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Asymmetric addition of achiral organomagnesium reagents or organolithiums to achiral aldehydes or ketones: a review

Matthew R. Luderer [a,*], William F. Bailey [b,*], Mark R. Luderer [b], Justin D. Fair [b], Robert J. Dancer [c], Michael Bech Sommer [c]

[a] *Department of Natural Science, University of Pittsburgh at Greensburg, Greensburg, PA 15601, USA*
[b] *Department of Chemistry, University of Connecticut, Storrs, CT 06269, USA*
[c] *H. Lundbeck A/S, Process Chemistry, DK-2500, Copenhagen, Denmark*

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ABSTRACT

The enantioselective preparation of chiral secondary and tertiary alcohols via addition of an achiral organomagnesium reagent or an organolithium to an achiral aldehyde or ketone in a chiral medium is reviewed. The review is written in chronological order and contains 113 references to literature through late 2008.

Contents

1. Introduction

The formation of a carbon–carbon σ-bond via nucleophilic addition of an organometallic reagent to a carbonyl substrate constitutes one of the most elementary transformations in organic synthesis. The dawn of organometallic chemistry dates to 1849 with Frankland's early work on organozinc compounds.[1] By the turn of the 20th century, the routine use of organozinc reagents in organic synthesis was largely supplanted by main-group organometallics thanks to the rapid growth of Grignard chemistry[2] and the development of practical routes to organolithium compounds.[3] Attempts to effect enantioselective addition of these main-group organometallics to achiral carbonyl substrates has a long, rich history that has been reviewed only sporadically.[4]

Given current interest in the use of organozinc reagents for asymmetric addition to carbonyl substrates[5–7] as well as chemistry involving chromium,[8] titanium,[9] and aluminum organometallics[10] for this purpose, it seemed worthwhile to survey the literature dealing with attempts to effect the asymmetric addition of an organomagnesium reagent or an organolithium to an achiral aldehyde (Fig. 1) or ketone.

2. 1940–1949

The genesis of enantioselective addition to carbonyl compounds dates to a 1940 report by Betti and Lucchi[11] on the reaction of methylmagnesium iodide with benzaldehyde in the presence of *N*,*N*-dimethylbornylamine as solvent to give optically active 1-phenylethanol. However, Tarbell and Paulson were unable to replicate these results and concluded that the slight optical rotation observed by Betti and Lucchi apparently originated from an

* Corresponding authors. Tel.: +1 860 486 2163; fax: +1 860 486 2981 (W.F.B.).
E-mail address: William.Bailey@uconn.edu (W.F. Bailey).

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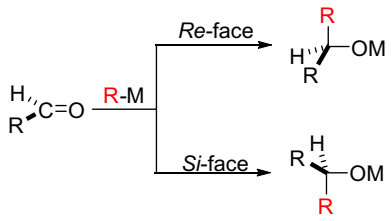
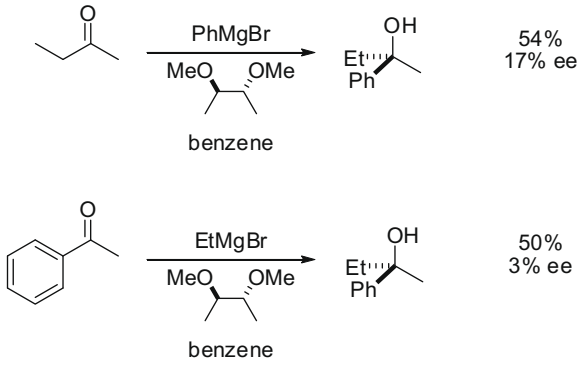


Figure 1. Addition of an organometallic to an achiral aldehyde.

optically active by-product generated from the *N*,*N*-dimethylbornylamine solvent.[12]

3. 1950–1959

In the 1950s, Wright et al. reported what appears to be the first successful enantioselective addition of Grignard reagents to achiral carbonyl substrates.[13,14] In these early studies, chiral ethers were employed as cosolvents in an effort to promote an asymmetric addition. Enantioselectivities were quite poor. For example, as illustrated in Scheme 1, the reaction of 2-butanone with phenylmagnesium bromide in benzene containing (2*R*,3*R*)-(+)-dimethoxybutane afforded (*R*)-(+)-2-phenyl-2-butanol in 54% yield and 17% ee.[13,14] Similarly, reaction of acetophenone with ethylmagnesium bromide in benzene containing the same ether afforded the same enantiomer, (*R*)-(+)-2-phenyl-2-butanol, in 50% yield but only in 3% ee. Wright later reported that addition of dimethylmagnesium to benzaldehyde in benzene containing (2*R*,3*R*)-(+)-dimethoxybutane gave (*S*)-(−)-1-phenylethanol with an ee of ~20%.[15]

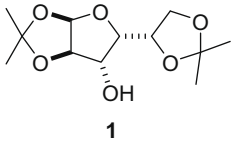


Scheme 1. Grignard additions in the presence of (2*R*,3*R*)-(+)-dimethoxybutane.

In a similar vein, Blomberg and Coops reported that the diether, (2*R*,3*R*)-(+)-dimethoxybutane, was more effective than a monoether in promoting asymmetric addition of Grignard reagents to aldehydes and ketones.[16,17]

4. 1960–1969

The carbohydrate, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **1** (Fig. 2), was found by Inch et al. to promote the addition



1

Figure 2. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose.

of Grignard reagents to ketones with good enantioselectivity:[18] Reaction of cyclohexyl phenyl ketone with methylmagnesium bromide in the presence of **1** (1:3.5:2 molar ratio) in diethyl ether afforded (*R*)-(+)-1-cyclohexyl-1-phenylethanol in 95% yield and 70% ee. Other sugar derivatives were also found to promote asymmetric addition, but none surpassed the effectiveness of **1**.

Nozaki et al. investigated the ability of (−)-sparteine **2** (Fig. 3) to promote asymmetric addition of Grignard and organolithium reagents to aldehydes and ketones.[19,20] Treatment of benzaldehyde with ethylmagnesium bromide in the presence of **2** in toluene solvent at −70 °C afforded (*R*)-(+)-1-phenyl-1-propanol in 15% yield and 22% ee. Under similar conditions, the addition of ethylmagnesium bromide to acetophenone gave the racemic alcohol in 11% yield. The reaction of benzaldehyde with *n*-BuLi in the presence of **2** in hexane solvent at −70 °C gave (*R*)-(+)-1-phenyl-1-pentanol in 90% yield and 6% ee.

2

Figure 3. (−)-Sparteine.

5. 1970–1979

Seebach et al. performed the first comprehensive investigation of the addition of organolithium reagents in the presence of various chiral ligands prepared from diethyl tartrate.[21–25] Ligands were screened in the reaction of *n*-BuLi with benzaldehyde in pentane solvent at −78 °C: some representative results from these studies are summarized in Table 1.[23–25] In short, ligands that contained three or four heteroatoms and were C_2 symmetric exhibited the lowest selectivities (**3**, **5**, **7**–**11**; Table 1, entries 1, 3, 5–10); a C_2-symmetric ligand containing six heteroatoms displayed the highest selectivity (**6**; Table 1, entry 4).

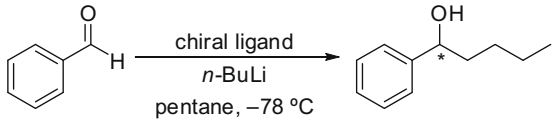
Battioni and Chodkiewicz investigated the effect of the chiral amino alcohols (+)-cinchonine, ephedrine, and *N*-methylephedrine on the asymmetric addition of diethylmagnesium to aldehydes and ketones in diethyl ether solvent at room temperature.[26] The product alcohols were obtained with ee values ranging from 0% to 20%.

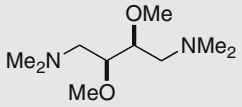
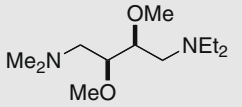
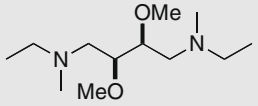
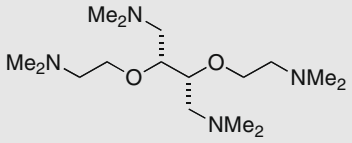
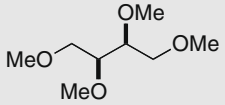
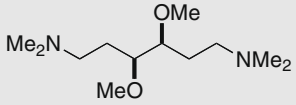
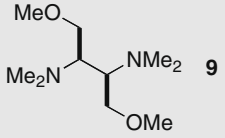
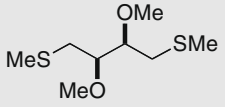
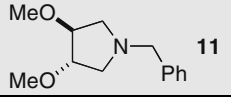
The ability of tridentate chiral oxazolines **12** and **13** complexed with Grignard reagents to effect asymmetric addition to aldehydes and ketones was studied by Meyers and Ford.[27] For example, as shown in Scheme 2, addition of methylmagnesium bromide to ethyl phenyl ketone at −20 °C in THF was studied both in the presence of the alkoxymagnesium halide **12a** (prepared by treatment of **12** with one equivalent of methylmagnesium bromide), and in the presence of the corresponding *O*-methyl ether, **13**. The reactions afforded 2-phenyl-2-butanol in comparable yields and ee but with opposite absolute configuration.

Iffland and Davis examined the ability of enantiomerically pure (+)-2-methyltetrahydrofuran as solvent to promote asymmetric Grignard additions to aldehydes and ketones.[28] The highest ee observed in this study, a modest 11%, was found for the reaction of phenylmagnesium bromide with pivaldehyde to give (*R*)-(+)-2,2-dimethyl-1-phenyl-1-propanol in 57% yield.

Mukaiyama's group[29–32] found that (2*S*,2′*S*)-(−)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine **14** was very effective as a chiral medium for the asymmetric addition of dialkylmagnesiums or alkyllithiums to aldehydes. The results of addition of organolithiums to aldehydes in the presence of **14** are summarized in Table 2. The addition of *n*-PrLi to benzaldehyde

Table 1
Effect of ligand structure on the asymmetric addition of *n*-BuLi to benzaldehyde at −78 °C in pentane[23–25]



Entry	Chiral ligand	Ligand/ *n*-BuLi (mol equiv)	Abs. config.	ee (%)
1	 **3**	4	(*R*)	23
2	 **4**	10	(*R*)	34
3	 **5**	4	(*R*)	30
4	 **6**	2	(*S*)	52
5	 **7**	10	(*R*)	30
6	 **8**	10	(*R*)	15
7	 **9**	1	(*S*)	16
8	 **10**	5	(*S*)	16
9	 **11**	1	(*R*)	17

(Table 2, entry 3) afforded a modest ee of 39%; however, the addition of *n*-BuLi to benzaldehyde afforded product in a much higher ee of 72% (Table 2, entry 4). PhLi gave the lowest ee (Table 2, entry 7).

