Additions to Aldehydes Catalyzed by 426[a]

entry	aldehyde	*T* (°C)	yield (%)	ee (%)[b]	config
1	benzaldehyde	r.t.	92	96 (99)	*S*
2	*p*-chlorobenzaldehyde	r.t.	88	96 (99)	*S*
3	*p*-methoxybenzaldehyde	r.t.	88	95 (99)	*S*
4	cyclohexanecarboxaldehyde	r.t.	90	97 (99)	*S*
5	isovaleraldehyde	r.t.	77	81	*S*
6	undecylic aldehyde	r.t.	80	77	*S*

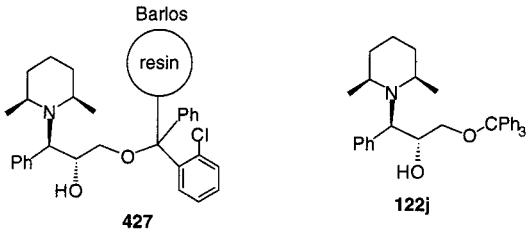
[a] The reactions were carried out in toluene/CH_2Cl_2 (1:1) solution overnight. [b] Data in parentheses were obtained by using monomer catalysts (*S*)-**62**.

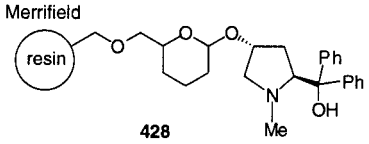
Table 100. Diethylzinc Additions to Aldehydes Catalyzed by 427[a]

entry	aldehyde	conv (%)	ee (%)	config
1	benzaldehyde	99	94	*S*
2	*o*-fluorobenzaldehyde	96	88	*S*
3	*m*-fluorobenzaldehyde	98	94	*S*
4	*p*-fluorobenzaldehyde	>99	95	*S*
5	*o*-methylbenzaldehyde	91	91	*S*
6	*m*-methylbenzaldehyde	93	94	*S*
7	*p*-methylbenzaldehyde	93	94	*S*
8	*o*-methoxybenzaldehyde	88	86	*S*
9	*m*-methoxybenzaldehyde	>99	94	*S*
10	*p*-methoxybenzaldehyde	86	94	*S*
11	1-naphthaldehyde	86	86	*S*
12	2-naphthaldehyde	82	90	*S*
13	3-cyclohexenecarboxaldehyde	86	98	*S*
14	isovaleraldehyde	99	90	*S*

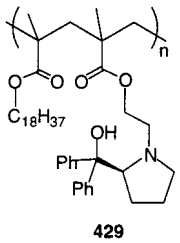
[a] The reactions were carried out in toluene in the presence of 8 mol % of **427** at 0 °C for 24 h.

polymer-supported ligand **428** catalyzed the diethylzinc addition to benzaldehyde with 89% ee.

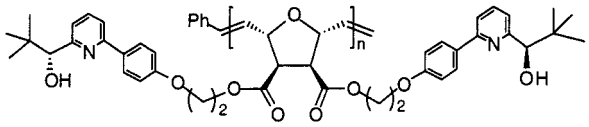




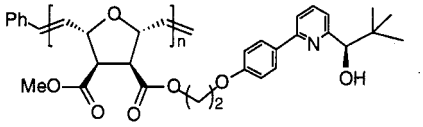
The soluble polymer-supported amino alcohol **429** was used by Kragl and co-workers in a membrane reactor for the diethylzinc addition to benzaldehyde.[204] It was found that the enantioselectivity of this reaction was strongly dependent on the initial substrate and reagent ratio. Excess diethylzinc yielded (*S*)-1-phenylpropanol with up to 80% ee, but excess benzaldehyde gave (*R*)-1-phenylpropanol with 50% ee. This phenomenon was also observed with other aldehydes in this reaction system.



Soluble polymers **430** and **431** were prepared by Bolm et al. by a ring-opening metathesis polymerization.[205] These polymers gave 71−73% ee for the diethylzinc addition benzaldehyde at 0 °C or room temperature. Their enantioselectivity was lower than their corresponding monomer ligands, which showed up to 87% ee.

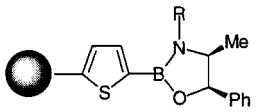


430

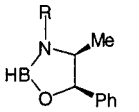


431

The polymer-supported oxazaborolidines **432a,b**, prepared by El Moualij and Caze, showed significantly reduced enantioselectivity from their monomer ligands **433a,b**.[206] These polymers were made from the copolymerization of the 2-vinylthiophene monomers with styrene and cross-linked with divinylbenzene. In the diethylzinc addition to benzaldehyde, polymer **432a** gave 16% ee but monomer **433a** gave 62% ee. Similarly, polymer **432b** gave 35% ee but monomer **433b** gave 75% ee.



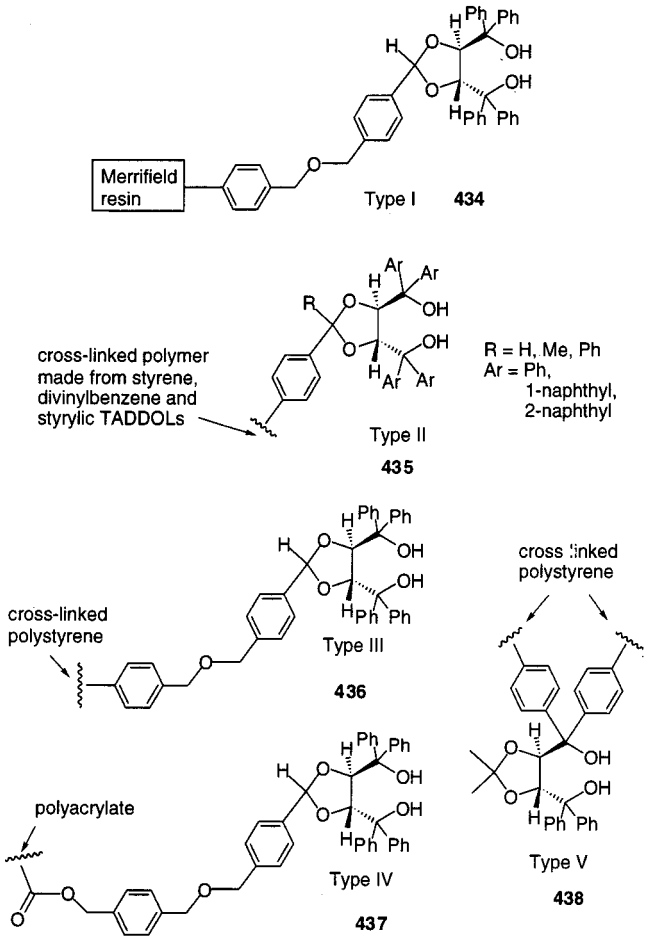
432a: R = H
432b: R = Me



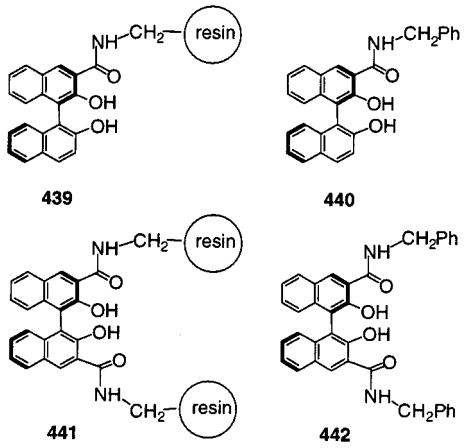
433a: R = H
433b: R = Me

Seebach and co-workers reported a series of polymer-supported Ti-TADDOLates for the diethylzinc addition to aldehydes.[207] Five different types of polymer-supported TADDOlates, I−V, were prepared and studied. The Type I polymer ligand **434** was a Merrifield resin-supported TADDOL with a flexible spacer between the polymer support and chiral ligand. The Type II and III ligands **435** and **436** were made by incorporating the TADDOL ligand into cross-linked polystyrenes either without a spacer (**435**) or with a flexible spacer (**436**). The Type IV ligand **437** used a polyacrylate support. The Type V ligand **438** was made by branching out the TADDOL monomer into a cross-linked polystyrene. All of these polymers (20 mol %) were used to catalyze the reaction of diethylzinc with benzaldehyde in the presence of 1.2 equiv of $Ti(O^iPr)_4$ in toluene at −30 °C. In general, Type I−IV polymers gave 93−98% ee and high yield but the Type V ligand **438** much lower (75% ee). These polymers can be regenerated by treatment with acid after reaction, and the recovered polymers showed no decrease in enantioselectivity.

Wang and co-workers attached a BINOL ligand to polystyrene beads through an amide bond to generate **439** by the standard solid-state peptide synthesis.[208] In the presence of $Ti(O^iPr)_4$ and 20 mol % of **439**, diethylzinc addition to aromatic aldehydes proceeded with 34−82% ee. In a few cases, the enantioselectivity of **439** was higher than its monomer ligand **440**.



The C_2-symmetric polymer ligand **441** was also prepared, and it showed high enantioselectivity for the reaction of diethylzinc with aromatic aldehydes in the presence of excess $Ti(O^iPr)_4$ (up to 99% ee, Table 101). The enantioselectivity for aliphatic aldehydes was much lower. There was significant improvement for certain substrates from monomer **442** (e.g., 63% ee for the diethylzinc addition to benzaldehyde) to the polymer catalyst, but the reactions catalyzed by the polymer were slower due to diffusion limitation of the polymer matrix.



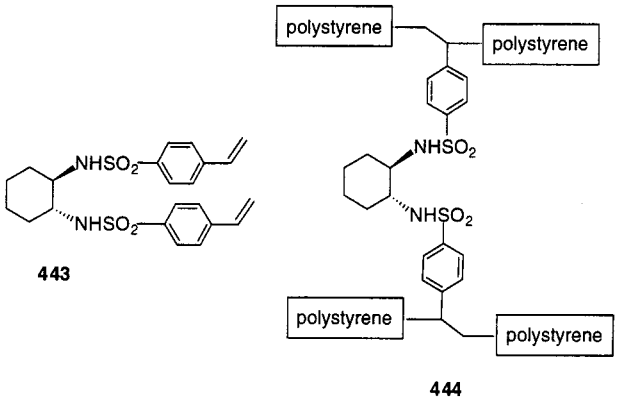
Halm and Kurth used monomer **443** as a cross-linking reagent in the polymerization of styrene.[209]

Table 101. Diethylzinc Additions to Aldehydes Catalyzed by 441[a]

entry	aldehyde	*t* (h)	yield (%)	ee (%)
1	benzaldehyde	24	93	97
2	*o*-chlorobenzaldehyde	25	92	91
3	*m*-chlorobenzaldehyde	24	89	94
4	*p*-chlorobenzaldehyde	30	88	92
5	*o*-methoxybenzaldehyde	24	92	89
6	*m*-methoxybenzaldehyde	28	78	92
7	*p*-methoxybenzaldehyde	48	90	83
8	*m*-nitrobenzaldehyde	54	88	99
9	*p*-nitrobenzaldehyde	54	90	96
10	*p*-*N*,*N*-dimethylaminobenzaldehyde	18	97	57
11	3,5-dimethoxybenzaldehyde	24	93	95
12	piperonal	30	89	65
13	1-bromo-2-naphthaldehyde	28	95	95
14	cinnamaldehyde	28	97	93
15	2-naphthaldehyde	48	89	94
16	2-methoxy-1-naphthaldehyde	24	87	99
17	isobutyraldehyde	72	65	78
18	undecylic aldehyde	72	52	65
19	2-butenal	60	61	88

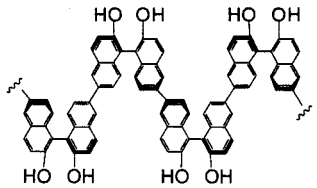
[a] The reactions were carried out in CH_2Cl_2 at 0 °C using 20 mol % of **441** and 1.8 equiv of $Ti(O^iPr)_4$.

The resulting polymer beads (**444**) were used to catalyze the diethylzinc addition to benzaldehyde in the presence of $Ti(O^iPr)_4$, which gave up to 98% ee, similar to the use of the monomer **443**. For other aromatic aldehydes, polymer **444** showed ≤83% ee.

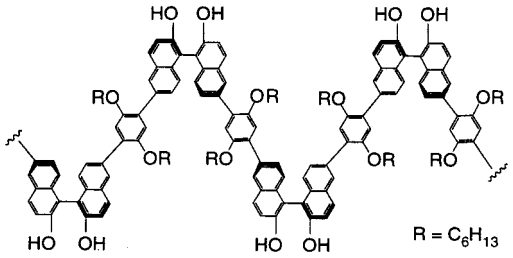


b. Main Chain Chiral Polymer Catalysts

A class of main chain chiral polymers based on optically active binaphthyls, such as (*R*)-**445**, was designed and synthesized for asymmetric catalysis by Pu and co-workers.[159,210−218] Because of the rigidity and stereoregularity of (*R*)-**445**, its catalytic sites should have a better defined microenvironment than the traditional flexible and sterically irregular polymer-supported catalysts. Thus, it might be possible to systematically modify the structure and function of these new polymer catalysts.

