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Enantioselective Addition of Alkyllithium Reagents to Aldehydes Induced by Chiral Lithium Alkoxides.

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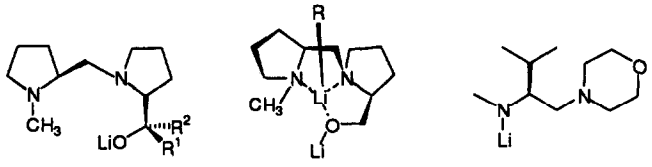
Abstract: Enantioselective induction by some chiral lithium alkoxides in the addition of methyllithium to benzaldehyde has been examined. A detailed study of 2-substituted lithium 1-phenyl-2-(N,N-dimethylamino)-ethoxides in the addition of achiral alkyllithium reagents to aldehydes in THF and diethyl ether at -78 °C has been carried out. The *ee*'s are generally higher in the former solvent. The configuration of the newly formed chiral center is opposite to that of the 1-carbon of the alkoxide and independent of that of its 2-carbon atom. The *ee* of the product is generally increased by increasing the size of 2-substituent. Enantioselectivity is decreased by the addition of LiCl and $LiClO_4$ but is little affected by the presence of the predominant enantiomer of the lithium alkoxide produced in the reaction.

Introduction

The findings of McGarrity, Ogle, Brich, and Loosli[1] that tetrameric butyllithium in THF forms a series of mixed tetramers with lithium butoxide and that these species react more rapidly with benzaldehyde than the homotetramer have important implications concerning the synthetic use of organolithium compounds. In particular, the formation of mixed aggregates provides a means of introducing chirality into formally achiral reagents. Some examples of this concept have been described in the literature.

In 1978, Mukaiyama and his coworkers[2] reported that highly enantioselective additions of simple achiral alkyllithium reagents to aldehydes can be achieved by the adding lithium alkoxides **1** of the 2-hydroxymethyl-pyrrolidinylpyrrolidine derivatives obtained from (S)-proline to the reaction mixtures at low temperatures. The enantioselectivity was found to depend on solvent as well as the structures of the reactants and the chiral lithium alkoxides. The highest optical purity reported (95%) was obtained for the addition of butyllithium to

benzaldehyde in the presence of the primary alkoxide **1** ($R^1 = R^2 = H$) in dimethoxyehane/dimethyl ether (1:1) at -123 °C. These workers speculated that the enantioselective addition might involve a species such as **2**.



1 **2** **3**

Alberts and Wynberg[3] have shown that the addition of ethyllithium to benzaldehyde in the presence of the optically pure lithium alkoxide of (+)-(R)-1-phenylpropanol-d_1 leads to an enantiomeric excess of unlabelled (+)-(R)-1-phenylpropanol, a phenomenon they call 'enantioselective autoinduction.' They ascribed this result to the formation of a mixed aggregate of unknown structure. Earlier, Seebach[4] had suggested that the enantioselectivities induced by the chiral lithamide **3** in aldol reactions and Michael additions of the lithium enolate of cyclohexanone are due to mixed aggregate formation and Alberts and Wynberg[5] subsequently showed that the aldol reaction with a lithium enolate also exhibits enantioselective autoinduction.

As part of broader study of the mechanistic role of aggregates and mixed aggregates in the chemistry of organic lithium compounds, we undertook a survey of a number of reactions of simple alkyllithium reagents with aldehydes in the presence of optically active lithium alkoxides. Our intent was to examine the generality of enantiomeric induction through mixed aggregate formation and to select systems suitable for further structural and mechanistic studies.

Determination of Enantiomeric Excess

The reactions in this survey all yielded low molecular weight secondary alcohols, the optical purities of which were readily determined by gas liquid chromatography using a prototype of a now commercially available β-Dex 120 capillary column supplied by Supelco Co. The column consists of a fused silica capillary column that is statically coated with 10% w/w of permethylated β-cyclodextrin[6] in a (65/35 mole/mole) polymethyl/polyphenylsiloxane copolymer. The column, which is 30m in length, with an ID of 200μm and with a film thickness of 0.2μm, was installed in a Hewlett Packard 5890 gas chromatograph.

In the chromatograms of the racemic forms of all four secondary alcohols, $RCH(OH)CH_3$ (R = Ph, *tert*-Bu) and $RCH(OH)CH_2CH_2CH_2CH_3$ (R = Ph, *tert*-Bu), produced in the reactions the peaks from the two enantiomers were baseline resolved. Assignments of the peaks for the enantiomers were made using partially optically active mixtures, the signs of rotation of which were determined polarimetrically.

A Survey of Some Readily Available Alkoxides.

Table I summarizes the efficacy of the lithium alkoxides of some readily available optically active alcohols in promoting the enantioselective addition of methyllithium to benzaldehyde. The first point of interest is that all seven compounds examined do induce some degree of enantioselectivity. As noted by Mukaiyama in his studies of **1,** enantioselective induction is strongly solvent dependent. We had expected that, of the two solvents employed in this study, diethyl ether would be more effective than THF as we had previously found with lithium phenolates that the former solvent more strongly supported mixed aggregate formation with lithium salts[7]. However, with the exception noted below, higher enantioselectivities are obtained in THF.