Significant solvent effects were observed in the reaction of *n*-BuLi with benzaldehyde in the presence of **14**.[31] The non-coordinating solvent, hexane, exhibited the lowest selectivity (20% ee), while coordinating solvents, such as dimethyl ether, diethyl ether, dimethoxyethane, dimethoxymethane (DMM), or THF, displayed better selectivity. Dimethoxymethane as solvent gave the highest enantioselectivity (72% ee). When the temperature of the reaction was lowered from −78 °C to −123 °C, and a 1:1 ratio of DMM–Me_2O was used as solvent, the addition of *n*-BuLi to benzaldehyde proceeded to give product with an ee of 95%.[31]

Similar reaction of benzaldehyde with organomagnesium reagents in the presence of the lithium salt of **14** gave product with modest ee: these results are summarized in Table 3. In contrast to the reactions of benzaldehyde with organolithiums, noncoordinating solvents were often superior to ethereal solvents in the additions of organomagnesium reagents. When the reactions were performed with dialkylmagnesium reagents in the presence of **14**, the resulting alcohol was always of the (*R*)-configuration; however, the organolithium reagents gave alcohols of varying absolute configuration.

6. 1980–1989

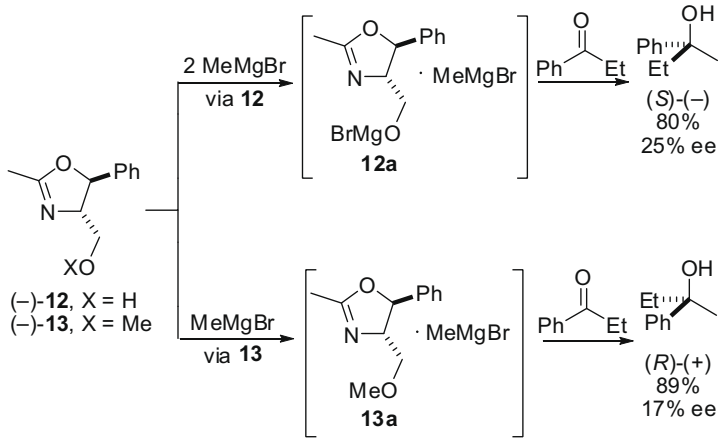
Mukaiyama et al. also used ligand **14** to prepare optically active alkynyl alcohols.[33] For example, treatment of benzaldehyde with lithium trimethylsilylacetylide and **14** in dimethyl ether at −123 °C, followed by removal of the trimethylsilyl moiety, afforded (*S*)-(+)-1-phenyl-2-propyn-1-ol in 87% yield and 92% ee.[33] Johnson et al. applied this methodology,[34] as illustrated in Scheme 3, to produce an alkynyl alcohol substrate, used in the synthesis of corticoids, in 70% yield and 90% ee.

Mazaleyrat and Cram studied the addition of alkyllithiums to aldehydes in the presence of chiral C_2-symmetric binaphthyl-based diamines **15** and **16** (Fig. 4).[35] Treatment of benzaldehyde with *n*-BuLi in the presence of (*R*,*R*)-**15** (molar ratio of 1.0:1.2) in diethyl ether at −120 °C afforded (*R*)-(+)-1-phenyl-1-pentanol in 73% yield and 95% ee; employing (*R*)-**16** gave the alcohol in 71% yield and 58% ee. When the ratio of (*R*)-**16** to organolithium was reduced to 0.0077, an ee of 7% was obtained, indicating that the rate of catalyzed addition exceeds the rate of non-catalyzed addition.

Whitesell and Jaw reported the use of (*R*)-(−)-*N*-(tetrahydrofur-2-yl)methylpyrrolidine **17** as a chiral mediator in the addition of alkyllithiums and Grignard reagents to benzaldehyde (Table 4).[36] Modest yields and low ee, favoring the (*R*)-enantiomer, characterized the reactions.

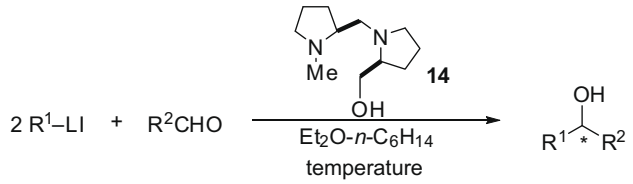
Colombo et al. studied the C_2-symmetric (*S*)-(−)-proline-based ligands, **18** and **19**, in the addition of *n*-BuLi to benzaldehyde at −85 °C.[37] The results are summarized in Table 5. The highest enantioselectivity observed in this study was 36% ee using ligand **18** in dimethoxymethane (DMM) solvent (Table 5, entry 10). It is interesting to note that the presence of **18** in the reaction mixture resulted in alcohol having an absolute configuration of (*R*), while **19** gave alcohol with an absolute configuration of (*S*). Moreover, solutions of *n*-BuLi containing a large quantity of a lithium salt (i.e., equimolar amounts of $LiClO_4$ or LiI) resulted in virtually racemic product.[37]

Eleveld and Hogeveen were the first to investigate the ability of chiral lithium amides to effect the asymmetric addition of *n*-BuLi to benzaldehyde to produce (*S*)-(−)-1-phenyl-1-pentanol.[37] Several (*S*)-α-methylbenzylamine-based ligands **20**–**24** (Fig. 5) were examined in reactions run at low temperature in various solvents using a 1.0:2.7:4.0 molar ratio of benzaldehyde–*n*-butyllithium–ligand. Ligand **20** afforded product with low ee (7–14%) in various solvents. Increasing the structural rigidity of the ligand by including more lithium-complexing moieties resulted in increased selectivity. Thus, replacement of a phenyl group by a 2-pyridyl group (ligand **21**) increased the enantioselectivity of the addition to 37–40% ee. Introduction of an *ortho*-methoxy group on the phenyl ring (ligand **22**) also increased the asymmetric induction (54–65% ee), and inclusion of a methoxy group in the ligand **23** increased the ee to 83%. Employing **23** in a mixed solvent of DMM–Et_2O



Scheme 2. Addition of methylmagnesium bromide to ethyl phenyl ketone in the presence of **12a** or **13a**.

Table 2
Organolithium addition to aldehydes in the presence of **14**[29]



Entry	R^1	R^2	Temp (°C)	Yield (%)	ee (%)	Abs. config.
1	Me	Ph	−78	82	21	*R*
2	Et	Ph	−123	32	39	*R*
3	*n*-Pr	Ph	−123	55	39	*S*
4	*n*-Bu	Ph	−123	60	72	*S*
5	*i*-Bu	Ph	−123	59	16	*S*
6	*n*-Bu	*i*-Pr	−123	47	56	*S*
7	Ph	*n*-Bu	−123	46	11	*R*

Table 3
Addition of organomagnesium reagents to benzaldehyde in the presence of the lithium salt of **14**[30,32]

Entry	Organomagnesium	Solvent	Temp (°C)	Yield (%)	ee (%)
1	*n*-BuMgBr	Et_2O	−78	90	47
2	*n*-Bu_2Mg	Et_2O	−78	93	68
3	*n*-Bu_2Mg	Et_2O	−123	89	73
4	*n*-Bu_2Mg	Me_2O	−123	84	43
5	*n*-Bu_2Mg	THF	−110	91	59
6	*n*-Bu_2Mg	DMM	−78	87	51
7	*n*-Bu_2Mg	DME	−78	96	28
8	*n*-Bu_2Mg	Toluene	−78	93	60
9	*n*-Bu_2Mg	Toluene	−110	94	88
10	Me_2Mg	Toluene	−110	56	34
11	Et_2Mg	Toluene	−110	74	92
12	*n*-Pr_2Mg	Toluene	−110	90	70
13	*i*-Pr_2Mg	Toluene	−110	59	40
14	*i*-Bu_2Mg	Toluene	−110	81	42

(1:1 ratio) and lowering the reaction temperature from −100 °C to −120 °C afforded product in 90% ee. Somewhat surprisingly, there was little difference in enantioselectivity of reactions run in the presence of **20** or the amino alcohol **24**.

Tomioka et al. utilized C_2-symmetric 3,4-diarylpyrrolidine-based chiral diamine ligands, **25** and **26**, in the asymmetric addition of Grignard and organolithium reagents to aldehydes.[39,40] Results are summarized in Table 6. Both **25** and **26** effected asymmetric addition of Grignard reagents to aromatic aldehydes. The more sterically demanding **26** gave a slightly higher ee (Table 6, cf., entries 1 and 5); decreasing the temperature increased the asymmetric induction (Table 6, cf., entries 1–4). All reactions gave the alcohol with an absolute configuration of *S*. Other organometallic reagents were employed with less success (Table 7).[39,40]

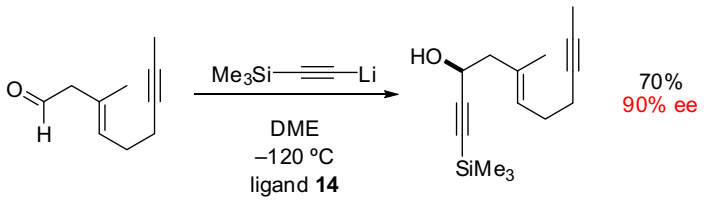
The addition of phenoxymetal halides was found to affect the outcome of the reaction of butylmagnesium bromide with benzaldehyde in the presence of **25** (Table 8).[40] The addition of coordinating phenoxymetal halides either increased the selectivity (Table 8, entries 6 and 7), or had very little effect (Table 8, entries 2–5). The highly coordinating phenoxyaluminum compound increased the asymmetric induction from 20% to 56% ee (Table 8, cf. entries 1 and 7).[40]

Kanoh et al. studied the addition of organolithiums to aldehydes in the presence of C_2-symmetric biphenyl-based chiral amines **27** and **28** (Table 9).[41] In general, the chiral amine ligands **27** and **28** gave results similar to those reported by Cram (Fig. 4).[35] However, running the reaction at −120 °C in Et_2O gave an outstanding 99% ee (Table 9, entry 5).