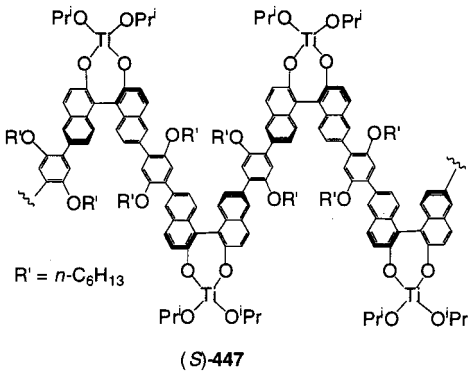


Polymer (*R*)-**445** was used to catalyze the reaction of benzaldehyde with diethylzinc.[213,214] In the presence of this polymer, diethylzinc reacted with benzaldehyde at room temperature in methylene chloride to give 1-phenylpropanol with only 13% ee. A significant amount of side product, benzyl alcohol, was also observed. Since (*R*)-**445** was insoluble in the reaction solvent, the soluble binaphthyl polymer (*R*)-**446** was prepared by introduction of flexible hexyloxyl groups. When this polymer was used to catalyze the diethylzinc addition to benzaldehyde, it produced 1-phenylpropanol with 40% ee.



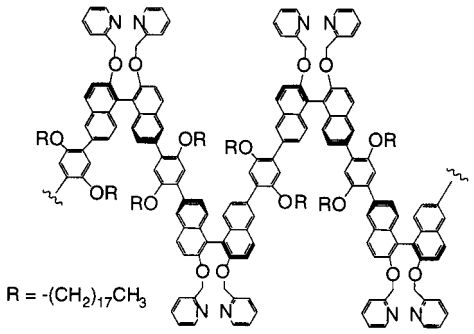
(*R*)-**446**

Polymer (*S*)-**446** containing the enantiomeric binaphthyl units of (*R*)-**446** was used to catalyze the diethylzinc addition in the presence of Ti(O^iPr)$_4$.[215] The reactions were carried out at 0 °C for 5 h in toluene by using 20 mol % of (*S*)-**446** and 1.4 equiv of Ti(O^iPr)$_4$. The observed ee for the reaction of benzaldehyde with diethylzinc was 86%, and for the reaction of 1-naphthaldehyde, it was 92%. The catalytic properties of this polymer are very similar to those of the monomeric BINOL catalyst. The catalytically active species for this reaction might be the polybinaphthyl titanium complex (*S*)-**447** generated from the reaction of (*S*)-**446** with Ti(O^iPr)$_4$.



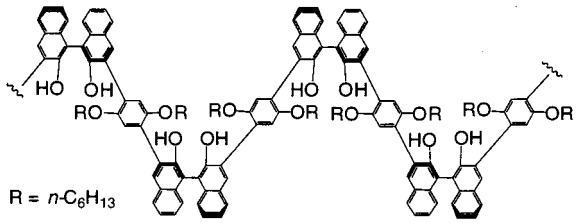
(*S*)-**447**

Although the titanium-based polybinaphthyl catalyst (*S*)-**447** showed good enantioselectivity for the reaction of diethylzinc with aryl aldehydes, it required the use of an excess amount of Ti(O^iPr)$_4$ over the substrates as other chiral diol ligands. To avoid the large amount of Ti(O^iPr)$_4$ and to develop a more efficient catalytic process for the diethylzinc addition, efforts were made to further modify the binaphthyl polymers. Polymer (*R*)-**448** containing pyridine groups in the binaphthyl units was synthesized.[214] However, this polymer could not catalyze the diethylzinc addition to benzaldehyde.



(*R*)-**448**

Another polymer (*R*)-**449** was then synthesized by conducting the polymerization at the 3,3′-positions of the binaphthyl monomer.[213,214] Two molecular weights of this polymer, (*R*)-**449a** (M_w = 6700, PDI = 1.5) and (*R*)-**449b** (M_w = 24 000, PDI = 2.5), were obtained by using two different polymerization conditions. Both of these polymers were soluble in common organic solvents and displayed very sharp and well-resolved NMR signals. Their steric and electronic environments at the binaphthyl units are different from those of polymers (*R*)-**445** and (*R*)-**446** because of the 3,3′-substituents.



(*R*)-**449**

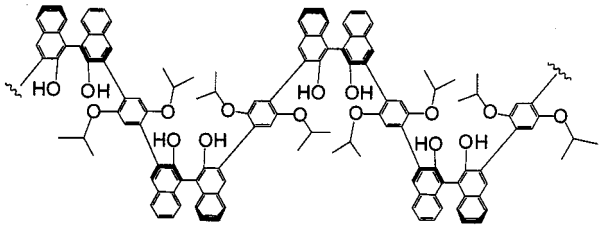
In the presence of 5 mol % of (*R*)-**449a** at 0 °C in toluene solution, the diethylzinc addition to benzaldehyde proceeded with excellent enantioselectivity (92% ee) and complete chemical selectivity without the addition of Ti(O^iPr)$_4$ (entry 1, Table 102). This polymer also showed high enantioselectivity for the reaction of *para*-substituted benzaldehydes and cinnamaldehyde (88−94% ee) and up to 83% ee for the reaction of aliphatic aldehydes. After completion of the reaction, (*R*)-**449a** was recovered conveniently by precipitation with methanol. The catalytic properties of the recovered polymer were almost the same as those of the original polymer. The high molecular weight polymer (*R*)-**449b** also showed similar catalytic properties to those of the low molecular weight polymer (*R*)-**449a**. Thus, the catalytic properties of these polymers were independent of the method of the polymer preparation, the molecular weight of the polymer, and the molecular weight distribution. Polymer (*S*)-**449**, made of *S* binaphthyl units, showed the opposite enantioselectivity (entry 16, Table 102).

Table 102. Diethylzinc Additions to Aldehydes Catalyzed by the Polymers 449[a]

entry	polymer	aldehyde	yield (%)	ee (%)[a]	config
1	(*R*)-**449a**	benzaldehyde	89	92	*R*
2	(*R*)-**449a**	benzaldehyde	91	92[b]	*R*
3	(*R*)-**449a**	*p*-methylbenzaldehyde	90	93[b]	*R*
4	(*R*)-**449a**	*p*-chlorobenzaldehyde	94	93[b]	*R*
5	(*R*)-**449a**	*p*-methoxybenzaldehyde	84	88[b]	*R*
6	(*R*)-**449a**	*p*-*tert*-butylbenzaldehyde	63	74[b]	*R*
7	(*R*)-**449a**	*o*-fluorobenzaldehyde	86	35[b]	*R*
8	(*R*)-**449a**	*o*-methoxybenzaldehyde	90	59[b]	*R*
9	(*R*)-**449a**	cinnamaldehyde	86	89[b]	*R*
10	(*R*)-**449a**	3,3,7-trimethyl-6-octenal	67	83[b]	*c*
11	(*R*)-**449a**	nonyl aldehyde	89	74	*R*
12	(*R*)-**449a**	cyclohexanecarboxaldehyde	70	83[b]	*R*
13	(*R*)-**449a**	hexanal	65	74[b]	*R*
14	(*R*)-**449b**	benzaldehyde	90	93	*R*
15	(*R*)-**449b**	*p*-chlorobenzaldehyde	95	94	*R*
16	(*S*)-**449**	benzaldehyde	94	93	*S*

[a] All the reactions were carried out in toluene solution at 0 °C in the presence of 5 mol % (based on the repeating unit) of the polymers. [b] The recycled polymer was used. [c] The absolute configuration of the product was not determined. $[\alpha]_D = -13.25$ ($c = 1.95$, THF).

Polymer (*R*)-**450** containing sterically more bulky isopropyl groups than the hexyl groups in (*R*)-**449** was also prepared.[216] This polymer was soluble in common organic solvents. The diethylzinc addition catalyzed by (*R*)-**450** was slightly lower in rate as well as in enantioselectivity. The ee observed for the reaction of benzaldehyde was 89%, and for the reaction of cyclohexanecarboxaldehyde it was 79%. This demonstrates that a more bulky alkyl group in the polymer was not favorable for the catalysis.



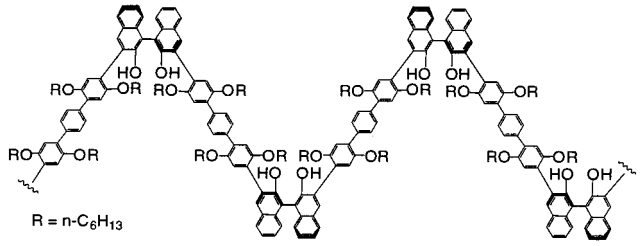
(*R*)-**450**

The catalytic properties of (*R*)-**449** were compared with those of the monomer catalyst (*R*)-**352**.[158,159] It was found that the monomer was a more enantioselective catalyst especially for *ortho*-substituted benzaldehydes as well as aliphatic aldehydes. Since the phenylene dialkoxy linker in polymer (*R*)-**449** could act as a dual ligand to coordinate to the zinc centers on both of the adjacent binaphthyl units when reacted with diethylzinc, there was interference between the catalytic sites. This could cause the observed differences in enantioselectivity since the monomer catalyst should not have similar catalytic site interference. Thus, polymer (*R*)-**451** with the binaphthyl units separated by a much longer rigid phenylene linker was prepared.[159,217] As expected, this polymer exhibited very high and general enantioselectivity (91−98% ee) for the reaction of diethylzinc or dimethylzinc with a broad range of aldehydes (Table 103). It is the most generally enantioselective polymeric catalyst for the dialkylzinc addition to aldehydes. Therefore, the rigidity and stereoregularity of polymer (*R*)-**451** preserved the catalytic properties of the monomer catalyst (*R*)-**352**. Polymer (*R*)-**451** was recovered almost quantitatively by precipitation with excess methanol, and the recovered polymer had the same enantioselectivity as the original polymer.

Table 103. Dialkylzinc Addition Catalyzed by the Polymer (*R*)-451[a]

entry	R_2Zn	aldehyde	yield (%)	ee (%)	config
1	Et_2Zn	benzaldehyde	92	98	*R*
2	Et_2Zn	benzaldehyde	90	98[b]	*R*
3	Et_2Zn	*p*-methylbenzaldehyde	90	98	*R*
4	Et_2Zn	*p*-chlorobenzaldehyde	94	98	*R*
5	Et_2Zn	*p*-methoxybenzaldehyde	89	97	*R*
6	Et_2Zn	*o*-fluorobenzaldehyde	88	91	*R*
7	Et_2Zn	*o*-methoxybenzaldehyde	90	93	*R*
8	Et_2Zn	*m*-methoxybenzaldehyde	93	98	*R*
9	Et_2Zn	2-naphthaldehyde	95	96	*R*
10	Et_2Zn	1-naphthaldehyde	93	98	*R*
11	Et_2Zn	hexanal	71	98	*R*
12	Et_2Zn	octyl aldehyde	85	97	
13	Et_2Zn	nonyl aldehyde	88	97	*R*
14	Et_2Zn	cyclohexanecarboxaldehyde	81	98	*R*
15	Et_2Zn	isovaleraldehyde	65	98	*R*
16	Et_2Zn	cinnamaldehyde	93	92[c]	*R*
17	Et_2Zn	α-methyl-*trans*-cinnamaldehyde	92	97	
18	Me_2Zn	benzaldehyde	92	93	*R*
19	Me_2Zn	octyl aldehyde	78	89	*R*

[a] The reactions were carried out in the presence of 5 mol % (based on the repeating unit) of (*R*)-**451** and 2 equiv of diethylzinc or 3 equiv of dimethylzinc in toluene at 0 °C unless indicated otherwise. [b] The recovered catalyst was used. [c] The solvent was a 1:1 mixture of toluene:diethyl ether.



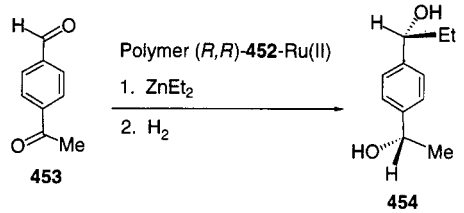
(*R*)-**451**

Polymer (*R*)-**451** was used to catalyze the diphenylzinc addition to propionaldehyde and *p*-methoxybenzaldehyde as well and gave 85% and 92% ee, respectively.[159,182] The high enantioselectivity of this polymer was very similar to that of the monomer ligand (*R*)-**352**, but the reaction conditions were modified. After the reaction, the polymer was easily recovered with retention of the catalytic properties.