No obvious trend is apparent in this limited survey. The secondary alkoxides in Table I do give better results than the primary ones but none achieves the levels of enantioselectivity reported for the primary alkoxides **1**. Furthermore, the presence of one or two pendant tertiary amine functions in **5**, **6** and **7**, which obviously contribute to the efficacy of Mukaiyama's compound **1**, does not appear to result in enhanced enantioselectivity. However, of the compounds examined, the secondary alkoxide **8** in THF gave the highest enantiomeric excess. The level of enantioselectivity induced by the binaphthyl derivative **10** is disappointing as this ligand is effective in enantioselective reductions of aldehydes and ketones by lithium aluminum hydride.[8]

Lithium 2-Substituted 1-Phenyl-2-(N,N-Dimethylamino)ethoxides

Because lithium N-methylpseudoephedrinate **8** gave the best result of the compounds in Table I, we have studied this and several structurally and stereochemically related compounds in more detail.

The enantioselectivities induced in the addition of methyllithium to benzaldehyde by four compounds are given in Table II. A striking feature is that the configuration of the product is opposite to that of C(1) and independent of the configuration at C(2). The effects of the nature and relative configuration of the 2-substituent on the magnitude of the enantioselectivity are dependent on the solvent. In diethyl ether, the alkoxide **11,** which lacks a 2-substituent, is relatively ineffective. In this solvent, the diastereomeric 2-methyl alkoxides, **8** and **12**, exhibit similar enantioselectivities and are more effective than the 2-phenyl derivative, **13**. In THF, however, **8** and **12** promote very different levels of selectivity and both are less effective than **13**. Lithium ephedrinate **12** is unique amongst the compounds in Tables I and II in that it affords higher enantioselectivity in diethyl ether than in THF.

We have examined the effects of concentrations of methyllithium and lithium alkoxide on enantioselectivity for both **8** and **13**. The pertinent data are contained in Table III. A lithium alkoxide-to-methyllithium ratio of 2:1 is optimum for both alkoxides in THF.

Table I. Enantioselective Addition of Methyllithium to Benzaldehyde in Diethyl Ether and THF at -78 °C in the Presence of Various Chiral Lithium Alkoxides.

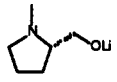
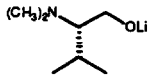
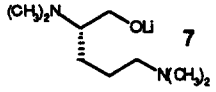
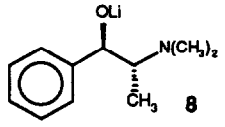
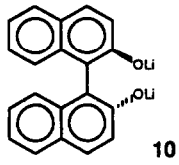
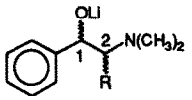
Lithium Alkoxide	ee (%)			
	Diethyl Ether		THF	
 **4**	4	(R)-(+)	12	(R)-(+)
 **5**	5	(R)-(+)	7	(R)-(+)
 **6**	0		6	(S)-(-)
 **7**	1	(R)-(+)	2	(S)-(-)
 **8**	20	(S)-(+)	37	(S)-(+)
 **9**	3.5	(R)-(+)	10	(R)-(+)
 **10**	1	(R)-(+)	5	(R)-(+)

Table II. Enantioselective Addition of Methyllithium (0.18 M) to Benzaldehyde (0.08 M) Induced by Lithium 1-Phenyl-2-(N,N-Dimethylamino)ethoxides (0.16 M) in Diethyl Ether and THF at -78 °C.



		Enantiomeric Excess (%)			
	Lithium alkoxide	Diethyl Ether		THF	
11	(1S), R = H	2	(R)-(+)		(S)-(-)
12	(1R), R = (2S)-CH_3	17	(S)-(-)	7	(S)-(-)
8	(1R), R = (2R)-CH_3	20	(S)-(-)	37	(S)-(-)
13	(1R), R = (2S)-Ph	12	(S)-(-)	55	(S)-(-)

Table III. The Effect of Concentration of Lithium Alkoxides (**8**, **13**) on Enantioselectivity of the Addition of Methyllithium to Benzaldehyde (0.08 M) in THF at -78 °C.

Alkoxide (M)	MeLi (M)	ee (%)
8		
0.04	0.18	13
0.08	0.18	13
0.16	0.18	38
0.32	0.18	38
13		
0.08	0.08	52
0.16	0.08	73
0.16	0.16	56
0.32	0.16	79
0.48	0.16	74

Lithium (1R,2S)-2-(N,N-dimethylamino)-1,2-diphenylethoxide **13** in THF is clearly the most effective of the alkoxides we have tested for the induction of enantioselectivity in the addition of methyllithium to benzaldehyde, and we therefore have applied it to the reactions of several other pairs of reactants. Table IV contains the results. Both methyl - and butyllithium exhibit less facial selectivity in their additions to pivaldehyde than to benzaldehyde, in spite of the greater steric demand of a *tert*-butyl group relative to a phenyl substituent. The result obtained for the addition of butyllithium to benzaldehyde indicates that **13** is

more effective than Mukaiyama's compound **1**, which affords an ee of only 48% under the same conditions. It is interesting that Oppolzer and Radinov[9] have found that **13** is also highly effective for achieving enantioselective additions of alkenylzinc bromides to aldehydes.