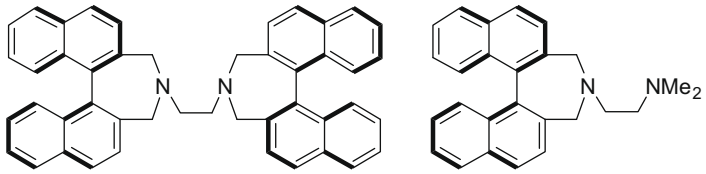
In order to avoid the formation of complex organometallic aggregates in ethereal solvents, Noyori and coworkers designed a chiral binaphthol-based lithium/magnesium reagent, **29**, to promote the asymmetric addition of dialkylmagnesiums to aldehydes.[42] As illustrated in Scheme 4, reaction of the binaphthol with two equivalents of *n*-BuLi followed by one equivalent of dialkylmagnesium gave **29**, whose structure was confirmed by NMR spectroscopy.[42]

The reaction of benzaldehyde with the reagent, **29**, derived from *n*-BuLi and diethylmagnesium gave (*S*)-(−)-1-phenyl-1-propanol in 93% yield and 92% ee when run at −100 °C in a 1:1 mixture of THF–DME. As illustrated by the results summarized in Table 10, the choice of solvent had an effect on the ee of the product alcohol. In the presence of 4 mol equiv of HMPA added to the THF solvent, the product ee decreased to 6% (Table 10, entry 9). Reactions of **29** with aliphatic aldehydes were also successful, giving products with ee ranging from 37% to 85%.[42]

Studies by Alberts and Wynberg involved ascertaining whether the lithium alkoxide of (*R*)-(+)-1-phenyl-1-propanol-d_1 (the product of the reaction) would have any asymmetric inducting effect on the addition of ethyllithium to benzaldehyde.[43] Indeed, when benzaldehyde was added to a solution of a mixture of lithium (*R*)-(+)-1-phenyl-1-propanolate-d_1 and ethyllithium, (*R*)-(+)-1-phenyl-1-propanol was formed in 17% ee. The authors defined, 'the effect of a product ligand acting on the stereochemical course of the reaction as *the principle of enantioselective autoinduction*.'[43]



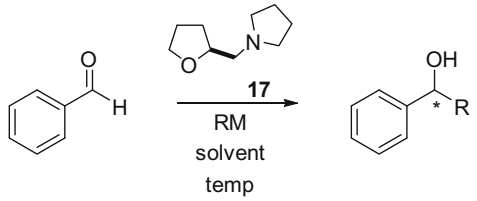
Scheme 3. Asymmetric preparation of alkynyl alcohols.



(*R*,*R*)-**15** (*R*)-**16**

Figure 4. Chiral C_2 symmetric binaphthyl-based diamines.

Table 4
Addition of various organometallics to benzaldehyde in the presence of **17**[36]



Entry	RM	Temp (°C)	Solvent	Yield (%)	ee (%)
1	MeLi	−78	Pentane	38	19
2	*n*-BuLi	−78	Pentane	36	17
3	MeMgCl	25	Diethyl ether	18	0

Clearly, the product of the reaction of an organometallic with a carbonyl substrate results in a species that itself may participate in the reaction as a new and changing aggregate.

7. 1990–1999

Weber and Seebach were the first to report the successful asymmetric addition of Grignard reagents to ketones and to give chiral tertiary alcohols in greater than 95% ee.[44,45] These studies involved the use of TADDOLs (α,α,α′,α′,-tetraaryl-1,3-dioxolan-4,5-dimethanols),[46] **30** or **31**, which are readily prepared from (*R*,*R*)- or (*S*,*S*)-tartrate and arylmagnesium bromides. As depicted in Scheme 5, the chiral TADDOLate reagents, **30a** or **31a**, were prepared by treatment of **30** or **31** with three equivalents of an alkyl Grignard (method 1), or stepwise (method 2), by initial treatment with 2 equiv of an alkyl Grignard (for deprotonation) followed by one equivalent of the same or of a different alkyl Grignard.

The method used for preparation of **30a** and **31a** is important in determining the outcome of the reactions with ketones and aldehydes. Specifically, using method 1, a Grignard reagent in diethyl ether may be used, but it must be added in one portion to a well-stirred solution of **30** or **31** at −70 °C. However, if diethyl ether is present during the deprotonation with the Grignard reagent via method 2, enantioselectivities are drastically reduced. The reactions of these TADDOL-derived reagents with a wide variety of methyl ketones were evaluated and very high enantioselectivities were observed. The results of these studies are summarized in Table 11.

The following conclusions were drawn by Seebach et al. from these studies: (1) addition of ethyl or propylmagnesium bromide to acetophenone occurs from the *Re*-face; (2) with only 0.25 equiv of **30a**, addition of butylmagnesium bromide to acetophenone occurred enantioselectively (84% ee); (3) steric hindrance lowers the rate of reaction; (4) in some cases **31a** will give higher selectivity than **30a**; (5) aliphatic methyl ketones give lower enantioselectivity vis-à-vis aromatic methyl ketones; (6) heteroaromatic ketones also give high selectivity; and, (7) all selectivity is lost when diethyl ether rather than THF is used as solvent.

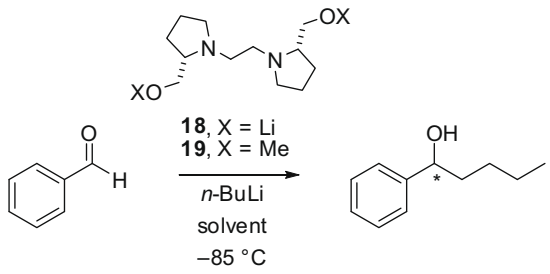
Reactions of benzaldehyde with TADDOLates, proceed with lower selectivity than those of methyl ketones. However, as illustrated in Scheme 6, choice of solvent affects the selectivity in the benzaldehyde reactions: the use of diethyl ether solvent leads to formation of an excess of the (*S*)-enantiomer (60% ee); THF gives an excess of the (*R*)-enantiomer (58% ee). The authors note that it is difficult to rationalize these results because the reactions are heterogeneous and the mechanism of Grignard addition is still in question.

Markó et al. observed an interesting trend in the addition of Grignard reagents to cyclohexanecarboxaldehyde in the presence of chiral diamine **32**.[47] As shown in Table 12, the size of the Grignard reagent affected the degree of asymmetric induction. Increasing the size of the Grignard reagent from methyl to butyl increased the ee of the product (Table 12, entries 1–4).[47] However, *t*-BuMgCl was unreactive (Table 12, entry 9). Moreover, the addition of *i*-PrMgCl to cyclohexanecarboxaldehyde in the presence of **32** displayed inverse temperature dependence.[47] Commonly, a decrease in temperature results in an increase in selectivity, with only a few examples demonstrating the opposite.[48] However, as illustrated by the data summarized in Table 13, an increase of more than 30% ee was observed on increasing the reaction temperature from −40 °C to +35 °C. The authors did not propose a rationale for these findings.

Jackman et al. investigated the addition of MeLi to benzaldehyde in the presence of various chiral lithium alkoxides (**33**–**39**, shown in Fig. 6).[49] Lithium alkoxide **37** gave the highest selectivity; all other alkoxide ligands were rather ineffective. The results of the addition of MeLi to benzaldehyde in the presence of ligands **40**–**42**, similar in structure to **37**, are summarized in Table 14.[49]

Inspection of data summarized in Table 14 reveals that the solvent has an effect on the enantioselectivity. Comparison of the results from reactions employing ligands **41** and **37** (Table 14, cf.,

Table 5
Addition of *n*-BuLi to benzaldehyde in the presence of C_2-symmetric (*S*)-(−)-proline-based ligands.[37]



Entry	Molar ratio			Ligand	Solvent	Ligand concentration	ee (*R*/*S*) (%)
	PhCHO	*n*-BuLi	Ligand				
1	1	1	1	**18**	Et_2O	0.2	15 (*R*)
2	1	1	1	**18**	DME	0.2	19 (*R*)
3	1	1	1	**18**	DMM	0.2	22 (*R*)
4	1	1	1	**18**	DMM	0.05	20 (*R*)
5[a]	1	1	1	**18**	DMM	0.2	15 (*R*)
6	1	1	2	**18**	DMM	0.2	30 (*R*)
7	1	1	2	**18**	DMM	0.05	26 (*R*)
8[a]	1	1	2	**18**	DMM	0.2	20 (*R*)
9	1	2	2	**18**	DMM	0.2	26 (*R*)
10	1	2	3	**18**	DMM	0.2	36 (*R*)
11	1	3	3	**18**	DMM	0.2	30 (*R*)
12	1	4	3	**18**	DMM	0.2	25 (*R*)
13	1	2	4	**18**	DMM	0.2	33 (*R*)
14	1	2	3	**19**	*n*-Hexane	0.2	15 (*S*)

[a] Reactions performed at −60 °C.

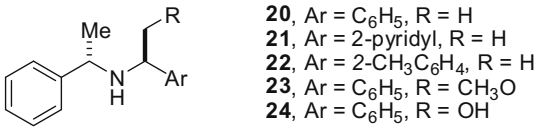
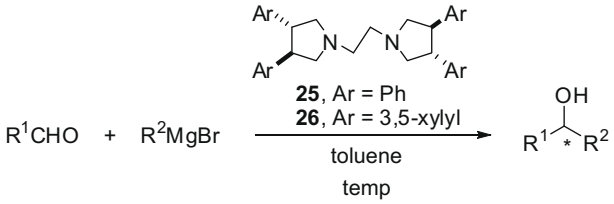


Figure 5. (*S*)-α-Methylbenzylamine-based ligands.

Table 6
Addition of Grignard reagents to aldehydes in the presence of **25** or **26**[39,40]

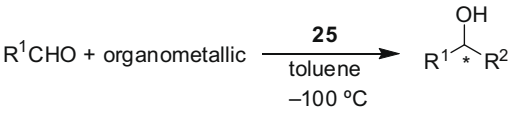


Entry	R^1	R^2	Ligand[a]	Temp (°C)	Yield (%)	ee (%)
1	Ph	α-Nap	**25**	−100	92	71
2	Ph	α-Nap	**25**	−78	96	64
3	Ph	α-Nap	**25**	−45	94	55
4	Ph	α-Nap	**25**	−20	59	38
5	Ph	α-Nap	**26**	−100	94	75
6	*t*-Bu	Ph	**25**[b]	−100	82	60
7	*c*-hex	Ph	**26**	−100	68	55
8	*i*-Pr	Ph	**25**[b]	−100	68	47
9	*n*-Bu	Ph	**25**[b]	−100	73	40

[a] Ratio: $R^1CHO:R^2MgBr$:ligand = 1:2.5:3.
[b] Ratio: $R^1CHO:R^2MgBr$:ligand = 1:1.25:1.5.

entries 2 and 3) indicates that alcohol with the same absolute configuration was obtained from both reactions; no explanation was offered for this observation.[49]

Table 7
Addition of organometallic reagents to aldehydes in the presence of **25**[40]



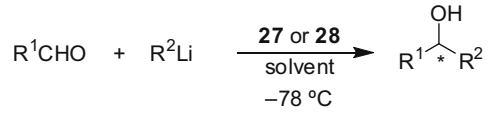
Entry	R^1	Organometallic	Yield (%)	ee (%)
1	Ph	*n*-BuLi	79	6
2	Ph	Bu_2Mg	86	0
3	Ph	BuMgCl	88	13
4	Ph	BuMgBr	86	20
5	Bu	Ph_2Mg	75	25
6	Bu	PhMgBr	80	32

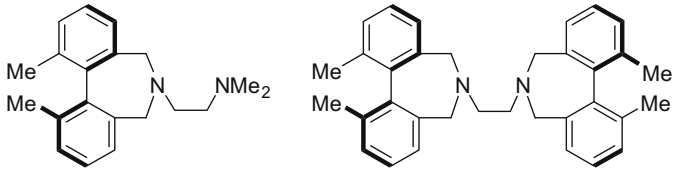
Table 8
Addition of butylmagnesium bromide to benzaldehyde in the presence of **25** and a phenoxymetal halide[40]

Entry	$ArOMX_n$	Yield (%)	ee (%)
1	None	86	20
2	PhOMgBr	86	28
3	2-MeOPhOMgBr	62	17
4	3,5-Me_2PhOMgBr	80	17
5	2,6-*t*-Bu-4-MePhOMgBr	93	23
6	2,4,6-Me_3PhOMgBr	58	43
7	2,4,6-$Me_3PhOAlCl_2$	61	56

Kang et al. studied the asymmetric addition of 2-lithio-1,3-dithiane to various aldehydes in the presence of (−)-α-isosparteine **43**; the results are summarized in Table 15.[50] Enantioselective addition in the presence of **43** was reasonably successful for aromatic aldehydes (Table 15, entries 1–3), but aliphatic aldehydes reacted with somewhat poorer selectivities (Table 15, entries 4–7).