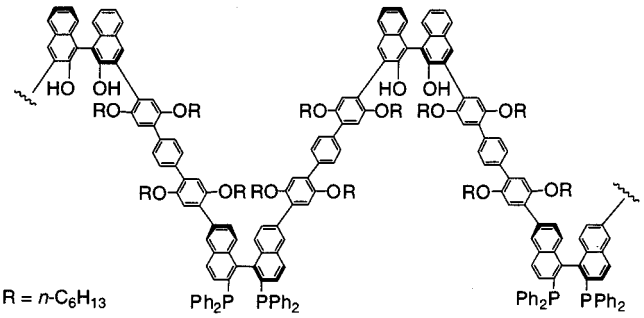
Polymer (*R*,*R*)-**452** containing two distinctively different catalytic sites, BINOL and BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl], was further synthesized by Pu and co-workers.[218] The BINAP

portion of this polymer was used to bind with Ru(II) centers, and the resulting multifunctional polymer was used to catalyze a tandem asymmetric reaction of **453** including the diethylzinc addition to the aldehyde carbonyl and the hydrogenation of the ketone carbonyl (Scheme 22). This process generated

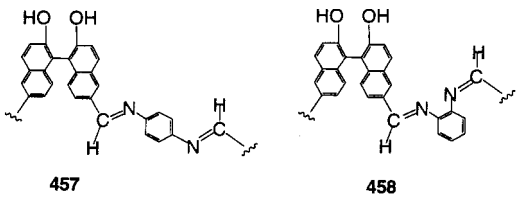
Scheme 22. Sequential Asymmetric Diethylzinc Addition and Hydrogenation



the chiral diol **454** with 94% ee for the diethylzinc addition step and 87% de for the hydrogenation step. Compound **455** underwent the same process to give **456** with 94% ee and 75% de.

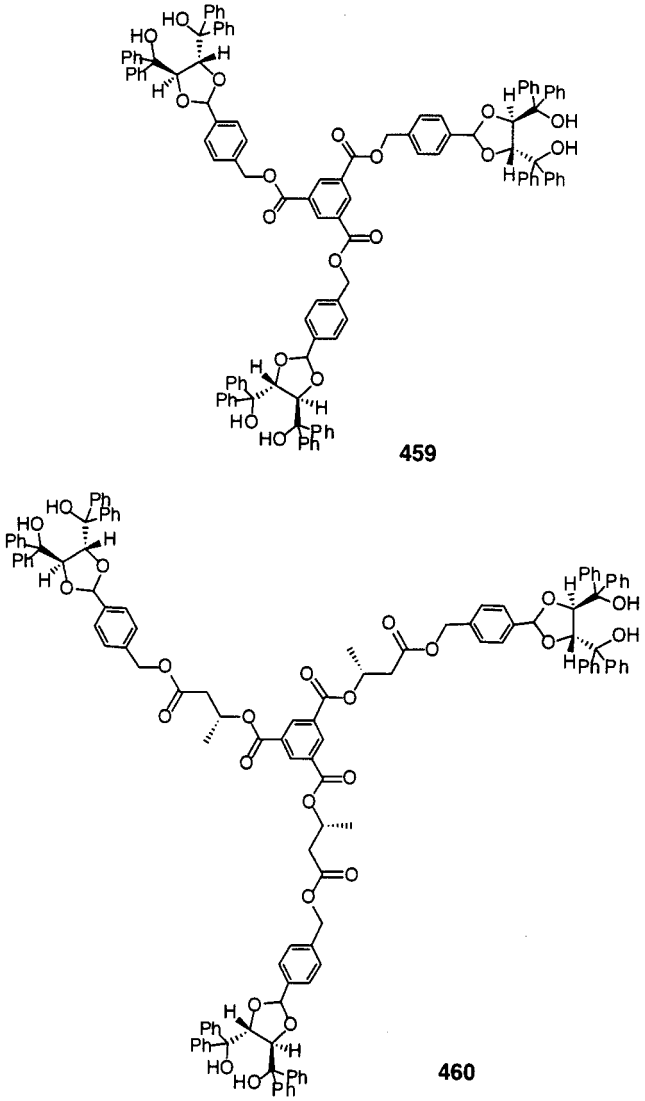


Yu and co-workers studied the chiral polybinaphthyls **457** and **458**.[219] These polymers catalyzed the reaction of diethylzinc with aldehydes with up to 85% ee in the presence of 1.4 equiv of $Ti(O^iPr)_4$. Polymer **457** showed better enantioselectivity than **458**. The recovered polymers had similar catalytic properties.



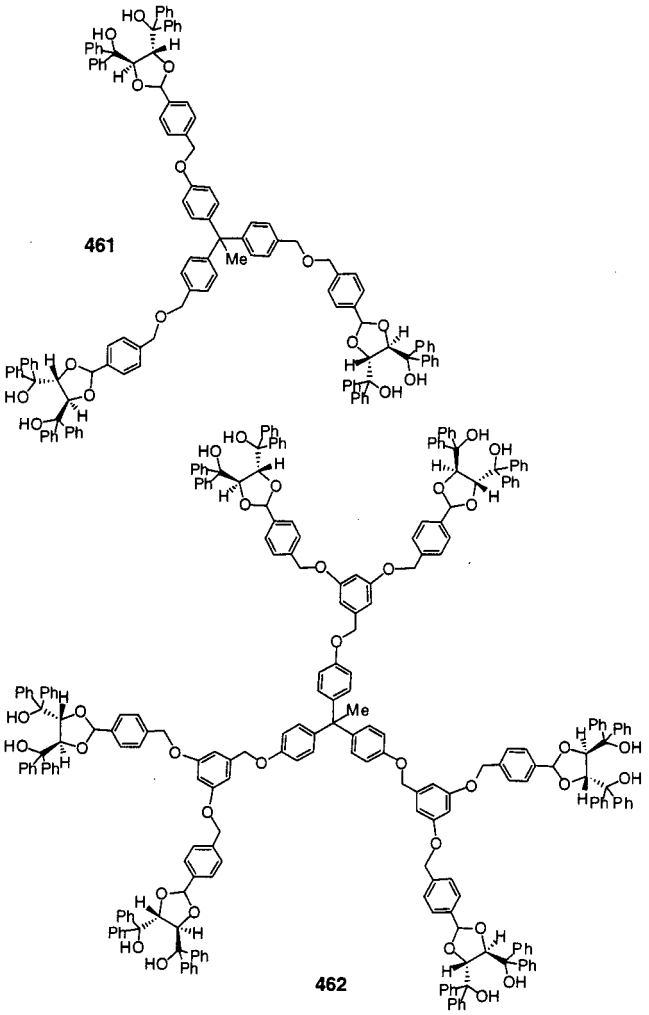
c. Dendrimer Ligands

Dendrimers are macromolecules that branch out from a center like trees. Their periphery units increase exponentially as the generation increases. Seebach and co-workers synthesized dendritic TADDOL derivatives for the asymmetric organozinc addition. Compounds **459**−**462** had the TADDOL species in the periphery of the dendrimers,[207] while compounds **463**−**469** had the TADDOL unit located in the center of the dendritic structure.[220] All of these



dendritic ligands exhibited high enantioselectivity for the diethylzinc addition to benzaldehyde with the use of 20 mol % of the dendrimers and 1.2 equiv of $Ti(O^iPr)_4$. Dendrimers **459**−**462** showed 94−98% ee for the reaction of diethylzinc with benzaldehyde. From the zeroth-generation dendrimer **463** to the fourth-generation dendrimer **467**, the enantioselectivity decreased from 97% to 89% ee. For dendrimers **468** and **469**, even though the configuration of the chiral centers in the dendritic arms was inverted, both gave very similar enantioselectivity (96% and 97% ee, respectively). The enantioselectivity of **468** and **469** was also almost the same as that of the second-generation dendrimer **465** (96% ee), which has no chiral centers in the dendritic arms. These results demonstrate that the stereocontrol is provided by the TADDOL core rather than the dendritic arms.

The dendritic styryl TADDOLs **470** and **471** were used as cross-linkers to copolymerize with styrene.[221] The resulting polymer beads were treated with $Ti(O^iPr)_4$ and then tested for the reaction of diethylzinc with benzaldehyde. They showed up to 88% ee. Both of the dendrimer-based heterogeneous catalysts had



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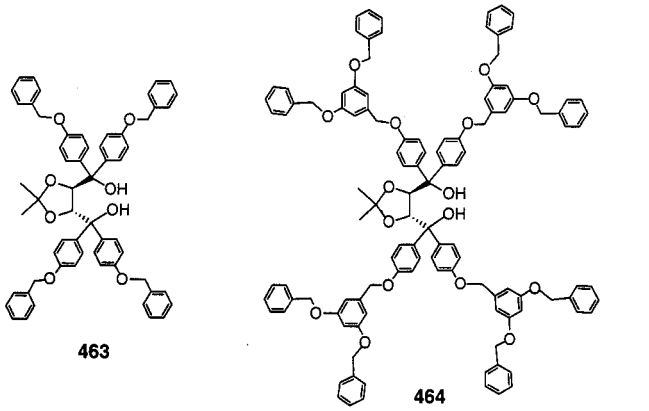

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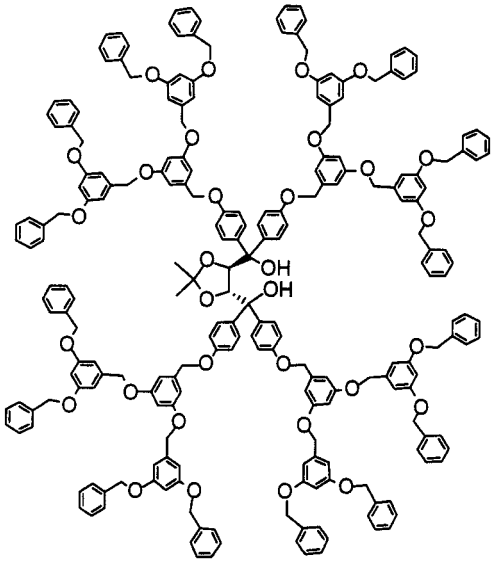

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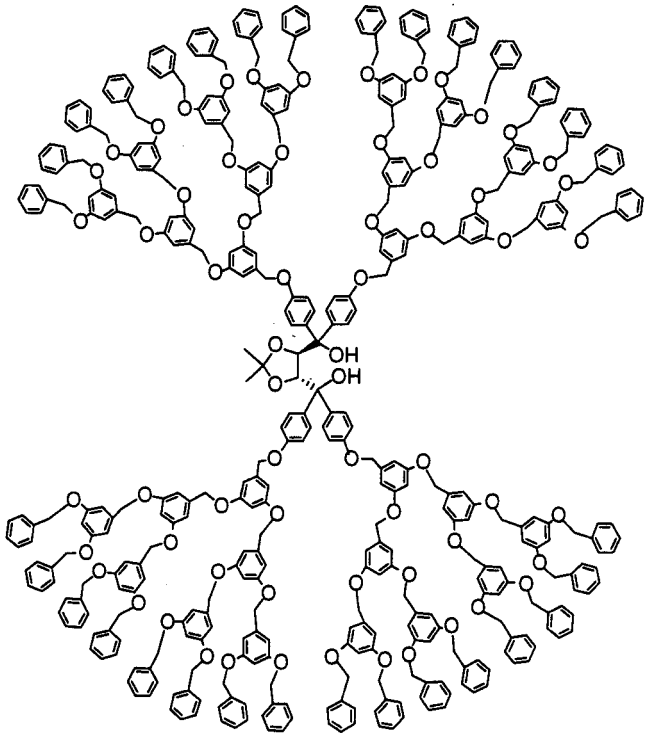
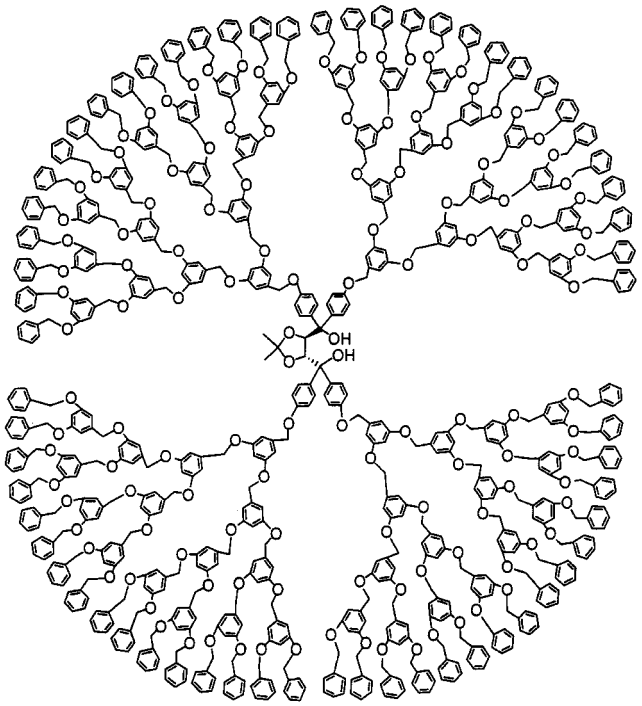


466

similar catalytic properties. These materials were found to be more active than the catalyst derived from polymer **435** that was linearly linked to the TADDOL monomer. Thus, the catalytic sites in these dendritic cross-linked polymers are more accessible.