Table IV. Asymmetric Induction in the Addition of Alkyllithium Reagents (RLi) to Aldehydes (R'CHO) in the Presence of Lithium (1R,2S)-2-(N,N-dimethylamino)-1,2-diphenylethoxide **13** in THF at -78 °C.

[8]	R	[RLi]	R'	[R'CHO]	ee (%)	Config.
0.33	Methyl	0.17	Phenyl	0.08	79	S-(-)
0.28	Methyl	0.14	*tert*-Butyl	0.07	46	S-(-)
0.29	Butyl	0.15	Phenyl	0.07	75	S-(-)
0.29	Butyl	0.15	*tert*-Butyl	0.07	31	S-(-)

We have examined the degree of enantioselectivity induced by both **8** and **13** as a function of the extent of reaction. This was achieved by adding aliquots of the aldehyde and determining the % ee of the product after each addition. The results are given in Table V. Within experimental error, the presence of the optically active product, lithium 1-phenylethoxide, does not contribute to the enantioselectivity. In other words, enantioselective autoinduction[3] does not occur in the presence of **8** or **13**. This result suggests that the lithium alkoxide product does not reduce the concentration of **8** (or **13**)/methyllithium mixed aggregate to the extent that other mixed aggregates or the homoaggregates contribute significantly to the addition process.

Table V. Enantioselectivity as a Function of % Reaction for the Addition of Methyllithium (0.18 M) to Benzaldehyde (0.08 M) in THF at -78 °C in the Presence of Optically Active Lithium Alkoxides **8** (0.16 M) and **13** (0.16 M).

	ee (%)	
% Reaction	**8**	**13**
10	21	53
20	19	49
50	20	49
70	21	52
90	18	53

It is known from the work of Brown[10] and Günther[11] that methyllithium forms mixed aggregates in solution with lithium halides and we have shown that this also occurs with lithium perchlorate.[7] The data in Table VI indicate that lithium chloride and perchlorate tend to quench the enantioselectivity induce by **8** and a reasonable hypothesis is that they do so by forming mixed aggregates with either **8** or methyllithium, or both, to the exclusion of the species responsible for the enantioselectivity.

Table VI. The Effects of Inorganic Salts on the Enantioselectivity Induced by Lithium N-methylpseudoephedrinate **8** (0.16 M) of the Addition of Methyllithium (0.18 M) to Benzaldehyde (0.08 M) in Diethyl Ether at -78 °C.

[LiCl] M	[$LiClO_4$] M	ee (%)
-	-	20
0.05	-	9
0.1	-	4.5
-	0.1	4

Conclusions:

Our purpose in undertaking this study was not primarily to discover new methods for asymmetric syntheses but rather to define some of the complexities of these reactions and to find systems that give reasonably high enantioselectivities, which might therefore be good subjects for a detailed mechanistic investigation. Nevertheless, the alkoxide **13** may find use in these types of asymmetric synthesis, particularly if temperatures below -78 °C are employed. The lithium alkoxide **13** also appears to be the system of choice for further mechanistic studies.

There seems little doubt that mixed aggregates are the species responsible for the enantioselectivity. The effects of the additions of simple inorganic salts of lithium lend strong support to this thesis. The observation that the optimum ratio of both **8** and **13** to methyllithium is 2:1 does not define the stoichiometry of the reactant since methyllithium, lithium alkoxide, three mixed tetramers, and possibly a mixed dimer may coexist in equilibrium. In a preliminary study, the ^7Li NMR spectrum of a mixture of **12** and methyllithium in diethyl ether at -70 °C was found to contain a number of resonances consistent with the existence of a complex mixture of aggregates. Elucidation of the structures of the species present in **13**/$LiCH_3$ mixtures must await careful low temperature NMR studies. The identification of the actual reactant will then require studies of

reaction kinetics and the Rapid Injection NMR (RINMR) method developed by McGarrity[1] could be used for this purpose.

The presence of the tertiary amine function two carbon atoms removed from the oxygen anion, or of similar chelating groups, may be a necessary, though not sufficient, condition for enantioselectivity. It is known that such groups chelate with lithium ions in tetramers[12,13,14] and in doing so stabilize tetramers relative to lower aggregates.[15] In addition, this chelation presumably helps to create the steric environment necessary for enantioselection.

The difference in enantioselectivity in diethyl ether and THF is clearly of mechanistic significance and may arise because the mixed aggregate is less solvated in diethyl ether. The presence of solvent molecules attached to the lithium cations will certainly also be a factor in defining the steric environment in which the addition reaction occurs.

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