Table 9
Addition of organolithiums to aldehydes in the presence of ligands **27** or **28**[41]

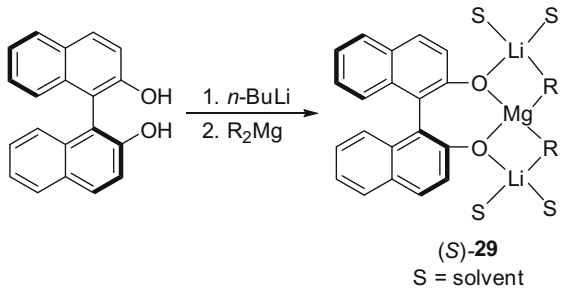




(*R*)-**27** (*R*,*R*)-**28**

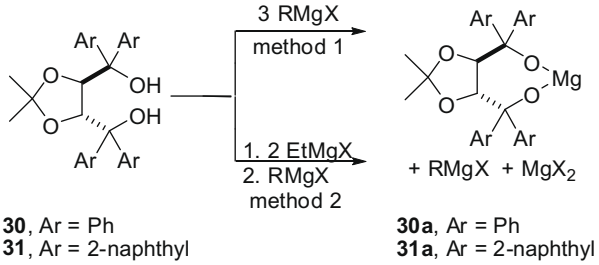
Entry	Ligand	R^1	R^2	Solvent	Yield (%)	ee (*R*/*S*) (%)
1	(*S*)-**27**	*n*-Bu	Ph	Et_2O	95	53 (*S*)
2	(*S*)-**27**	*n*-Bu	Ph	PhMe	93	33 (*S*)
3	(*S*,*S*)-**28**	*n*-Bu	Ph	Et_2O	88	86 (*S*)
4	(*R*,*R*)-**28**	*n*-Bu	Ph	Et_2O	75	86 (*R*)
5	(*R*,*R*)-**28**	*n*-Bu	Ph	Et_2O	62	99 (*R*)[a]
6	(*S*,*S*)-**28**	*n*-Bu	Ph	PhMe	74	27 (*S*)
7	(*R*)-**27**	Ph	*n*-Bu	Et_2O	59	18 (*S*)
8	(*S*,*S*)-**28**	Ph	*n*-Bu	Et_2O	53	18 (*R*)
9	(*S*)-**27**	$PhCH_2$	Ph	PhMe	64	0
10	(*S*,*S*)-**28**	$PhCH_2$	Ph	PhMe	48	0

[a] Reaction performed at −120 °C.



(*S*)-**29**
S = solvent

Scheme 4. Chiral binaphthol-based lithium/magnesium reagent.



30, Ar = Ph
31, Ar = 2-naphthyl

30a, Ar = Ph
31a, Ar = 2-naphthyl

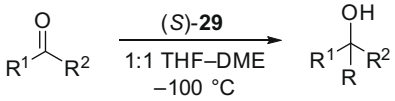
Scheme 5. TADDOL-derived reagents.

Corruble et al. investigated lithium amides, **44**, derived from substituted 3-aminopyrrolidines, as chiral ligands in the addition of *n*-BuLi to selected aldehydes (Table 16).[51] The enantioselectivities varied from fair (Table 16, entries 6–8) to virtually racemic (Table 16, entry 4). The authors presented spectroscopic evidence for the formation of a hemiaminal-like intermediate (**45**, Scheme 7) generated by addition of the aldehyde to **46** prior to complexation with *n*-BuLi and reaction with another molecule of aldehyde to produce **47**.[51]

The effect of variation in the ligand structure **48** on the outcome of the addition of *n*-BuLi to *o*-tolualdehyde was investigated. The results, summarized in Table 17, demonstrate that there is no obvious correlation between ligand structure and selectivity. The introduction of additional sites for potential coordination did not lead to an increase in enantioselectivity (Table 17, entries 4 and 5); introduction of a second, non-coordinating, (*R*)-configured stereocenter in the ligand leads to an increase in selectivity (Table 17, entry 10), but a constitutionally identical stereocenter of (*S*)-configuration caused a drop in selectivity (Table 17, entry 11).[52]

In an effort to understand the origin of enantioselectivity in these reactions, Corruble et al. investigated the structures of the lithium amides by ^1H and ^{13}C NMR. The 3-aminopyrrolidine lithium amide complex, **49**, exhibited a very complex spectrum, indicating that several species were present in solution. On the other hand, **50** exhibited a clean spectrum and the structure of **50a**, depicted in Figure 7, was assigned.[53,54] The complex of **50a** with *n*-BuLi was characterized as **51** (Fig. 8) by ^1H, ^6Li, and ^{13}C NMR. With this structure in hand, the authors proposed a model,

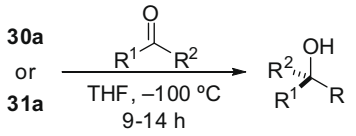
Table 10
Enantioselective addition of reagent **29** to aldehydes and ketones[42]



Entry	R_2Mg	R^1	R^2	Solvent	Yield (%)	ee[a] (%)
1	CH_3	C_6H_5	H	1:1 THF–DME	75	82
2	C_2H_5	C_6H_5	H	Et_2O	82	64
3	C_2H_5	C_6H_5	H	THF	90	85
4	C_2H_5	C_6H_5	H	THF + 2 equiv DME	96	88
5	C_2H_5	C_6H_5	H	1:1 THF–DME	93	92
6	C_2H_5	C_6H_5	H	DME	94	73
7	C_2H_5	C_6H_5	H	1:1 DME–hexane	80	84
8	C_2H_5	C_6H_5	H	1:1 DME–toluene	95	81
9	C_2H_5	C_6H_5	H	THF + 4 equiv HMPA	60	6
10	C_2H_5	C_6H_5	H	THF + 2 equiv TMEDA	92	85
11	C_2H_5	*p*-$MeOC_6H_4$	H	1:1 THF–DME	98	83
12	C_2H_5	*p*-ClC_6H_4	H	1:1 THF–DME	88	68
13	C_2H_5	$C_6H_5CH{=}CH$	H	1:1 THF–DME	97	37
14	C_2H_5	$C_6H_5CH_2CH_2$	H	1:1 THF–DME	40	85
15	C_2H_5	*n*-C_6H_{13}	H	1:1 THF–DME	86	85
16	*n*-C_4H_9	C_6H_5	H	1:1 THF–DME	98	88

[a] The (*S*)-enantiomer was obtained in all cases.

Table 11
Reactions of methyl ketones with reagents derived from TADDOLs **30a** or **31a**[44,45]



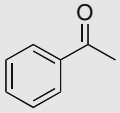
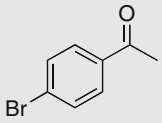
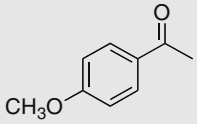
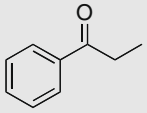
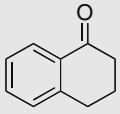
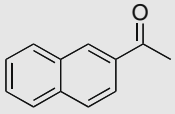
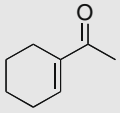
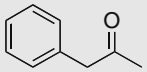
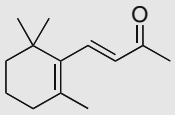
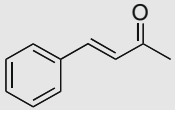
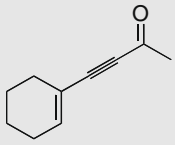
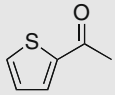
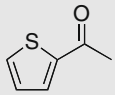
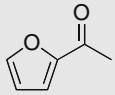
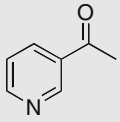
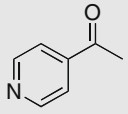
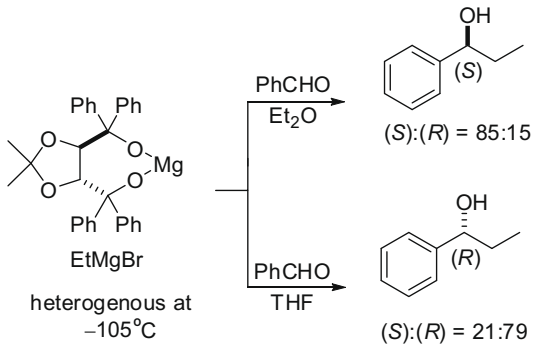
Entry	Ketone	TADDOL	R in RMgBr	Yield (%)	ee (rotation)[a] (%)
1		**30a**	Et	62	98 (*R*)-(+)
2		**30a**	*n*-Pr	84	>98 (*R*)-(+)
3		**30a**	*n*-Bu	75	>98 (*R*)-(+)
4		**30a**	*n*-Hex	58	>98 (+)
5		**30a**	*n*-Oct	58	>98 (+)
6		**30a**	CH_2Ph	14	70 (*R*)-(+)
7		**30a**	$(CH_2)CH{=}CH_2$	60	>98 (−)
8		**30a**	Et	60	98 (+)
9		**30a**	Et	76	92 (+)
10		**30a**	*n*-Bu	7	90 (−)
11		**30a**	Et	28	89 (+)
12		**31a**	Et	12	94 (+)
13		**30a**	Et	75	98 (+)
14		**30a**	Et	55	71 (−)
15		**30a**	Et	22	50
16		**30a**	Et	64	83 (−)
17		**31a**	Et	25	77 (−)
18		**30a**	Et	40	70

Table 11 (*continued*)

Entry	Ketone	TADDOL	R in RMgBr	Yield (%)	ee (rotation)[a] (%)
19		**30a**	Et	88	75
20		**30a**	Et	43	96 (+)
21		**30a**	$(CH_2)CH{=}CH_2$	30	97
22		**30a**	Et	24	90
23		**30a**	Et	53	66
24		**30a**	Et	51	96 (+)
25		**30a**	Et	96	>98 (+)
26		**30a**	$(CH_2)CH{=}CH_2$	51	98 (+)

[a] A % ee > 98 means the minor enantiomer was undetectable; in those entries where the rotation sign is missing, the alcohols had very small optical rotations, or not enough sample was available for measurement.