For comparison with **470**, the cross-linkable monomers **472**−**474** were synthesized.[222] These monomers were copolymerized with styrene, and the resulting polymer beads were treated with $Ti(O^iPr)_4$. In this study, the polymeric titanium complex containing 0.1 mmol g^{-1} of **470** was found to catalyze the reaction of diethylzinc with benzaldehyde with 96% ee. There was little change in enantioselectivity even after 20 cycles. Both the catalytic activity and enantioselectivity of this heterogeneous catalyst were almost identical to those of the homogeneous monomer catalyst. The loading of the ligand in the polymer was found to have a significant influence on the catalytic behavior. The higher loading of **470** led to poorer results. The catalytic properties of the materials derived from **472**−**474** showed large changes during multiple runs, thus making them less stable than **470**.

Seebach and co-workers also used a series of the styryl-derived BINOL dendritic monomers (*S*)-**475**−(*S*)-**479** and their immoblized versions obtained by copolymerization with styrene to catalyze the asymmetric diethylzinc addition to benzaldehyde in the presence of $Ti(O^iPr)_4$.[223] All these materials showed



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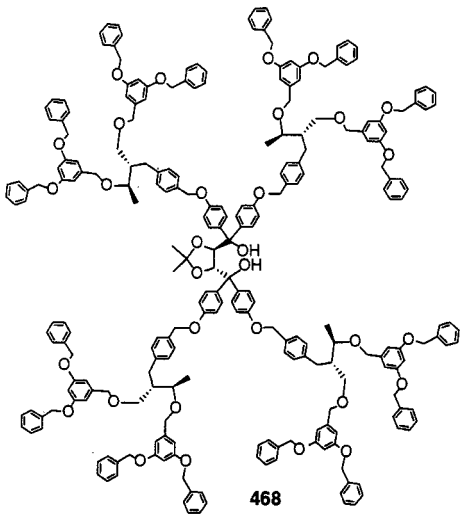

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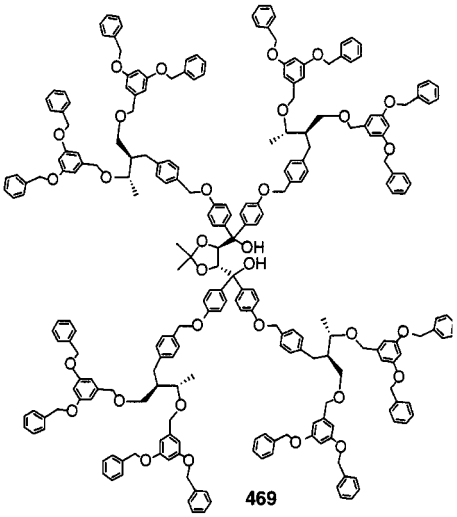

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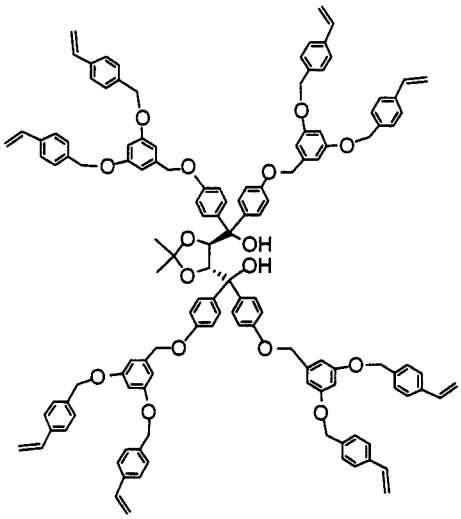

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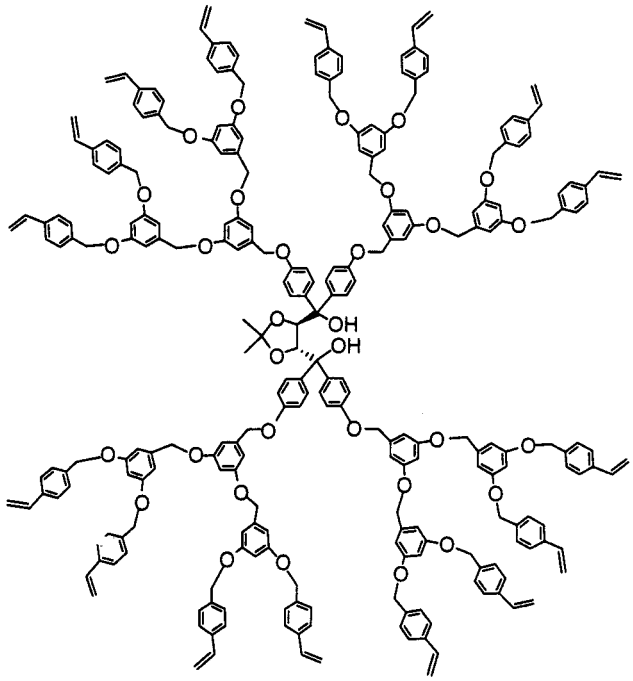

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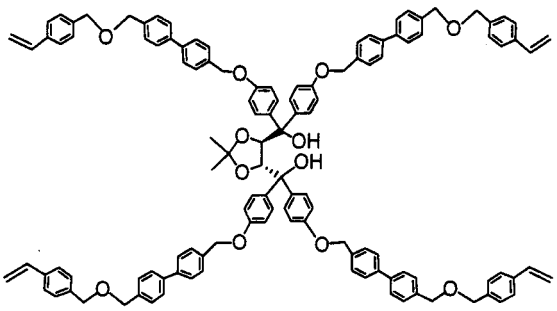
similar enantioselectivity (80−86% ee) as well as catalytic activity to those of BINOL itself. The enantioselectivity of the cross-linked polymer of (*S*)-**476** was shown to have the most stable enantioselectivity even after 20 catalytic cycles.

Compounds **480**−**483** were studied by Bolm and co-workers.[224] In the presence of 5 mol % of these ligands, diethylzinc added to benzaldehyde with 84−88% ee at 0 °C in toluene. Lower catalyst loading required longer reaction time and gave slightly lower ee. A positive nonlinear relationship existed between the ee of the pyridyl alcohol (*S*)-**481** and the ee of the product. Using 5 mol % of (*S*)-**481** with 52% ee produced (*S*)-1-phenylpropanol with 84% ee and 48% yield.

The binaphthyl-based dendrimer (*S*)-**484** was used to catalyze the asymmetric reaction of benzaldehyde with diethylzinc by Pu and co-workers.[225] It was found that this dendrimer behaved very differently from the small BINOL molecule. Dendrimer (*S*)-**484** showed much higher catalytic activity than



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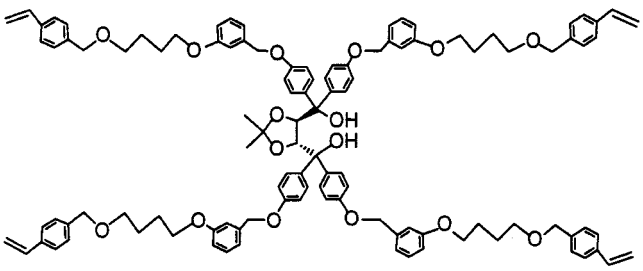

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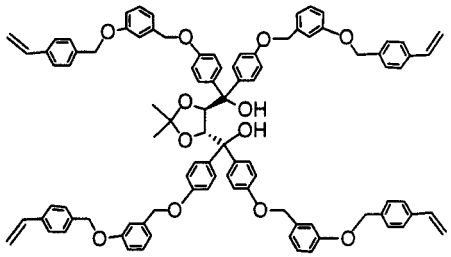

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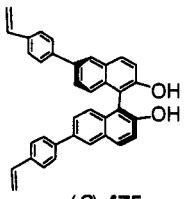
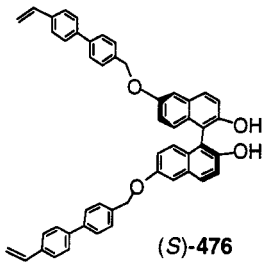
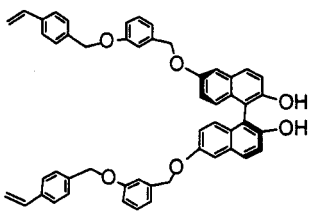


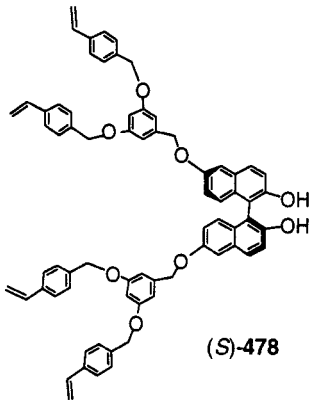
(*S*)-475



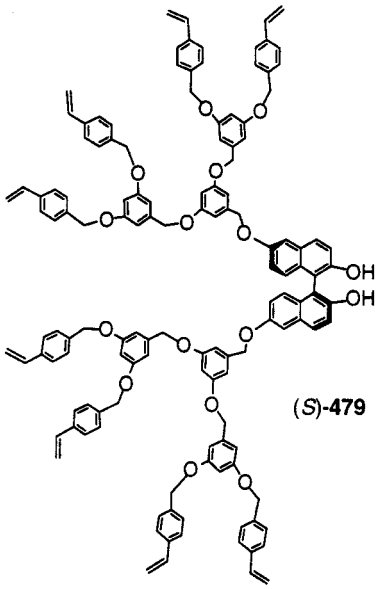
(*S*)-476



(*S*)-477



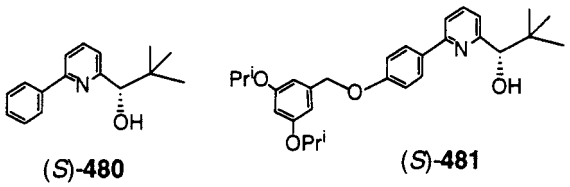
(*S*)-478



(*S*)-479

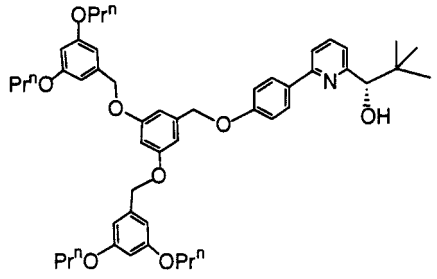
(*S*)-BINOL and also generated the opposite enantiomeric product. In the presence of (*S*)-**484** (5 mol %) in toluene solution, a 99% conversion of benzaldehyde was observed in 24 h at room temperature. However, only 37% conversion was observed under the same condition when BINOL was used. The enantioselectivities of both (*S*)-**484** and (*S*)-BINOL were very low (11% and 33% ee, respectively). The increased catalytic activity of (*S*)-**484** over BINOL indicates that the zinc complex generated from the reaction of (*S*)-**484** with diethylzinc might have a much higher Lewis acidity than the zinc complex generated from BINOL. The zinc complex formed from the reaction of BINOL with diethylzinc was found to likely exist as aggregates in solution through intermolecular Zn−O−Zn bonds. This should greatly reduce the Lewis acidity of the zinc center. Such an aggregate could not form in the case of (*S*)-**484** due to the large dendritic arms. These bulky and rigid dendritic arms prevented (*S*)-**484** from forming oligomers through Zn−O−Zn bonds yet still allowed small molecules such as benzaldehyde and diethylzinc to approach the chiral core for the catalytic reaction. The opposite enantioselectivity of (*S*)-**484** versus (*S*)-BINOL also indicated that the in situ generated catalytically active species when these ligands were used were very different. It may be monomeric for (*S*)-**484** but oligomeric for BINOL.