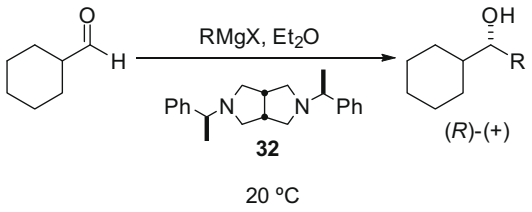
Scheme 6. Effect of solvent on additions of TADDOLates to benzaldehyde.

illustrated in Figure 8, that accounts for the observed enantioselectivity in the addition of *n*-BuLi to aldehydes.[53]

Schön and Naef screened a series of 1-amino-1,2-diphenylethanols **52** as chiral ligands for the enantioselective addition of *n*-BuLi to benzaldehyde.[55] As evidenced by the data summarized in Table 18, the enantioselectivity is greatly influenced by the substitution on the nitrogen of **52**. When a nitrogen atom with three different substituents is complexed to a metal, it too becomes a stereogenic center. Employing ligands that contain a nitrogen atom capable of becoming a stereogenic center generally led to an increase in the selectivity of additions (Table 18, cf., entries 1–3 and 4–9). With these results in mind, ligand **52b** was designed and it was found to be superior to **52a** in effecting asymmetric addition of organolithiums to benzaldehyde (Table 19).[55]

Knollmüller et al. investigated the ability of (+)-camphor-derived 1,4-aminoalcohol ligands **53**–**59** (Fig. 9) to induce asymmetry

Table 12
Grignard addition to cyclohexanecarboxaldehyde in the presence of **32**[47]



Entry	RMgX	Yield (%)	ee (%)
1	MeMgI	79	8
2	EtMgBr	87	14
3	*n*-PrMgCl	71	22
4	*n*-BuMgCl	73	33
5	*n*-PentMgCl	62	34
6	*n*-HexMgCl	67	35
7	*i*-PrMgCl	87	34
8	*i*-BuMgCl	63	37
9	*t*-BuMgCl	0	—

in the addition of *n*-BuLi as well as *n*-BuMgBr to benzaldehyde.[56] Enantioselectivities observed in these additions were poor to modest; the highest selectivity (37% ee) was obtained when **58** was employed as ligand in the addition of *n*-BuMgBr to benzaldehyde.[56]

Aspinall et al. investigated the ability of chiral lanthanide binaphtholates to induce asymmetry when MeLi or *n*-BuLi was added to various aldehydes.[57] The proposed structure of $Li_3[Ln(S\text{-binol})_3]$ **60** is shown in Figure 10.

The addition of MeLi to benzaldehyde in diethyl ether at −98 °C in the presence of **60**-La resulted in product having an ee of 69%,

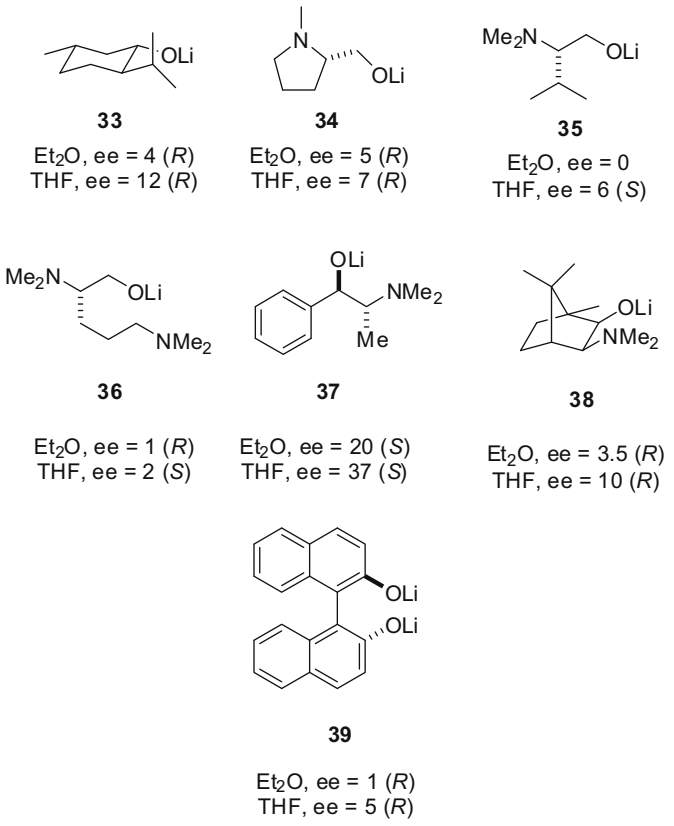
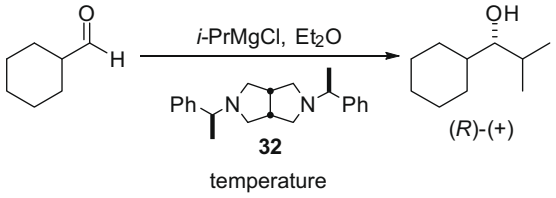


Figure 6. Chiral lithium alkoxide ligands evaluated for asymmetric addition of MeLi to benzaldehyde.[49]

Table 13
Variation in enantioselectivity with temperature in the addition of isopropylmagnesium chloride to cyclohexanecarboxaldehyde in the presence of **32**[47]



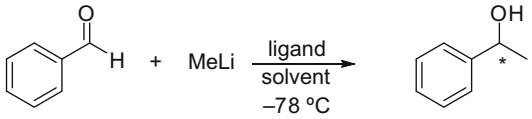
Entry	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	− 40	48	84	9
2	−20	48	83	14
3	−10	48	88	17
4	0	24	86	22
5	10	16	85	27
6	20	2	87	34
7	35	1	73	42

while addition of MeLi to benzaldehyde in diethyl ether at −98 °C in the presence of either **60**-Y or **60**-Yb achieved only 11% or 3% ee, respectively. The variation in ee was attributed to changes in the ionic radius of the lanthanide which, in turn, changed the geometry of the chiral binding site. The results of the addition of MeLi and *n*-BuLi to various aldehydes in the presence of **60**-La are summarized in Table 20.[57]

8. 2000–2008

Hilmersson and co-workers at Göteborg University have reported on extensive investigations of the ability of lithium amides

Table 14
Asymmetric addition of MeLi to benzaldehyde in diethyl ether or THF[49]



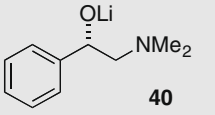
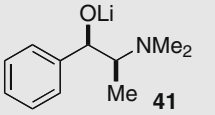
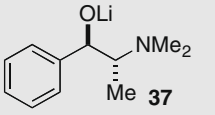
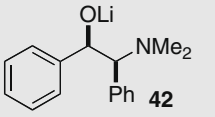
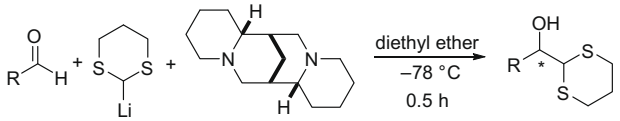
Entry	Lithium alkoxide	ee in diethyl ether (%)	ee in THF (%)
1	 **40**	2 (*R*)	0
2	 **41**	17 (*S*)	7 (*S*)
3	 **37**	20 (*S*)	37 (*S*)
4	 **42**	12 (*S*)	55 (*S*)

Table 15
The Addition of 2-lithio-1,3-dithiane to aldehydes in the presence of isosparteine[50]



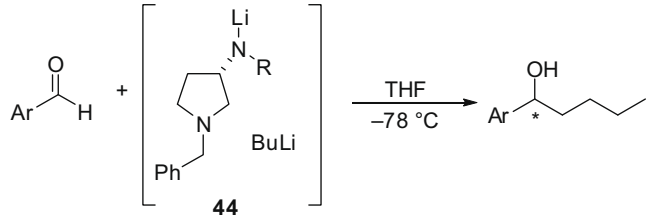
43

Entry	R	Yield (%)	ee[a] (%)
1	Ph	73	70
2	*p*-Cl-Ph	83	40
3	2-Naphthyl	80	32
4	$(Ph)_2CH$	47	49
5	$CH_3(CH_2)_5$	81	32
6	$(CH_3)_3C$	78	10
7	$c\text{-}C_6H_{11}$	84	6

[a] The (*S*)-enantiomer was obtained in all cases.

derived from aminoethers to effect asymmetric addition of organolithiums to aldehydes.[58–63] The aminoether **23**, developed sometime ago by Eleved and Hogeven,[38] was compared to a structurally less complex aminoether, **61**, in reactions of *n*-BuLi with various aldehydes.[58] As demonstrated by the results summarized in Table 21, the lithium salts of both **23** and **61** were effective as ligands for the enantioselective addition of *n*-BuLi to various aldehydes.[58] Neither ligand can be considered superior: the more effective ligand depended on which aldehyde was employed. NMR studies demonstrated that the reactive species in solution consists of three complexes in equilibrium: (1) homo-aggregated *n*-BuLi; (2) lithium amide dimers, (Li-**23**)$_2$ or (Li-**61**)$_2$; and (3) a mixed 1:1 complex, illustrated in Figure 11, between *n*-BuLi and the lithium amide (Li-**23**–*n*-BuLi) or (Li-**61**–*n*-BuLi).[60,61]

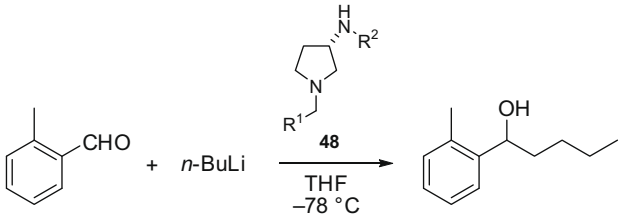
Table 16
The addition of *n*-BuLi to aromatic aldehydes in the presence of 3-aminopyrrolidine-based ligands[51]



Entry	R[a]	Ar	Yield (%)	ee[b] (%)
1	$PhCH_2$	Ph	60	20
2	t-$BuCH_2$	Ph	50	17
3	α-Naphthyl-CH_2	Ph	56	18
4	o-$MeOC_6H_4CH_2$	Ph	54	3
5	$PhCH_2$	o-Tolyl	57	49
6	Cyclohexyl	o-Tolyl	63	67
7	Cyclopentyl	o-Tolyl	63	63
8	Ph_2CH	o-Tolyl	70	73

[a] The molar ratio of Li amide:*n*-BuLi:ArCHO was 1.5:2.5:1.0.
[b] The (*R*)-enantiomer was obtained in all cases.