In the presence of $Ti(O^iPr)_4$, (*S*)-**484** became highly enantioselective for the reaction of aldehydes with diethylzinc.[225] In toluene, (*S*)-**484** (20 mol %) and $Ti(O^iPr)_4$ (1.4 equiv) catalyzed the reaction of 1-naphthaldehyde with diethylzinc with 100% conversion and 90% ee in 5 h. No side product was observed. Under similar conditions, (*S*)-**484** gave 100% conversion and 89% ee for the reaction of benzaldehyde with diethylzinc in the presence of $Ti(O^iPr)_4$. The catalytic properties of (*S*)-**484** were very similar to those of BINOL in the presence of the titanium complex.[156] The same enantiomeric product was produced by using either (*S*)-**484** or (*S*)-BINOL in the presence of $Ti(O^iPr)_4$. This study indicates that unlike the reaction in the absence of $Ti(O^iPr)_4$, the asymmetric reaction of aldehydes with diethylzinc in the presence of the titanium complex might involve structurally similar catalytically active species when either the chiral dendrimer (*S*)-**484** or the small molecule BINOL was used. Since the titanium complex of (*S*)-**484** was not expected to generate any dimeric or

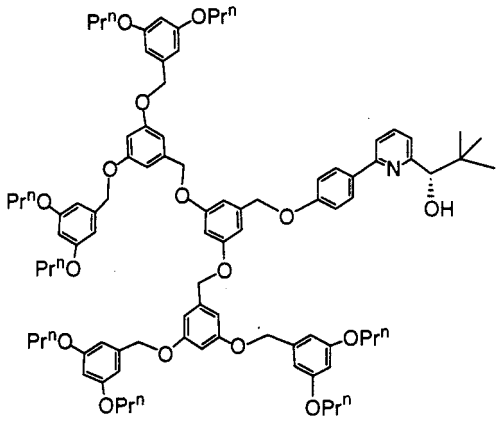


(*S*)-**480**

(*S*)-**481**



(*S*)-**482**



(*S*)-**483**

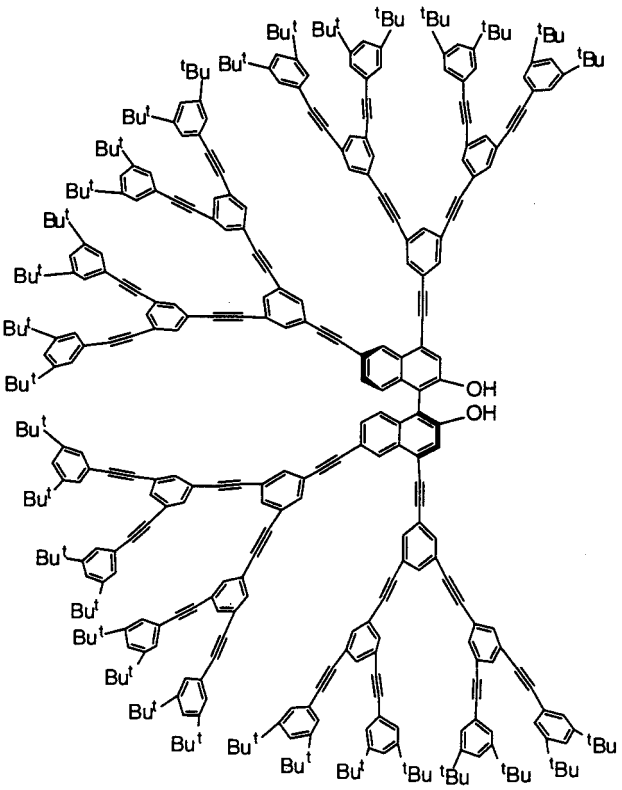
oligomeric structure through the binaphthyl core, the catalytically active species formed from the interaction of BINOL with $Ti(O^iPr)_4$ might also be monomeric. In these catalytic reactions, (*S*)-**484** was easily recovered from the reaction mixture by precipitation with methanol due to the large size differences between this dendritic molecule and the products and reagents.

Soai and co-workers reported the use of dendrimers **485** and **486** containing rigid branches and chiral amino alcohol periphery groups for the dialkylzinc additions.[226] It was found that both dendrimers showed similar enantioselectivity for the dialkylzinc addition to aromatic aldehydes (77−86% ee). Their enantioselectivity was lower than that of their monomeric ligand **422**, which gave 92% ee for the diethylzinc addition to benzaldehyde.[199]

9. Organozinc Additions on Inorganic Solid Supports

Chiral catalysts were also anchored to inorganic supports for the reaction of dialkylzincs to aldehydes. The early work of Soai on using alumina or silica gel supported amino alcohols for this reaction gave low enantioselectivity (<60% ee).[227]

The heterogeneous catalyst **487** was made by Laspéras et al. by covalently binding an chiral ephedrine on mesoporous micelle-templated silicas

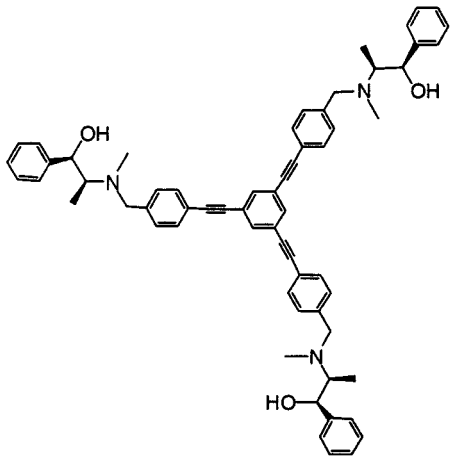


(*S*)-**484**

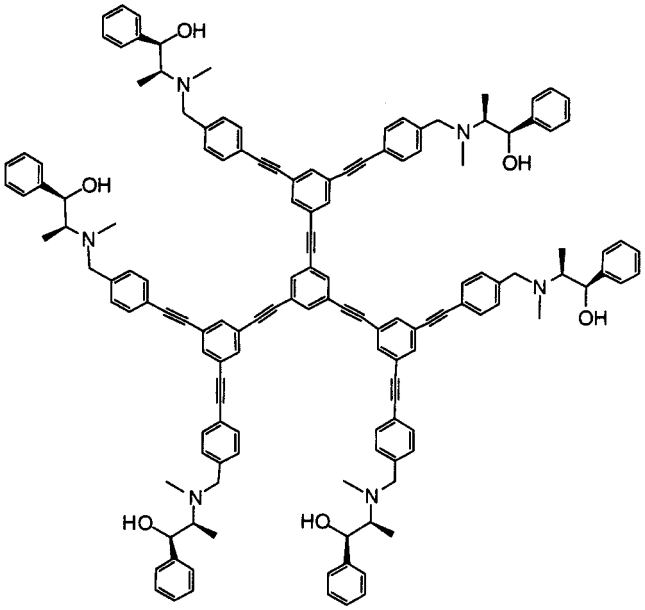
(MTS).[228a] It showed low ee (35−37%) for the reaction of diethylzinc with benzaldehyde. The heterogeneous catalyst containing high surface densities of the amino alcohol ligand and organics showed up to 76% ee.[228b] Kim and co-workers made catalysts **488** and **489** by attaching chiral pyrrolidinemethanol derivatives to the mesoporous silica with a different range of pore sizes.[229] The free surface hydroxyl groups in **489** were partially capped with TMS groups. MCM-41 and SAB-15 are amorphous silica materials having a similar hexagonal pore array but with different pore dimensions. It was found that the MCM-41-based catalysts **488b** and **489b** showed better enantioselectivity than those based on SBA-15. The TMS-capped materials were also better than those uncapped. Addition of ^{n}BuLi to these materials significantly improved their enantioselectivity. However, the enantioselectivity (16−75% ee) of these silica-supported catalysts was still much lower than that of their monomer catalyst **490** (93% ee).

Heckel and Seebach linked TADDOL ligand onto porous silica gel to prepare the solid-supported titanium complex **491**.[230] This material catalyzed the diethylzinc addition to benzaldehyde in toluene at −20 °C in the presence of excess $Ti(O^iPr)_4$ to give (*S*)-1-phenylpropanol with up to 96% ee (98% es) and >95% yield. The catalytic properties of this heterogeneous catalyst are almost the same as its corresponding homogeneous small molecule catalyst. Catalyst **491** could be washed with HCl/H_2O and reconverted to the titanate of the same enantioselectivity even after 10−20 runs.

Quartz exists in nature as either the D or L enantiomorphological form. Soai et al. reported the



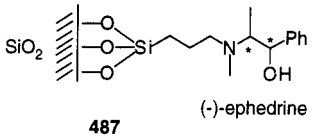
485



486

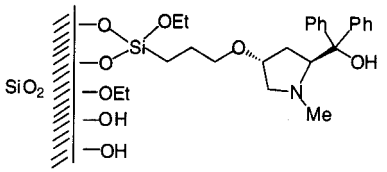
use of D or L quartz crystals to catalyze the reaction of diisopropylzinc with **492** at 0 °C in toluene (Scheme 23).[231] The enantioselectivity of this process reached as high as 93−97% ee for the formation of **493**. The chiral configuration of the product was controlled by the morphology of quartz. The D quartz led to (*S*)-**493**, and the L quartz led to (*R*)-**493**. This asymmetric catalysis might have proceeded with a very small initial enantiomeric enrichment induced by the chiral quartz crystal to generate **493**, which then went through an autocatalytic chiral amplification process to give the high ee product. The chiral induction of this process showed a majority rule effect. When the D/L or L/D ratio was 9:1, the product chirality was determined by the major chiral crystals and the reactions retained their high enantioselectivity (95% ee and 95−96% yield).

Enantiomorphic sodium chlorate ($NaClO_3$) crystals were also used by Soai et al. to carry out the diisopropylzinc addition to the aldehyde **492**.[232] It was demonstrated that almost all of the sodium chlorate crystals formed from a stirred solution have the same chiral form. When *d*-$NaClO_3$ crystal was used to

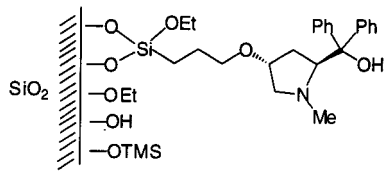


(-)-ephedrine

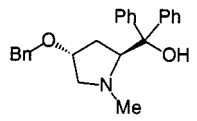
487



488a: amophous silica
488b: MCM-41
488c: SBA-15

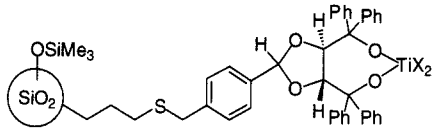


489a: amophous silica
489b: MCM-41
489c: SBA-15



490

catalyze the reaction of **492** with diisopropylzinc, (*S*)-**493** was produced with 96−98% ee at room temperature in toluene. When *l*-$NaClO_3$ crystal was used to catalyze this reaction under the same conditions, (*R*)-**493** was produced with 96−98% ee. The yields of these processes were in the range of 90−98%. When the D/L or L/D ratio was 3:1, the product chirality was determined by the major chiral crystals and the reactions retained their high enantioselectivity (97% ee and 90−92% yield).

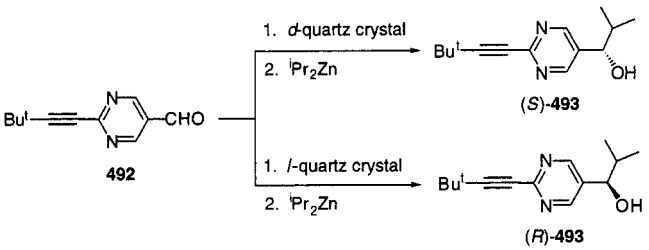


491

10. Summary [233]

Because of the tremendous effort of a great number of researchers, the catalytic asymmetric dialkylzinc addition to aldehydes has become a mature method. Ligands of diverse structures have been obtained, and high enantioselectivity for all different types of aldehydes have been achieved. Among the representative excellent catalysts are compounds **1**, **8**, **120**, **325**, **352**, and **360** discussed above. However, compared to the well-developed dialkylzinc addition, the catalytic asymmetric reactions of aryl-, vinyl-, and alkynylzinc reagents with aldehydes are still very much under developed. Although catalysts such as (*S*)-**402** and **210** prepared by Pu[182,183] and Bolm[185,186] have shown good enantioselectivity for the reaction of diphenylzinc with certain aromatic and aliphatic aldehydes, the generality of these catalysts for other

Scheme 23. Asymmetric Catalysis by Chiral Quartz Crystals



arylzinc reagents have not been studied. The vinylzinc additions using ligands **1** and **412** reported by Oppolzer[188] and Wipf[193] were highly enantioselective for certain aromatic aldehydes but not as good for aliphatic aldehydes. Carreira discovered highly enantioselective alkynylzinc additions to aldehydes promoted by the chiral amino alcohol **415**, but this process was not catalytic yet.[196,197] Ishizaki achieved good enantioselectivity for the catalytic alkynylzinc addition to certain aldehydes by using compounds **160**, but the enantioselectivity for simple linear aliphatic aldehydes was low.[194] Another much less explored area is the organozinc addition to ketones. Yus[174] and Fu[184] showed very promising results by using ligands **381** and **406** for both dialkylzinc and diphenylzinc additions to ketones, but the scope of these reactions were still very limited.

Therefore, more work is needed for the aryl-, vinyl-, and alkynylzinc additions and for the organozinc addition to ketones, although many good catalysts have been obtained for the dialkylzinc addition to aldehydes. Development of these reactions will allow the catalytic asymmetric synthesis of a great variety of functional chiral alcohols that are either the structural units or synthons of many important organic molecules as well as molecules of biological functions.

Macromolecular chiral catalysts have become a very attractive research subject in recent years because these materials offer the advantages of simplified product isolation, easy recovery of the generally quite expensive chiral catalysts, and potential use for continuous production. Three types of macromolecules including flexible achiral polymers anchored with chiral catalysts, rigid and sterically regular main chain chiral polymers, and chiral dendrimers have been used for the asymmetric organozinc addition to aldehydes. Among these materials, the binaphthyl-based polymers such as (*R*)-**451** developed by Pu have shown very high and general enantioselectivity.[159,210,217] Study of the binaphthyl polymers in the asymmetric organozinc addition has demonstrated that it is possible to systematically modify the structure and function of the rigid and sterically regular polymer for the development of highly enantioselective polymer catalysts. The catalytic properties of highly enantioselective monomer catalysts can also be preserved in the rigid and sterically regular polymer provided the catalytically active species of the monomer catalyst is not its aggregate. The TADDOL-based polymers[207] and dendrimers[222] prepared by Seebach showed very high and stable enantioselectivity for the diethylzinc addition to benzaldehyde even after many cycles. These studies on macromolecular chiral catalysts demonstrate that these materials are potentially very useful for practical applications.