Table 17
Addition of *n*-BuLi to *o*-tolualdehyde in THF at −78 °C in the presence of 3-aminopyrrolidine lithium amides[52]



Entry	R^1	R^2	Yield (%)	ee (*R*/*S*) (%)
1	Me	c-C_6H_{11}	72	63 (*R*)
2	Ph	c-C_6H_{11}	72	67 (*R*)
3	β-Naphthyl	c-C_6H_{11}	67	76 (*R*)
4	$MeOCH_2$	c-C_6H_{11}	80	51 (*R*)
5	o-$MeOC_6H_4$	c-C_6H_{11}	71	60 (*R*)
6	α-Naphthyl	c-C_6H_{11}	65	50 (*R*)
7	Me	Ph_2CH	66	64 (*R*)
8	Ph	Ph_2CH	77	73 (*R*)
9	β-Naphthyl	Ph_2CH	98	64 (*R*)
10	β-Naphthyl	PhCH(Me) (*R*)	95	77 (*R*)
11	β-Naphthyl	PhCH(Me) (*S*)	91	51 (*S*)

Building on these results, the Davidsson group investigated a variety of chiral lithium amides **62**–**68**, illustrated in Figure 12, as ligands for asymmetric addition of *n*-BuLi to benzaldehyde.[61] The chiral lithium amides performed either very well (Table 22, entries 1, 2, and 6) or very poorly (Table 22, entries 3–5, 7, and 8). As before, NMR studies confirmed a mixed 1:1 complex between *n*-BuLi and the lithium amide.[61]

The effect of solvent on the enantioselectivity of addition of *n*-BuLi to benzaldehyde in the presence of various lithium amides derived from enantiomerically pure aminoethers was also explored.[62] As illustrated by the data summarized in Table 23, the nature of the solvent system greatly affects the asymmetric induction. In general, a mixture of diethyl ether–DMM or diethyl ether–THF gave results superior to those obtained in experiments conducted in pure diethyl ether. In virtually all cases, a mixture of pentane–toluene as solvent resulted in racemic product (these results are not included in Table 23).[62]

Chiral lithium amides derived from aminosulfides were also screened for their ability to promote asymmetric addition of organolithiums to benzaldehyde; the results of these experiments are summarized in Table 24.[63] Moderate to excellent enantioselectivities were obtained from the addition of organolithiums to benzaldehyde in the presence of the aminosulfides. The addition of MeLi to benzaldehyde in a mixture of diethyl ether and THF gave high ee's (Table 24, entries 2, 10, and 12); the use of pure diethyl ether as the solvent resulted in either low selectivity or no product. When *n*-BuLi was employed, solvent effects were less pronounced. In all instances, lowering the temperature improved the enantioselectivity.[63]

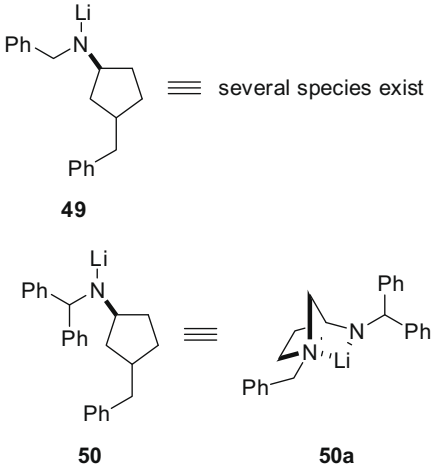
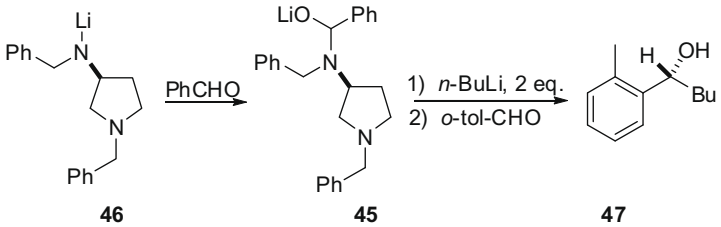


Figure 7. Proposed solution state structures of 3-aminopyrrolidine-derived ligands.

In all cases studied, aminosulfide ligands were found to be superior to structurally identical aminoether ligands in their ability to mediate asymmetric addition of *n*-BuLi to benzaldehyde.[63] It might well have been expected that the stronger chelation between lithium and the oxygen of the aminoether ligands would lead to higher selectivities with such ligands. Apparently, in this instance, strong chelation is not an important factor.[63]



Scheme 7. Hemiaminal-like intermediate in the reaction of aldehydes with substituted 3-aminopyrrolidine lithium amides.

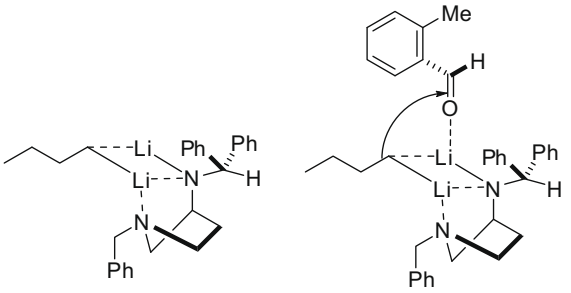
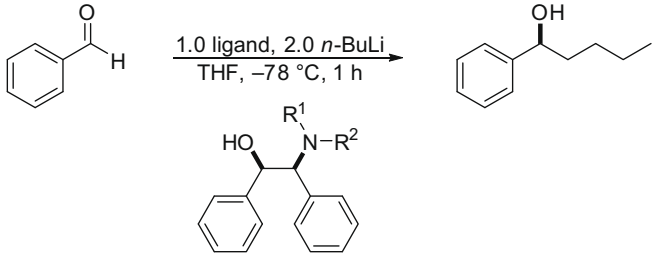


Figure 8. Possible origin of enantioselectivity in additions of alkyllithiums to aldehydes involving 3-aminopyrrolidine-derived ligands.

Table 18
Addition of *n*-BuLi to benzaldehyde in the presence of ligands with general structure **52**[55]



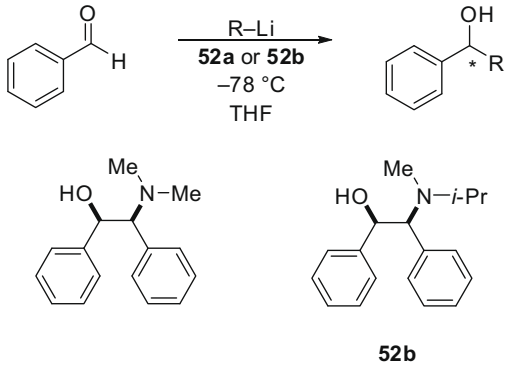
Entry	R^1	R^2	Yield (%)	ee[a] (%)
1	Me	Me	91	71
2		$-(CH_2)_2-$	78	57
3	*n*-Bu	*n*-Bu	91	25
4	Me	*n*-Bu	90	68
5	Me	*i*-Pr	85	78
6	Me	3-Pentyl	89	64
7	Me	Cyclohexyl	89	47
8	Me	Cyclopentyl	83	62
9	Me	2-Morpholinoethyl	77	50

[a] The (*S*)-enantiomer was obtained in all cases.

Tobe et al. investigated the reaction of *n*-BuLi with benzaldehyde in the presence of several chiral ligands (Scheme 8) derived from the dimethyl ether of *cis*-1-phenylcyclohexane-1,2-diol **69**.[64] No selectivity was observed when toluene was employed as solvent, a modest 52% ee was achieved in THF, and a low 15% ee was found in diethyl ether solvent. Further inspection of the reaction products revealed the formation of about 10% of **70** in both diethyl ether and THF. Only one diastereomer of **70** was present, but its absolute configuration was not determined.

The synthesis of the powerful reverse transcriptase inhibitor Efavirenz® **71** by highly enantioselective addition of lithium cyclopropylacetylide to ketone **72** represents the state-of-the-art in asymmetric addition of an organolithium to a carbonyl substrate.[65–68] As illustrated in Scheme 9, addition of lithium cyclopropylacetylide to **72** in the presence of the lithium alkoxide, **73**, derived from (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine, delivers alcohol **74** in 95% yield with an ee of >98%. NMR spectroscopic evidence suggested the existence of 1:3, 2:2, and 3:1 mixed tetramers (RLi:R*OLi) in relative concentrations that could be controlled by adjusting the lithium acetylide (RLi) and lithium alkoxide (R*OLi) ratios.[66] It was concluded that the high selectivity originated from

Table 19
Addition of organolithium reagents to benzaldehyde at −78 °C in THF in the presence of **52a** or **52b**[55]



Entry	Organolithium	**52a** (% ee)[a]	**52b** (% ee)[a]
1	MeLi	52	86
2	*n*-BuLi	71	78
3	*n*-HexLi	55	75
4	*t*-BuLi	1	2
5	$TMSCH_2Li$	58	85
6	TMS–C≡C–Li	39	75

[a] The (*S*)-enantiomer was obtained in all cases.

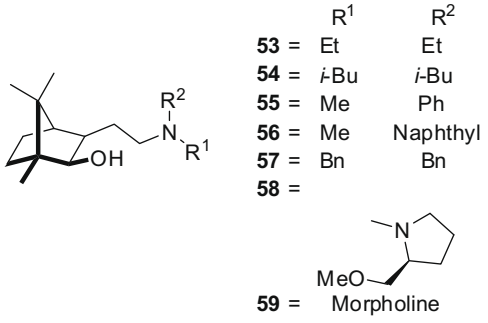


Figure 9. (+)-Camphor-derived 1,4-aminoalcohol ligands.

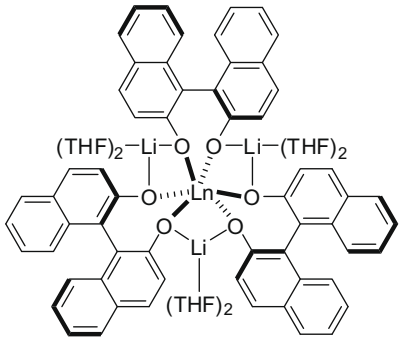
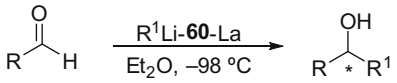
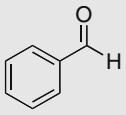
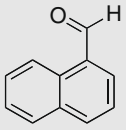
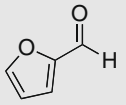
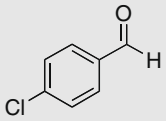
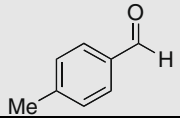


Figure 10. Proposed structure of lithium–lanthanide binaphtholate.

the C_2 symmetric $(RLi)_2$-$(R^*OLi)_2$ mixed tetramer. On this basis, 2.0 equiv of the lithium alkoxide **73**, and 2.0 equiv of lithium cyclopropylacetylide were allowed to equilibrate in THF at room temperature to produce the 2:2 mixed tetramer prior to the addition at −78 °C of 1.0 equiv of **72** to afford **74** in 95% yield and 98% ee.

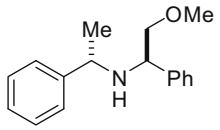
Table 20
Addition of MeLi or *n*-BuLi to aldehydes in the presence of **60**-La[57]



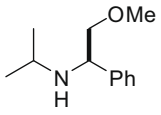
Entry	Substrate	R^1	Equiv of R^1Li	Solvent for R^1Li	Yield (%)	ee[a] (%)
1		Me	1	Et_2O	46	84
2		Me	2	Et_2O	72	69
3		*n*-Bu	1	Hexanes	0	–
4		*n*-Bu	2	Hexanes	74	63
5		*n*-Bu	1	Et_2O	40	39
6		*n*-Bu	2	Et_2O	58	67
7		Me	1	Et_2O	60	67
8		Me	2	Et_2O	93	74
9		*n*-Bu	2	Hexanes	33	67
10		*n*-Bu	2	Et_2O	52	56
11		Me	1	Et_2O	31	68
12		Me	2	Et_2O	40	70
13		Me	1	Et_2O	71	28
14		Me	2	Et_2O	78	33
15		Me	2	Et_2O	56	62

[a] The (*S*)-enantiomer was obtained in all cases.