11. Acknowledgments

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12. References

(1) (a) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823−2824. (b) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841−842.
(2) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
(3) For an early comprehensive review, see: Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
(4) For other reviews, see: (a) Evans, D. A. *Science* **1988**, *240*, 420−426. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (c) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (d) Soai, K.; Shibata, T. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, pp 911−922.
(5) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 5.
(6) Noyori, R.; Kawai, S. K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597
(7) Carruthers, W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Chapter 49.
(8) Hursthouse, M. B.; Motevaili, M.; O'Brien, P.; Walsh, J. R.; Jones, A. C. *J. Mater. Chem.* **1991**, *1*, 139.
(9) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128.
(10) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327−6335.
(11) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998.
(12) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77.
(13) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877.
(14) For reviews on nonlinear effect in asymmetric catalysis, see: (a) Girard, C.; Kagan, H. B.; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2922−2959. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997−3017.
(15) (a) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832−4842. (b) Kitamura, M.; Yamakawa, M.; Oka, H.; Suga, S.; Noyori, R. *Chem. Eur. J.* **1996**, *2*, 1171−1181 and references therein.
(16) Kitamura, M.; Suga, S.; Makoto, N.; Noyori, R.; Zhai, Z.-X.; Suga, H. *J. Phys. Chem.* **1994**, *98*, 12776−12781.
(17) For a quantitative analysis of the nonlinear effect in the asymmetric dialkylzinc addition catalyzed by **1**, see: Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800−9809.
(18) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605−3164.
(19) Soai, K.; Hatanaka, T.; Yamashita, T.; *J. Chem. Soc., Chem. Commun.* **1992**, 927−929.
(20) Soai, K.; Shimada, C.; Takeuchi, M.; Itabashi, M. *J. Chem. Soc., Chem. Commun.* **1994**, 567−568.
(21) Watanabe, M.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3125.
(22) Soai, K.; Inoue, Y.; Takahashi, T.; Shibata, T. *Tetrahedron* **1996**, *52*, 13355−13362.
(23) Shibata, T.; Hayase, T.; Aiba, Y.; Tabira, H.; Soai, K. *Heterocycles* **1997**, *46*, 235−240.
(24) (a) Soai, K.; Hayase, T.; Takai, K.; Sugiyama, T. *J. Org. Chem.* **1994**, *59*, 7908−7909. (b) Sato, I.; Saito, T.; Soai, K. *J. Chem. Soc., Chem. Commun.* **2000**, 2471−2472.
(25) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108−2113.
(26) Li, S.; Jiang, Y.; Mi, A. *Tetrahedron: Asymmetry* **1992**, *3*, 1467.

(27) Li, S.; Jiang, Y.; Mi, A.; Yang, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 885.
(28) (a) Delair, P., Einhorn, C.; Einhorn, J.; Luche, J. L. *J. Org. Chem.* **1994**, *59*, 4680−4682. (b) Delair, P.; Einhorn, C.; Dinhorn, J.; Luche, J. L. *Tetrahedron* **1995**, *51*, 165−172.
(29) Beliczey, J.; Giffels, G.; Kragl, U.; Wandrey, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1529−1530.
(30) Sibi, M. P.; Chen, J.-X.; Cook, G. R. *Tetrahedron Lett.* **1999**, *40*, 3301−3304.
(31) Goralski, C. T.; Chrisman, W.; Hasha, D. L.; Nicholson, L. W.; Rudolf, P. R.; Zakett, D.; Singaram, B. *Tetrahedron: Asymmetry* **1997**, *8*, 3863−3871.
(32) Kimura, K.; Sugiyama, E.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1992**, *33*, 3147−3150.
(33) Bellucci, C. M.; Bergamini, A.; Cozzi, P. G.; Papa, A.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **1997**, *8*, 895.
(34) Hanyu, N.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2000**, *41*, 4587.
(35) (a) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T.; *Tetrahedron: Asymmetry* **2000**, *11*, 2971−2979. (b) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4127−4136.
(36) Cherng, Y.-J.; Fang, J.-M.; Lu, T.-J. *J. Org. Chem.* **1999**, *64*, 3207−3212.
(37) Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron: Asymmetry* **1997**, *8*, 1869−1876.
(38) Philipova, I.; Dimitrov, V.; Simova, S.; *Tetrahedron: Asymmetry* **1999**, *10*, 1381−1391.
(39) Genov, M.; Dimitrov, V.; Ivanova, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3703−3706.
(40) Goldfuss, B.; Steigelmann, M.; Rominger, F. *Eur. J. Org. Chem.* **2000**, 1785−1792.
(41) (a) Dai, W.-M.; Zhu, H. J.; Hao, X.-J. *Tetrahedron: Asymmetry* **1995**, *6*, 1857−1860. (b) Dai, W.-M.; Zhu, H.-J.; Hao, X.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 2315−2337.
(42) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685−14692.
(43) (a) Palmieri, G. *Eur. J. Org. Chem.* **1999**, *805*, 5−811. (b) Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3361−3373.
(44) de Parrodi, C. A.; Juaristi, E.; Quintero-Cortés, L.; Amador, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1915.
(45) Iulino, A.; Pini, D.; Salvadori, P. *Tetrahedron: Asymmetry* **1995**, *6*, 739−744.
(46) Andrés, J. M.; Martínez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron: Asymmetry* **1994**, *5*, 67−72.
(47) Kossenjans, M.; Martens, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1409−1417.
(48) Tanner, D.; KornØ, H. T.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 14213−14232.
(49) Lawrence, C. F.; Nayak, S. K.; Thijs, L.; Zwanenburg, B.; *Synlett* **1999**, 1571−1572.
(50) Behnen, W.; Mehler, T.; Martens, J. *Tetrahedron: Asymmetry* **1993**, *4*, 1413−1416.
(51) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 1673−1679.
(52) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.
(53) Shibata, T.; Tabira, H.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 177.
(54) (a) Takemoto, Y.; Baba, Y.; Honda, A.; Nakao, S.; Noguchi, I.; Iwata, C.; Tanaka, T.; Ibuka, T. *Tetrahedron* **1998**, *54*, 15567−15580. (b) Takemoto, Y.; Baba, Y.; Noguchi, I.; Iwata, C. *Tetrahedron Lett.* **1996**, *37*, 3345−3346.
(55) Yang, X.; Shen, J.; Da, C.; Wang, R.; Choi, M. C. K.; Yang, L.; Wong, K.-y. *Tetrahedron: Asymmetry* **1999**, *10*, 133−138.
(56) Mehler, T.; Martens, J.; Wallbaum, S. *Synthetic Commun.* **1993**, *23*, 2691−2699.
(57) Cicchi, S.; Crea, S.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **1997**, *8*, 293−301.
(58) (a) Shi, M.; Satoh, Y.; Makihara, T.; Masaki, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2109−2112. (b) Shi, M.; Satoh, Y.; Masaki, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2547−2552.
(59) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264.
(60) (a) Soai, K.; Konishi, T.; Shibata, T. *Heterocycles* **1999**, *51*, 1421−1426. (b) Sato, I.; Saito, T.; Omiya, D.; Takizawa, Y.; Soai, K. *Heterocycles* **1999**, *51*, 2753−2758.
(61) Okaniwa, M.; Yamada, R.; Ibuka, T. *Tetrahedron Lett.* **2000**, *41*, 1047−1050.
(62) (a) Wallbaum, S.; Martens, J.; *Tetrahedron: Asymmetry* **1993**, *4*, 637−640. (b) Wilken, J.; Kossenjans, M.; Gröger, H.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2007−2015. (c) Wilken, J.; Gröger, H.; Kossenjans, M.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2761−2771. (d) Stingl, K.; Martens, J. *Liebigs Ann. Chem.* **1994**, 491−496. (e) Wassmann, S.; Wilken, J.; Martens, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4437−4445. (f) Kossenjans, M.; Soeberdt, M.; Wallbaum, S.; Harms, K.; Martens, J.; Aurich, H. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2353−2365. (g) Eilers, J.; Wilken, J.; Martens, J. *Tetrahedron: Asymmetry* **1996**, *7*, 2343−2357.
(63) Kotsuki, H.; Wakao, M.; Hayakawa, H.; Shimanouchi, T.; Shiro, M. *J. Org. Chem.* **1996**, *61*, 8915−8920.
(64) (a) Brunel, J.-M.; Constantieux, T.; Legrand, O.; Buono, G. *Tetrahedron Lett.* **1998**, *39*, 2961. (b) Legrand, O.; Brunel, J.-M.; Buono, G. *Tetrahedron Lett.* **1998**, *39*, 9419. (c) Legrand, O.; Brunel, J.-M.; Buono, G. *Tetrahedron Lett.* **2000**, *41*, 2105−2109.
(65) (a) Solà, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078−7082. (b) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M.; Riera, A. *J. Org. Chem.* **1999**, *64*, 3969−3974. (c) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970−4982. (d) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773−8776. (e) Vázquez, J.; Pericàs, M. A.; Maseras, F.; Lledós, A. *J. Org. Chem.* **2000**, *65*, 7303−7309.
(66) (a) Solà, L.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1559−1568. (b) A correction of the structural assignment appeared in *Tetrahedron: Asymmetry* **1997**, *8*, 3985.
(67) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthesis* **2000**, *1*, 165−176.
(68) Matsumoto, Y.; Chno, A.; Lu, S.-j.; Hayashi, T.; Oguni, N.; Hayashi, M. *Tetrahedron: Asymmetry* **1993**, *4*, 1763−1766.
(69) Kawanami, Y.; Mitsuie, T.; Miki, M.; Sakamoto, T.; Nishitani, K. *Tetrahedron* **2000**, *56*, 175−178.
(70) (a) Stingl, K.; Martens, J. *Synth. Commun.* **1992**, *22*, 2745−2756. (b) Dai, W.-M.; Zhu, H.-J.; Hao, X.-J. *Tetrahedron Lett.* **1996**, *37*, 5971−5974. (c) Lee, S. H.; Im, D. S.; Cheong, C. S.; Chung, B. Y. *Heterocycles* **1999**, *51*, 1913−1919.
(71) Nugent, W. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1369−1370.
(72) Rosner, T.; Sears, P. J.; Nugent, W. A.; Blackmond, D. G. *Org. Lett.* **2000**, *2*, 2511−2513.
(73) (a) Knollmüller, M.; Ferencic, M.; Gärtner, P.; Mereiter, K.; Noe, C. R. *Tetrahedron: Asymmetry* **1998**, *9*, 4009−4020. (b) Knollmüller, M.; Feerencic, M.; Gärtner, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3969−3975.
(74) Nakano, H.; Iwasa, K.; Hongo, H. *Heterocycles* **1997**, *44*, 435−442.
(75) (a) Bolm, C.; Ewald, M.; Relder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169−1190. (b) Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191−1203. (c) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205−207.
(76) Chelucci, G.; Soccolini, F. *Tetrahedron: Asymmetry* **1992**, *3*, 1235−1238.
(77) Kwong, H.-L., Lee, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3791−3801.
(78) Collomb, P.; von Zelewsky, A. *Tetrahedron: Asymmetry* **1998**, *9*, 3911.
(79) (a) Ishizaki, M.; Fujita, K.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 411−424. (b) Ishizaki, M.; Hoshino, O. *Chem. Lett.* **1994**, 1337−1340.
(80) Williams, D.; Fromhold, M. G. *Synlett* **1997**, 523−524.
(81) Macedo, E.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 549−558.
(82) Kang, J.; Kim, H. Y.; Kim, J. H. *Tetrahedron: Asymmetry* **1999**, *10*, 2523−2533.
(83) Kotsuki, H.; Nakagawa, Y.; Moriya, N.; Tateishi, H.; Ochi, M.; Suzuki, T.; Isobe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1165−1174.
(84) Kotsuki, H.; Hayakawa, H.; Tateishi, H.; Wakao, M.; Shiro, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3203−3212.
(85) (a) Wu, Y.; Yun, H.; Wu, Y.; Ding, K.; Zhou, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 3543−3552. (b) Yun, H.; Wu, Y.; Wu, Y.; Ding, K.; Zhou, Y. *Tetrahedron Lett.* **2000**, *41*, 10263−10266.
(86) (a) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002. (b) Zhang, H.; Chan, K. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 381.
(87) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382.
(88) Mino, T.; Oishi, K.; Yamashita, M. *Synlett* **1998**, 965−966.
(89) (a) Cozzi, P. G.; Papa, A.; Umani-Ronchi, A. *Tetrahedron: Lett* **1996**, *37*, 4613. (b) Fleischer, R.; Braun, M. *Synlett* **1998**, *12*, 1441−1443.
(90) (a) Cho, B. T.; Kim, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2901−2907. (b) Cho, B. T.; Kim, N. *Synth. Commun.* **1995**, *25*, 167−175. (c) Cho, B. T.; Kim, N. *Bull. Korean Chem. Soc.* **1994**, *15*, 931−932. (d) Cho, B. T.; Kim, N.; Khoo, J.-H. *Bull. Korean Chem. Soc.* **1996**, *17*, 1−2. (e) Cho, B. T.; Kim, N. *Tetrahedron Lett.* **1994**, *35*, 4115−4118.
(91) Yang, W. K.; Cho, B. T. *Tetrahedron: Asymmetry* **2000**, *11*, 2947−2953.
(92) (a) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1998**, *9*, 1489−1492. (b) Cho, B. T.; Chun, Y. S.; Yang, W. K. *Tetrahedron: Asymmetry* **2000**, *11*, 2149−2157.
(93) Ikota, N.; Inaba, H. *Chem. Pharm. Bull.* **1996**, *44*, 587−589.
(94) Bringmann, G.; Breuning, M. *Tetrahedron: Asymmetry* **1998**, *9*, 667−679.