Table 21
Addition of *n*-BuLi to aldehydes in (50/50 v/v) diethyl ether-dimethoxymethane at −116 °C in the presence of lithium amide derived from either **23** or **61**[58]

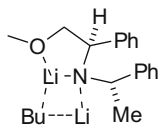


23

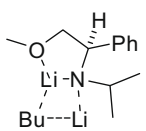


61

Entry	Lithium amide	RCHO	ee (%)
1	**23**	Ph	72
2	**61**		91
3	**23**	*c*-C_6H_{11}	91
4	**61**		>98.5
5	**23**	*i*-C_5H_9	90
6	**61**		65
7	**23**	*i*-C_3H_5	96
8	**61**		>98.5
9	**23**	*t*-C_4H_9	58
10	**61**		11



Li-**23**–*n*-BuLi



Li-**61**–*n*-BuLi

Figure 11. Mixed dimers of *n*-BuLi with Li-**23** and Li-**61**.

It is interesting to note that replacement of lithium cyclopropyl acetylide with *n*-BuLi under the same conditions afforded product in **c**a. 80% ee.[66]

The addition of *n*-BuLi to benzaldehyde in the presence of lithium alkoxide **73**, as well as analogs **75** and **76** (Fig. 13), was also investigated.[69] The highest selectivity observed was 90% ee favoring the (*S*)-enantiomer when the reaction was performed at −105 °C in the presence of **76** in THF solution. The lower selectivity of the *n*-BuLi additions vis-á-vis the lithium acetylide reactions suggests that π interactions in the transition state for this process may be important, and NMR studies supported this interpretation.[69]

Yong et al. investigated chiral organomagnesium amides (COMAs) as asymmetric alkylating agents for aldehydes.[70] As illustrated in Scheme 10, treatment of **77** with *n*-Bu_2Mg in diethyl ether produced **78** (confirmed by X-ray crystallography), which upon further treatment with benzaldehyde at −90 °C afforded (*R*)-(+)-1-phenylpentan-1-ol in 70% yield and 82% ee. Other aldehydes behaved similarly (Table 25), and variation of the COMA structure was found to have a pronounced effect on the enantioselectivity of the reaction (Table 26).[70]

Nishiyama et al. investigated the addition of PhLi or PhMgBr to chiral ruthenium-bis(oxazolinyl)pyridine-aldehyde complexes, **79**, illustrated in Scheme 11.[71] In this approach, the chiral ligand is complexed to the carbonyl substrate rather than the organometallic reagent. Structures were confirmed by X-ray diffraction, and it was determined that the *Si*-face of the carbonyl is preferentially exposed, locking the structure into an *s-trans* conformation. The results of the addition reactions are summarized in Table 27.

Goldfuss et al. investigated the use of anisyl fencholates **80**, illustrated in Figure 14, as ligands for the enantioselective addition

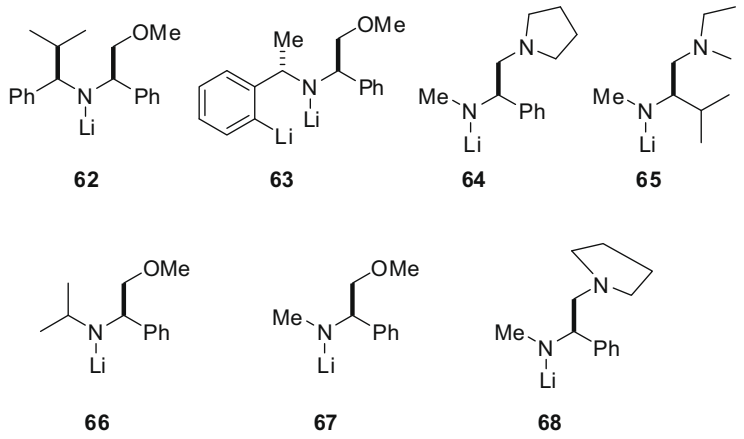
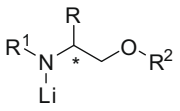


Figure 12. Structurally diverse lithium amide bases.

Table 22
Addition of *n*-BuLi to benzaldehyde at −116 °C in diethyl ether in the presence of structurally diverse lithium amide bases[61]

Entry	Lithium amide	ee (*R*/*S*) (%)
1	**23**	72 (*S*)
2	**62**	75 (*S*)
3	**63**	8 (*S*)
4	**64**	7 (*R*)
5	**65**	7 (*R*)
6	**66**	82 (*S*)
7	**67**	2 (*S*)
8	**68**	26 (*S*)

Table 23
Effect of solvent variation on the asymmetric addition of *n*-BuLi to benzaldehyde at −116 °C in the presence of lithium amides derived from chiral aminoethers[62]

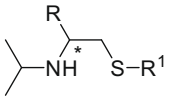


Entry[a]	Li-amide configuration	R	R^1	R^2	ee[b] (%)		
					Et_2O	Et_2O/DMM	Et_2O/THF
1	*S*	Me	*i*-Pr	Me	36	—	—
2	*R*	Ph	Me	Me	2	—	—
3	*S*	Ph	*i*-Pr	Me	82	91	85
4	*S*	Ph	*i*-Pr	Et	60	76	79
5	*S*	Ph	*i*-Pr	*i*-Pr	50	73	77
6	*S*	Ph	3-Pentyl	Me	48	63	72
7	*S*	Ph	3-Pentyl	Et	29	63	70
8	*S*	Ph	Cyclohexyl	Me	75	87	86
9	*S*	Ph	Cyclohexyl	Et	66	86	89
10	*S*	Benzyl	*i*-Pr	Me	60	68	67
11	*S*	Benzyl	*i*-Pr	Et	41	74	69
12	*S*	Benzyl	*i*-Pr	*i*-Pr	52	74	72
13	*S*	*i*-Pr	*i*-Pr	Me	61	78	78
14	*S*	*i*-Pr	*i*-Pr	Et	44	76	74
15	*S*	*i*-Pr	*i*-Pr	*i*-Pr	48	77	71

[a] Molar ratio of benzaldehyde:organolithium:ligand was 1.0:14.5:10.0.
[b] Absolute configuration of the product was opposite to that of the lithium amide.

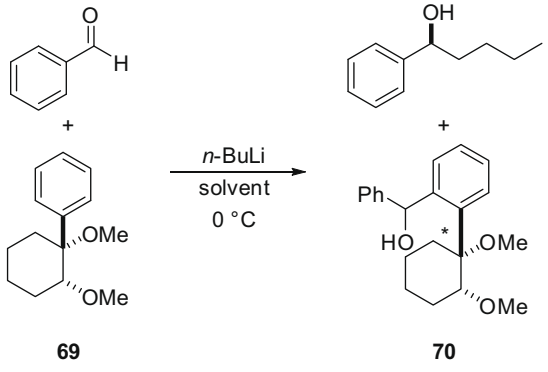
of *n*-BuLi to benzaldehyde.[72,73] The nature of the X substituent in **80** greatly affected the structure and composition of the aggregate (determined by X-ray crystallography). As illustrated in Figure 14, when X is hydrogen, a 1:3 ratio of *n*-BuLi to fencholate is observed **80a** and **80a**-Li. However, if the hydrogen is replaced with a $SiMe_3$ or TBDMS group, the ratio is altered to 2:2 **80b**, **80b**-Li and **80c**,

Table 24
Addition of MeLi or *n*-BuLi to benzaldehyde in the presence of lithium amides derived from chiral aminosulfides[63]



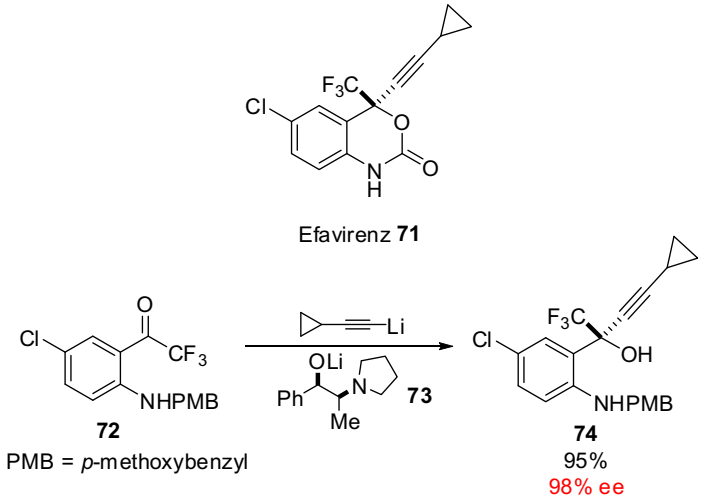
Entry[a]	RLi	R	R^1	Temp (°C)	Et_2O/THF % ee	Et_2O % ee
1	MeLi	Ph	Ph	−78	88 (*R*)	—
2	MeLi	Ph	Ph	−116	95 (*S*)	34 (*S*)
3	MeLi	Ph	Et	−78	85 (*R*)	—
4	MeLi	Ph	Et	−116	84 (*R*)	12 (*R*)
5	MeLi	CH_2Ph	Ph	−78	66 (*R*)	—
6	MeLi	CH_2Ph	Et	−78	75 (*R*)	—
7	MeLi	CH_2Ph	Et	−116	83 (*R*)	25 (*R*)
8	MeLi	*i*-Pr	Ph	−78	78 (*S*)	—
9	MeLi	*i*-Pr	Ph	−116	92 (*S*)	2 (*S*)
10	MeLi	*i*-Pr	Et	−116	92 (*R*)	27 (*R*)
11	*n*-BuLi	Ph	Ph	−78	90 (*R*)	79 (*R*)
12	*n*-BuLi	Ph	Ph	−116	>98.5 (*S*)	97 (*S*)
13	*n*-BuLi	Ph	Et	−78	85 (*R*)	61 (*R*)
14	*n*-BuLi	Ph	Et	−116	94 (*R*)	83 (*R*)
15	*n*-BuLi	CH_2Ph	Et	−116	81 (*R*)	58 (*R*)
16	*n*-BuLi	*i*-Pr	Ph	−78	84 (*S*)	41 (*S*)
17	*n*-BuLi	*i*-Pr	Ph	−116	97 (*R*)	87 (*R*)
18	*n*-BuLi	*i*-Pr	Et	−116	91 (*R*)	71 (*R*)

[a] Molar ratio of benzaldehyde:organolithium:ligand was 1.0:14.5:10.0.



Scheme 8. Reaction of *n*-BuLi with benzaldehyde in the presence of the dimethyl ether of *cis*-1-phenylcyclohexane-1,2-diol.