(95) Vyskocil, S.; Jaracz, S.; Smrcina, M.; Stícha, M.; Hanus, V.; Polásek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7727−7737.
(96) Keller, F.; Rippert, A. J. *Helv. Chim. Acta* **1999**, *82*, 125−137.
(97) Furusho, Y.; Tsunoda, A.; Aida, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 183−190.
(98) Nicolosi, G.; Patti, A.; Morrone, R.; Piattelli, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1639−1642.
(99) Dosa, P.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445.
(100) (a) Watanabe, M. *Synlett* **1995**, 1050−1052. (b) Watanabe, M.; Hashimoto, N.; Araki, S.; Butsugan, Y. *J. Org. Chem.* **1992**, *57*, 742−744.
(101) Watanabe, M. *Tetrahedron Lett.* **1995**, *36*, 8991−8994.
(102) Watanabe, M.; Komota, M.; Nishimura, M.; Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2193-2196.
(103) (a) Wally, H.; Widhalm, M.; Weissensteiner, W.; Schlögl, K. *Tetrahedron: Asymmetry* **1993**, *4*, 285−288. (b) Patti, A.; Nicolosi, G.; Howell, J. A. S.; Humphries, K. *Tetrahedron: Asymmetry* **1998**, *9*, 4381−4394.
(104) (a) Bolm, C.; Fernández, K. M.; Seger, A.; Raabe, G. *Synlett*, **1997**, 1051−1052. (b) Bolm, C.; Muñiz-Fernández, K.; Seger, A.; Raabe, G.; Günther, K. *J. Org. Chem.* **1998**, *63*, 7860−7867. (c) Bolm, C.; Muñiz, K.; Hildebrand, J. P. *Org. Lett.* **1999**, *1*, 491−493.
(105) Deng, W.-P.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 4689−4693.
(106) Zhang, W.; Yoshinaga, H.; Imai, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2000**, *10*, 1512−1514.
(107) (a) Malfait, S.; Pélinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2595−2610. (b) Malfait, S.; Pélinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1996**, *7*, 653−656.
(108) Maciejewski, L. A.; Goetgheluck, S. J.; Delacroix, O. A.; Brocard, J. S. *Tetrahedron: Asymmetry* **1996**, *7*, 1573−1576.
(109) Malfait, S.; Pélinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2207−2210.
(110) Fukuzawa, S.-i.; Kato, H. *Synlett* **1998**, 727.
(111) Fukuzawa, S.-i.; Tsuchiya, D.; Sasamoto, K.; Hirano, K.; Ohtaguchi, M. *Eur. J. Org. Chem.* **2000**, 2877−2883.
(112) Bastin, S.; Brocard, J.; Pélinski, L. *Tetrahedron Lett.* **2000**, *41*, 7303−7307.
(113) Bastin, S.; Delebecque, N.; Agbossou, F.; Brocard, J.; Pélinski, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1647−1651.
(114) (a) Heaton, S. B.; Jones, G. B. *Tetrahedron Lett.* **1992**, *33*, 1693−1696. (b) Jones, G. B.; Heaton, S. B. *Tetrahedron: Asymmetry* **1993**, *4*, 261−272. (c) Jones, G. B.; Huber, R. S.; Chapman, B. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1797−1809.
(115) Jones, G. B.; Guzel, M.; Chapman, B. J. *Tetrahedron: Asymmetry* **1998**, *9*, 901−905.
(116) Uemura, M.; Miyake, R.; Nakayama, K.; Shiro, M.; Hayashi, Y. *J. Org. Chem.* **1993**, *58*, 1238−1244.
(117) Allen, J. V.; Frost, C. G.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1993**, *4*, 649−650.
(118) Chan, T. H.; Zheng, G. Z. *Can. J. Chem.* **1997**, *75*, 629−633.
(119) (a) Zhu, H. J.; Zhao, B.-T.; Dai, W.-M.; Zhou, J.; Hao, X.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 2879−2888. (b) Dai, W.-M.; Zhu, H. J.; Hao, X.-J. *Tetrahedron: Asymmetry* **1996**, *7*, 1245−1248.
(120) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1997**, *62*, 3770−3771.
(121) Falorni, M.; Collu, C.; Conti, S.; Giacomelli, G. *Tetrahedron: Asymmetry* **1996**, *7*, 293−299.
(122) Huang, H.-L.; Lin, Y.-C.; Chen, S.-F.; Wang, C.-L.; Liu, L. T. *Tetrahedron: Asymmetry* **1996**, *7*, 3067.
(123) Aurich, H. G.; Biesemeier, F.; Geiger, M.; Harms, K. *Liebigs Ann./Recl.* **1997**, 423.
(124) (a) Poelert, M. A.; Hof, R. P.; Peper, N. C. M. W.; Kellogg, R. M. *Heterocycles* **1994**, *37*, 461−475. (b) Hof, R. P.; Poelert, M. A.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 31−34.
(125) Fitzpatrick, K.; Hulst, R.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1861−1864.
(126) (a) Kang, J.; Kim, J. W.; Lee, J. W.; Kim, D. S.; Kim, J. I. *Bull. Korean Chem. Soc.* **1996**, *17*, 1135−1142. (b) Kang, J.; Kim, D. S.; Kim, J. I. *Synlett* **1994**, 842−844. (c) Kang, J.; Lee, J. W.; Kim J. I. *J. Chem. Soc., Chem. Commun.* **1994**, 2009−2010.
(127) (a) Gibson, C. L. *J. Chem. Soc., Chem. Commun.* **1996**, 645−646. (b) Cran, G. A.; Gibson, C. L.; Handa, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1553−1556. (c) Fulton, D. A.; Gibson, C. L. *Tetrahedron Lett.* **1997**, *38*, 2019−2022.
(128) Gibson, C. L. *Tetrahedron: Asymmetry* **1999**, *10*, 1551−1561.
(129) Braga, A. L.; Appelt, H. R.; Schneider, P. H.; Silveira, C. C.; Wessjohann, L. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1733−1738.
(130) (a) Masaki, Y.; Satoh, Y.; Makihara, T.; Shi, M. *Chem. Pharm. Bull.* **1996**, *44*, 454−456. (b) Masaki, Y.; Oda, H.; Kazuta, K.; Usui, A.; Itoh, A.; Xu, F. *Tetrahedron Lett.* **1992**, *33*, 5089−5092.
(131) (a) Rijnberg, E.; Jastrzebski, J. T. B. H..; Janssen, M. D.; Boersma, J.; van Koten, G. *Tetrahedron Lett.* **1994**, *35*, 6521−6524. (b) Rijnberg, E.; Hovestad, N. J.; Kleij, A. W.; Jastrzebski, J. T. B. H.; Boersma, J.; Janssen, M. D.; Spek, A. L.; van Koten, G. *Organometallics* **1997**, *16*, 2847−2857.
(132) (a) Anderson, J. C.; Harding, M. *J. Chem. Soc., Chem. Commun.* **1998**, 393−394. (b) Anderson, J. C.; Cubbon, R.; Harding, M. James, D. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3461−3490.
(133) (a) Nakano, H.; Kumagai, N.; Kabuto, C.; Matsuzaki, H.; Hongo, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1233−1236. (b) Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1391−1401.
(134) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530−2535.
(135) Jin, M.-J.; Ahn, S.-J.; Lee, K.-S. *Tetrahedron Lett.* **1996**, *37*, 8767−8770.
(136) Aurich, H. G.; Soeberdt, M. *Tetrahedron Lett.* **1998**, *39*, 2553.
(137) Chelucci, G.; Berta, D.; Fabbri, D.; Pinna, G. A.; Saba, A.; Ulgheri, F. *Tetrahedron: Asymmetry* **1998**, *9*, 1933−1940.
(138) Hulst, R.; Heres, H.; Fitzpatrick, K.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2755.
(139) Bolm, C.; Müller, J.; Schlingloff, G.; Zehnder, M.; Neuburger, M. *J. Chem. Soc., Chem. Commun.* **1993**, 182.
(140) Bolm, C.; Müller, J. *Tetrahedron* **1994**, *50*, 4355.
(141) (a) Wirth, T. *Tetrahedron Lett.*, **1995**, *36*, 7849−7852. (b) Wirth, T.; Kulicke, K. J.; Fragale, G. *Helv. Chim. Acta* **1996**, *79*, 1957−1966. (c) Santi, C.; Wirth, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1019−1023.
(142) (a) Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1991**, *47*, 8251−8258. (b) Conti, S.; Falorni, M.; Giacomelli, G.; Soccolini, F. *Tetrahedron* **1992**, *48*, 8993−9000.
(143) Asami, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1687−1690.
(144) Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4165−4173.
(145) Pini, D.; Mastantuono, A.; Uccello-Barretta, G.; Iuliano, A.; Salvadori, P. *Tetrahedron* **1993**, *49*, 9613−9624.
(146) (a) Fuji, K.; Tanaka, K.; Miyamoto, H. *Chem. Pharm. Bull.* **1993**, *41*, 1557−1561. (b) Eriksson, J.; Arvidsson, P. I.; Davidsson, O. *Chem. Eur. J.* **1999**, *5*, 2356−2361. (c) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2717−2720.
(147) Harmata, M.; Kahraman, M.; *Tetrahedron: Asymmetry* **2000**, *11*, 2875−2879.
(148) (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99−101. (b) Schmidt, B.; Seebach, D. Angew. *Chem., Int. Ed. Engl.* **1991**, *30*, 1321−1323. (c) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D. *Helv. Chim. Acta* **1992**, *75*, 2171−2209. (d) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473−7484. (e) Seebach, D.; Beck A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363−4384. (f) Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohác, A.; Ganter, C.; Gawley, R. E.; Kühnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071−2210.
(149) (a) Dreisbach, C.; Kragl, U.; Wandrey, C. *Synthesis* **1994**, 911−912. (b) Waldmann, H.; Weigerding, M.; Dreisbach, C.; Wandrey, C. *Helv. Chim. Acta* **1994**, *77*, 2111−2116.
(150) Seebach, D.; Pichota, A.; Beck, A. K.; Pinkerton, A. B.; Litz, T.; Karjalainen, J.; Gramlich, V. *Org. Lett.* **1999**, *1*, 55−58.
(151) Qian, C.-T.; Gao, F.-F.; Sun, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1733−1740.
(152) You, J.-S.; Shao, M.-Y.; Gau, H.-M. *Organometallics* **2000**, *19*, 3368−3373.
(153) Bonetto, L.; Fornasier, R.; Tonellato, U. *Gazz. Chim. Ital.* **1995**, *125*, 63−64.
(154) Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 1957−1960.
(155) (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405−2494. (b) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (c) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (d) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977.
(156) (a) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233−6236. (b) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585−589. (c) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651−3655. (d) Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, ASAP Article.
(157) (a) Kitajima, H.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207−217. (b) Kitajima, H.; Ito, K.; Katsuki, T. *Chem. Lett.* **1996**, 343−344. (c) Kodama, H.; Ito, J.; Nagaki, A.; Ohta, T.; Furukawa, I. *Appl. Organometal. Chem.* **2000**, *14*, 709−714.
(158) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364.
(159) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940.
(160) (a) Ding, K.; Ishii, A.; Mikami, A. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 497. (b) Angeland, R.; Matsumoto, Y.; Korenaga, T.; Kudo, K.; Senda, M.; Mikami, K. *Chirality* **2000**, *12*, 544−547.
(161) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **2000**, *41*, 57−60.
(162) (a) Kostova, K.; Genov, M.; Philipova, I.; Dimitrov, V. *Tetrahedron: Asymmetry* **2000**, *11*, 3253−3256. (b) Chen, Y.-X.; Yang, L.-W.; Li, Y.-M.; Zhou, Z.-Y.; Lam, K.-H.; Chan, A. S. C.; Kwong, H.-L. *Chirality* **2000**, *12*, 510−513.

(163) (a) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657. (b) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095. (c) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S.; *Tetrahedron* **1992**, *48*, 5691. (d) Knochel, P.; Perea, J.; Almena, J.; Jones, P. *Tetrahedron* **1998**, 8275. (e) Knochel, P. *Synlett* **1995**, 393.
(164) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423−6424.
(165) Balsells, J.; Betancort, J. M.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3428−3430.
(166) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 3250.
(167) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1802.
(168) Hwang, C.-D.; Uang, B.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3979−3984.
(169) Paquette, L. A.; Zhou, R. *J. Org. Chem.* **1999**, *64*, 7929−7934.
(170) (a) Zhang, X.; Guo, C. *Tetrahedron Lett.* **1995**, *36*, 4947−4950. (b) Qiu, J.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 2665−2668.
(171) Guo, C.; Qiu, J.; Zhang, X.; Verdugo, D.; Larter, M. L.; Christie, R.; Kenney, P.; Walsh, P. J. *Tetrahedron* **1997**, *53*, 4145−4158.
(172) Ho, D. E.; Betancort, J. M.; Woodmansee, D. H.; Larter, M. L.; Walsh, P. J. *Tetrahedron Lett.* **1997**, *38*, 3867−3870.
(173) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1629−1644.
(174) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239−1242.
(175) Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2479−2496.
(176) Ito, K.; Kimura, Y.; Okamura, H.; Katsuki, T. *Synlett* **1992**, 573−574.
(177) Cho, B. T.; Chun, Y. S. *Synth. Commun.* **1999**, *29*, 521−531.
(178) (a) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3319−3325. (b) Shi, M.; Sui, W.-S. *Chirality* **2000**, *12*, 574−580.
(179) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **2000**, *11*, 835−841.
(180) Soai, K.; Hirose, Y.; Ohno, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1473−1474.
(181) Shibata, T.; Tabira, H.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 177.
(182) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222.
(183) Huang, W.-S.; Pu, L. *Tetrahedron. Lett.* **2000**, *41*, 145.
(184) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446.
(185) Bolm, C.; Muñiz, K. *J. Chem. Soc., Chem. Commun.* **1999**, 1295−1296.
(186) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465−3467.
(187) (a) Oppolzer, W.; Radinov, R. *Tetrahedron Lett.* **1988**, *29*, 5645. (b) Oppolzer, W.; Radinov, R. *Tetrahedron Lett.* **1988**, *32*, 5777.
(188) Oppolzer, W.; Radinov, R. *Helv. Chim. Acta* **1992**, *75*, 170.
(189) Bussche-Hünnefeld, J. L. von dem; Seebach, D. *Tetrahedron* **1992**, *48*, 5719.
(190) Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1257.
(191) Shibata, T.; Nakatsui, K.; Soai, K. *Inorg. Chim. Acta* **1999**, *296*, 33−36.
(192) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Xu, W. *Org. Synth.* **1996**, *74*, 205.
(193) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.
(194) Ishizaki, M.; Hoshino, O.; *Tetrahedron: Asymmetry* **1994**, *5*, 1901.
(195) Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. *Synthesis* **1999**, 1453.
(196) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *26*, 4233−4236.
(197) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373.
(198) (a) Itsuno, S. In *Polymeric Materials Encyclopedia; Synthesis, Properties and Applications*; Salamone, J. C., Ed.; CRC Press: Boca Raton, FL, 1996; Vol. 10, p 8078. (b) Itsuno, S.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S.; Fréchet, J. M. *J. Org. Chem.* **1990**, *55*, 304−310. (c) Itsuno, S.; Fréchet, J. M. *J. Org. Chem.* **1987**, *52*, 4140−4142. (d) Pu, L. *Tetrahedron: Asymmetry* **1998**, *9*, 1457.
(199) Watanabe, M.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 837−842.
(200) (a) Hodge, P.; Sung, D. W. L.; Stratford, P. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2335−2342. (b) Sung, D. W. L.; Hodge, P.; Stratford, P. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1463−1472.
(201) ten Holte, P.; Wijgergangs, J.-P.; Thijs, L.; Zwanenburg, B. *Org. Lett.* **1999**, *1*, 1095−1097.
(202) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Percàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309−6318.
(203) Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712−7713.
(204) (a) Kragl, U.; Dreisbach, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 642−644. (b) Dreisbach, C.; Wischnewski, G.; Kragl, U.; Wandrey, C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 875−878.
(205) Bolm, C.; Dinter, C. L.; Seger, A.; Höcker, H.; Brozio, J. *J. Org. Chem.* **1999**, *64*, 5730−5731.
(206) El Moualij, N.; Caze, C. *Eur. Polym. J.* **1995**, *31*, 193−198.
(207) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710−1740.
(208) (a) Yang, X.-W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295−296. (b) Yang, X.; Liu, D.; Wang, H.; Shen, J.; Da, C.; Wang, R.; Chan, A. S. C. *Tetrahedron* **2000**, *56*, 3511−3516.
(209) Halm, C.; Kurth, M. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 510−512.
(210) Pu, L. *Chem. Eur. J.* **1999**, *5*, 2227.
(211) Hu, Q.-S.; Zheng, X.-F.; Pu, L. *J. Org. Chem.* **1996**, *61*, 5200.
(212) Hu, Q.-S.; Vitharana, D.; Zheng, X.-F.; Wu, C.; Kwan, C. M. S.; Pu, L. *J. Org. Chem.* **1996**, *61*, 8370.
(213) Huang, W.-S.; Hu, Q.-S.; Zheng, X.-F.; Anderson, J.; Pu, L. *J. Am. Chem. Soc.* **1997**, *119*, 4313.
(214) Hu, Q.-S.; Huang, W.-S.; Vitharana, D.; Zheng, X.-F.; Pu, L. *J. Am. Chem. Soc.* **1997**, *119*, 12454.
(215) Yu, H.-B.; Zheng, X.-F.; Hu, Q.-S.; Pu, L. *Polym. Prepr.* **1999**,*40-(1)*, 546.
(216) Lin, Z.-M.; Hu, Q.-S.; Pu, L. *Polym. Prepr.* **1998**, *39(1)*, 235.
(217) Hu, Q.-S.; Huang, W.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 2798.
(218) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500.
(219) Dong, C.; Zhang, J.; Zheng, W.; Zhang, L.; Yu, Z.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2000**, *11*, 2449−2454.
(220) Rheiner, P. B.; Seebach, D. *Chem. Eur. J.* **1999**, *5*, 3221−3236.
(221) Rheiner, P. B.; Sellner, H.; Seebach, D. *Helv. Chim. Acta* **1997**, *80*, 2027.
(222) Sellner, H.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1918−1920.
(223) Sellner, H.; Faber, C.; Rheiner, P. B.; Seebach, D. *Chem. Eur. J.* **2000**, *6*, 3692−3705.
(224) Bolm, C.; Derrien, N.; Seger, A. *Synlett* **1996**, 387−388.
(225) Hu, Q.-S.; Pugh, V.; Sabat, M.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7528.
(226) Sato, I.; Shibata, T.; Ohtake, K.; Kodaka, R.; Hirokawa, Y.; Shirai, N.; Soai, K. *Tetrahedron Lett.* **2000**, *41*, 3123.
(227) Soai, K.; Watanabe, M. Yamamoto, A. *J. Org. Chem.* **1990**, *55*, 4832.
(228) (a) Laspéras, M.; Bellocq, N.; Brunel, D.; Moreau, P. *Tetrahedron: Asymmetry* **1998**, *9*, 3053−3064. (b) Abramson, S.; Laspéras, M.; Galameau, A.; Desplantier-Giscard, D.; Brunel, D. *J. Chem. Soc., Chem. Commun.* **2000**, 1773−1774.
(229) Bae, S. J.; Kim, S.-W.; Hyeon, T.; Kim, B. M. *J. Chem. Soc., Chem. Commun.* **2000**, 31−32.
(230) Heckel, A.; Seebach, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 163−165.
(231) Soai, K.; Osanai, S.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Sato, I. *J. Am. Chem. Soc.* **1999**, *121*, 11235−11236.
(232) Sato, I.; Kadowaki, K.; Soai, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1510.
(233) References added to the proof: (a) Polystyrene-bound BINOL and substituted BINOLS in the presence of $Ti(O^iPr)_4$ catalyzed the reaction of aldehydes with diethylzinc with 84−95% ee. Lipshutz, B. H.; Shin, Y.-J. *Tetrahedron Lett.* **2000**, *41*, 9515−9521. (b) Fluorine-substituted BINOL in the presence of $Ti(O^iPr)_4$ catalyzed the diethylzinc addition to 1-naphthaldehyde with up to 89% ee, similar to BINOL. Chen, Y.; Yekta, S.; Martyn, L. J. P.; Zheng, J.; Yudin, A. K. *Org. Lett.* **2000**, *2*, 3433−3436. (c) Thiazolidine derivatives catalyzed the diethylzinc addition to aryl and alkyl aldehydes with 52−90% ee. Meng, Q. L.; Li, Y. L.; He, Y.; Guan, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 4255−4261. (d) A tetrahedroBINOL ligand in combination with $Ti(O^iPr)_4$ catalyzed the reaction of diethylzinc with aldehydes with up to 93% ee. Shen, X. Q.; Guo, H.; Ding, K. L. *Tetrahedron: Asymmetry* **2000**, *11*, 4321−4327. (e) Amino alcohols containing 2,2′-bridged binaphthyl unit showed up to 97% ee for the diethylzinc addition to aromatic aldehydes. Arroyo, N.; Haslinger, U.; Mereiter, K.; Widhalm, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4207−4219. (f) Cobaltocene- and ferrocene-based chiral oxazolines catalyzed the diethylzinc addition to benzaldehyde with 8−75% ee. Jones, G.; Butler, D. C. D.; Richards, C. J. *Tetrahedron Lett.* **2000**. *41*, 9351−9354. (g) A ferrocenyl diselenide catalyzed the reaction of aldehydes with diethylzinc with low enantioselectivity (≤44% ee). Bolm, C.; Kesselgruber, M.; Grenz, A.; Hermanns, N.; Hildebrand, J. P. *New J. Chem.* **2001**, *25*, 13−15. (h) Chiral amino acid-derived tetracoordinated zinc complexes were observed to catalyze the diethylzinc addition to aryl and alkyl aldehydes with up to 96% ee. The corresponding polystyrene-supported complex showed lower enantioselectivity (up to 79% ee). Dangel, B. D.; Polt, R. *Org. Lett.* **2000**, *2*, 3003−3006. (i) Amino alcohols containing various sizes of N−O heterocycles catalyzed the diethylzinc addition to benzaldehyde with up to 98% ee. Juanes, O.; Rodriguez-Ubis, J. C.; Brunet, E.; Pennemann, H.; Kossenjans, M.; Martens, J. *Eur. J. Org. Chem.* **1999**, *12*, 3323−3333. (j) Amino alcohols with a bispidine framework gave 52−98% ee for the diethylzinc addition to aromatic and aliphatic aldehydes. Spieler, J.; Huttenloch, O.; Waldmann, H. *Eur. J. Org. Chem.* **2000**, *3*, 391−399. (k) 1,3-

Dithian-2-yl-substituted aliphatic aldehydes reacted with diethylzinc in the presence of chiral amino alcohols with up to 70% ee. Wilken, J.; Winter, M.; Stahl, I.; Martens, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1067−1071. (l) A bis[5]helicene-based diol catalyzed the reaction of diethylzinc with benzaldehyde with 81% ee without using $Ti(O^iPr)_4$. Dreher, S. D.; Katz, T. J.; Lam, K. C.; Rheingold, A. L. *J. Org. Chem.* **2000**, *65*, 815−822. (m) Chiral hydroquinolines as ligands for the diethylzinc addition to benzaldehyde with up to 61% ee. Chelucci, G.; Craba, S.; Saba, A.; Soccolini, F.; Sotgiu, G. *J. Mol. Catal. A: Chem.* **2000**, *164*, 173−179. (n) Pyridine *N*-oxide-based ligands gave ≤64% ee for the reaction of diethylzinc with benzaldehyde. Derdau, V.; Laschat, S.; Hupe, E.; König, W. A.; Dix, I.; Jones, P. G. *Eur. J. Inorg. Chem.* **1999**, *6*, 1001−1007. (o) Chiral sulfinylamines catalyzed the diethylzinc addition to benzaldehyde with low enantioselectivity (≤14% ee). Chan, W. H.; Lee, A. W. M.; Lin, J. *J. Chem. Research, Synop.* **1999**, 126−127. (p) A chiral 5,5′-(3,3′-bipyridyl)dialkanediol was found to carry out an autocatalysis for the diisopropylzinc addition to the corresponding dialdehyde with up to 75% ee. Tanji, S.; Nakao, T.; Sato, I.; Soai, K. *Heterocycles* **2000**, *53*, 2183−2189. (q) A polyacetylene substituted with the ephedrine units was shown to catalyze the dialkylzinc addition to benzaldehyde with ≤49% ee. Yashima, E.; Maeda, Y.; Okamoto, Y. *Polym. J.* **1999**, *31*, 1033−1036.

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