80c-Li. The fencholate having X = *t*-Bu also forms a 2:2 complex with *n*-BuLi having a slightly different geometry (**80d** and **80d**-



Scheme 9. Synthesis of an Efavirenz® intermediate.

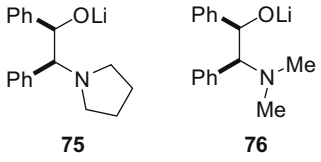
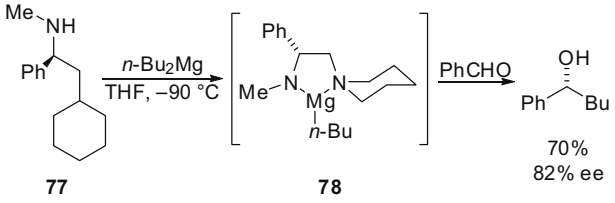
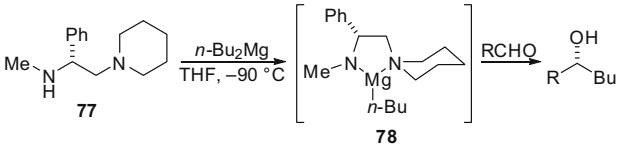


Figure 13. Analogs of lithium alkoxide **73**.



Scheme 10. COMAs as asymmetric alkylating agents.

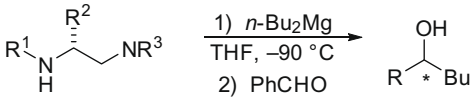
Table 25
Alkylation of aldehydes with **78**[70]



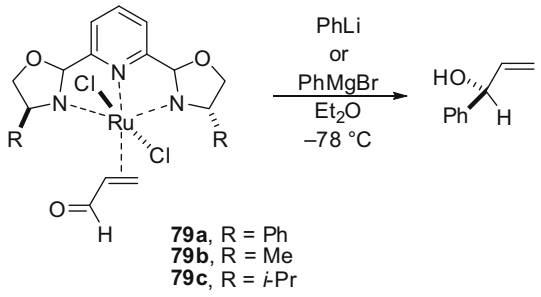
Entry	R	Yield (%)	ee (%)
1	Ph	76	78
2	Ph	70	82
3	4-$CH_3C_6H_4$	57	76
4	4-ClC_6H_4	50	66
5	1-Naphthyl	71	54
6	$MOMO(CH_2)_8$	34	64
7	$BnO(CH_2)_7$	41	68

Li). When X is a methyl group, a 2:4 complex is observed with a structure of two stacked six-membered rings **80e** and **80e**-Li. The results of the alkylation of benzaldehyde to form (*R*)-(+)-1-phenylpentan-1-ol by such complexes are summarized in Table 28.

Table 26
Effect of COMA structure on enantioselectivity of addition to benzaldehyde[70]



Entry	R^1	R^2	R^3	ee (%)
1	Me	Ph	$(CH_2)_5$	78 (*R*)
2	Me	Ph	$(CH_2)_4$	46 (*R*)
3	Me	Ph	$(CH_2)_6$	48 (*R*)
4	Me	Ph	Et_2	34 (*R*)
5	Et	Ph	$(CH_2)_5$	14 (*S*)
6	H	Ph	$(CH_2)_5$	22 (*S*)
7	*t*-Bu	Ph	$(CH_2)_5$	8 (*S*)
8	Me	*i*-Pr	$(CH_2)_5$	28 (*S*)
9	Me	$PhCH_2$	$(CH_2)_5$	44 (*S*)
10	Me	*t*-Bu	$(CH_2)_5$	50 (*S*)



Scheme 11. Addition of PhLi or PhMgBr to chiral ruthenium-bis(oxazolinyl)pyridine-aldehyde complexes.

Table 27
Asymmetric addition of PhLi and PhMgBr to complexes of aldehyde with **79**[71]

Entry	Complex	Ph–M	Solvent	Yield (%)	ee (%)
1	**79a**	PhLi	THF	51	54
2	**79a**	PhLi	Toluene	75	70
3	**79a**	PhLi	CH_2Cl_2	89	87
4	**79b**	PhLi	CH_2Cl_2	70	43
5	**79b**	PhLi	CH_2Cl_2	71	81
6	**79a**	PhMgBr	CH_2Cl_2	61	63
7	**79b**	PhMgBr	CH_2Cl_2	61	64

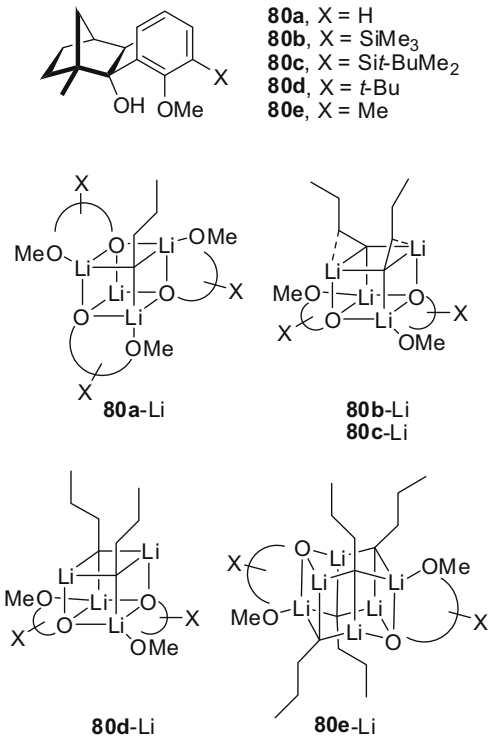


Figure 14. Aggregation states of several *n*-BuLi-anisyl fencholate complexes.

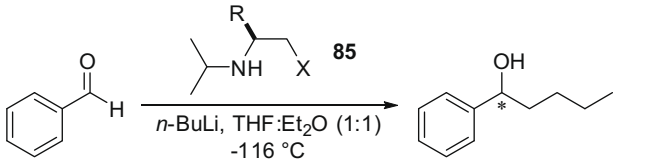
Table 28
Addition of *n*-BuLi to benzaldehyde at −78 °C in the presence of anisyl fencholates[72]

Entry	Fencholate	Fencholate:*n*-BuLi ratio	Yield (%)	ee (%)
1	**80a**	1:1	73	8
2	**80b**	1:1	86	66
3	**80c**	1:1	81	55
4	**80d**	1:1	84	51
5	**80e**	1:1	76	24
6	**80a**	1:3	30	14
7	**80b**	1:3	99	76
8	**80c**	1:3	99	62
9	**80d**	1:3	99	56
10	**80e**	1:3	92	28

Madaluano et al. investigated addition of vinyllithiums to various aldehydes in the presence of the lithium amide **81** derived from a chiral 3-aminopyrrolidine (Scheme 12).[74] Modest to good enantioselectivities (up to 61% ee) were observed in reactions of **82**, **83**, and **84** with *o*-tolualdehyde.

Hilmersson et al. explored the use of various substituted chiral amines **85** in the asymmetric addition of *n*-BuLi to benzaldehyde at

Table 29
Addition of *n*-BuLi to benzaldehyde at −116 °C in the presence of substituted chiral amines **85**[75]



Entry	R	X	Yield (%)	ee (%)
1	*i*-Pr	PPh_2	82	93
2	*i*-Pr	SPh	87	68
3	Bn	PPh_2	93	82
4	Bn	SPh	87	68
5	Bn	PPh_2	71	98
6	Ph	SPh	82	98
7	Ph	OPh	96	96

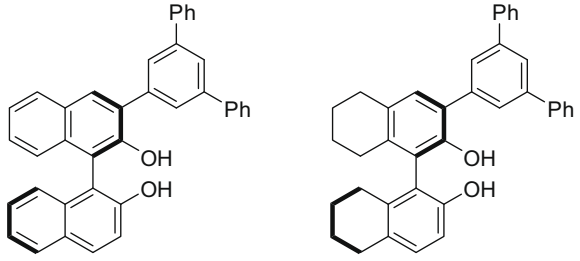
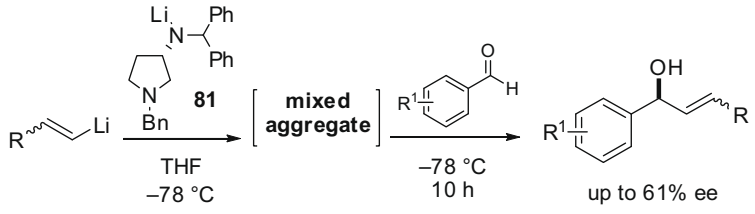


Figure 15. BINOL-like ligands.

−116 °C. The results of this study are summarized in Table 29.[75] The highest selectivities observed were from those ligands derived from phenylglycine containing a soft donor group such as the diphenylphosphino or phenylthio group (Table 29, entries 5 and 6, respectively).

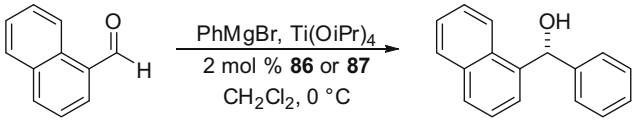
Harada and Muramatsu studied the reaction of Grignard reagents with aldehydes using a titanium(IV) catalyst derived from BINOL-like ligands **86** and **87** (Fig. 15).[76,77] For example, treatment of 1-naphthaldehyde with PhMgBr and titanium tetraisopropoxide in the presence of 2 mol % of **86** or **87** in methylene chloride at 0 °C afforded product in excellent yield favoring the (*R*)-enantiomer with selectivities ranging from 86% to 95% ee (Table 30).[77] Optimal conditions involved treating 1.2 equiv of PhMgBr with a total of 3.0 equiv of Ti(O*i*-Pr)$_4$ and 2 mol % of **87** (Table 29, entry 4). This methodology was applied to several other aldehydes and Grignard reagent combinations and the selectivities ranged from 9% to 96% ee.[76,77]



82, R = H
83, R = OEt (*Z*)
84, R = $SiMe_3$ (*E*)

Scheme 12. Addition of vinyllithiums to aldehydes in the presence of the lithium amide **81** derived from a chiral 3-aminopyrrolidine.

Table 30
Addition of PhMgBr and Ti(O*i*-Pr)$_4$ to 1-naphthaldehyde in CH_2Cl_2 at 0 °C in the presence of 2 mol % BINOL-like ligands **86** or **87**



Entry	Ligand	PhMgBr (equiv)	Ti(O*i*-Pr)$_4$ (equiv)	Yield (%)	ee (%)
1	**86**	2.2	5.8	94	86
2	**87**	2.2	5.8	98	94
3	**87**	1.2	4.0	98	92
4	**87**	1.2	3.0	97	95
5	**87**	1.2	2.2	99	91
6	**87**	1.2	1.7	90	87

9. Summary

In summary, the asymmetric addition of an organolithium or an organomagnesium reagent to an achiral aldehyde or ketone remains a challenge. There are only few reports of high enantioselectivity for such reactions, and successful methods often require non-ideal conditions (temperatures < −100 °C and equimolar quantities of chiral ligand).

Acknowledgment

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