Rational Design of Chiral Lithium Amides for Asymmetric Alkylation Reactions—NMR Spectroscopic Studies of Mixed Lithium Amide/Alkyllithium Complexes

Per I. Arvidsson, Göran Hilmersson, and Öjvind Davidsson*[a]

Dedicated to Prof. Per Ahlberg on the occasion of his 60th birthday

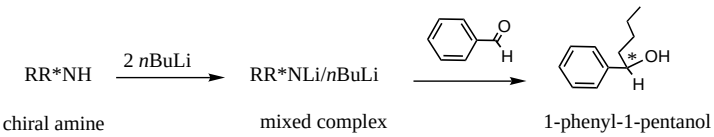
Abstract: Treatment of solutions of chiral lithium amides, containing internally coordinating groups, in diethyl ether (DEE) with alkyllithiums results in the formation of chiral lithium amide/alkyllithium mixed dimers. We report the use of eight different chiral lithium amides/*n*-butyllithium mixed dimers in the asymmetric alkylation of benzaldehyde in DEE solution at −116 °C. The addition product, (*S*)-1-phenyl-1-pentanol, was formed with enantiomeric excesses (*ee*'s) ranging from 0 to 82 %. In DEE/dimethoxy methane solvent mixtures the stereoselectivity was improved and gave the product in 91 % *ee*. Comparison of the ligand structures revealed that only one chiral center was necessary to obtain high enantioselectivity. Replacement of the internally coordinating methoxy group with a pyrrolidine group lowered the *ee* from 82 % to 24 %. Low-temperature ^{6}Li NMR studies of mixtures of these reagents in DEE revealed large differences in the concentration of the reactive mixed dimers formed. Full complexation of *n*BuLi to the chiral lithium amides is not necessary in order to obtain high enantioselectivity, as the result of an increased reactivity of the complexed *n*BuLi.

Keywords: alkylations · asymmetric synthesis · chiral lithium amides · mixed complexes · NMR spectroscopy

Introduction

Alkyllithium reagents are extensively used in organic synthesis and several different chemical transformations are achieved by the use of these reagents.[1] Possibly the most important is the formation of C–C bonds, which can be achieved either through lithiation–substitution, direct alkylation by an alkyllithium compound, or by aldol reactions.[2] However, only a few examples have been reported regarding the use of alkyllithium reagents in stereoselective C–C bond formation. The asymmetric inducers often contain lithium amide or lithium alkoxide functionalities and one or several stereogenic centers. Unfortunately, many of these compounds are of limited synthetic application, since their preparation requires substantial synthetic effort.[3, 4] Furthermore, only a few of these chiral ligands or auxiliaries gave products with enantiomeric excesses exceeding 60 %.[5]

Because organolithium compounds are known to form aggregates in solution, it is believed that chiral mixed complexes are formed between nonchiral alkyllithiums and chiral lithium amides (i.e., chiral inducers). Thus, chiral lithium amides induce asymmetry into the otherwise symmetric organolithium compounds. Provided that such chiral complexes are formed and react with benzaldehyde, it is possible to achieve asymmetric induction (Scheme 1).



Scheme 1. The use of chiral lithium amides for asymmetric alkylation.

Hogeveen and Eleveld reported the asymmetric addition of *n*-butyllithium (*n*BuLi) to benzaldehyde in the presence of the chiral lithium amide base Li-**1** in 1984. In diethyl ether (DEE) at −116 °C, they isolated (*S*)-1-phenyl-1-pentanol in 74 % *ee*. A 1:1 solvent mixture of diethyl ether and dimethoxy methane (DMM) was reported to give an enantioselectivity of 90 % in the same reaction. When THF or toluene was used as the solvent instead of DEE, the optical yields dropped to 68 % and 19 %, respectively. This result shows the strong solvent dependence of these reactions. The optimum ratio of benzaldehyde, *n*BuLi and **1** was found to be 1:6.7:4.

Only a few investigations of chiral lithium amide/alkyllithium mixed complexes have been reported.[6] In a previous study,

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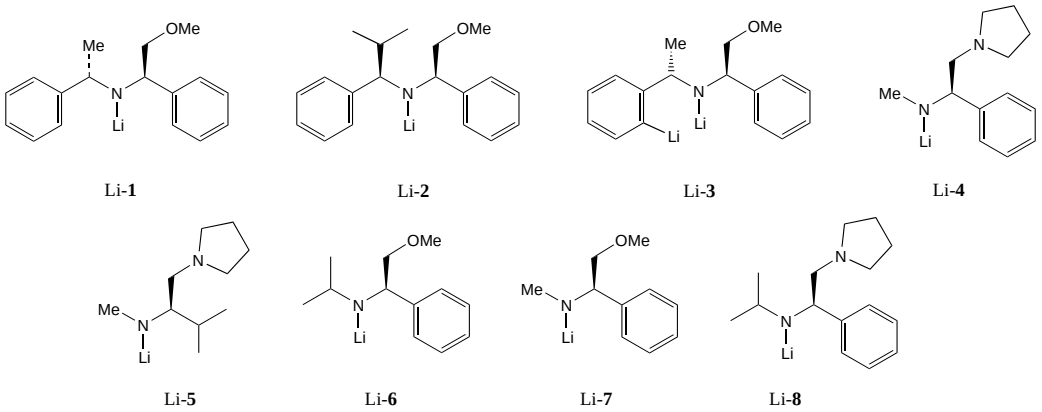

we showed that *n*BuLi is present in the above reaction mixture at $-90\,^{\circ}C$, both as homoaggregated tetramers and as the mixed aggregate Li-**1**/*n*BuLi. Based on these results, we suggested that the mixed complex Li-**1**/*n*BuLi is the reactive species responsible for the reported asymmetric alkylation reaction.

Homotetramers of *n*BuLi readily react with benzaldehyde to yield a racemic mixture of the addition product.[7] This is also clearly reflected in the choice of optimum experimental conditions, as the molar ratios of *n*BuLi and chiral lithium amide are critical for high stereoselectivity in the reaction. The large solvent dependence might be explained by the solvent-dependent equilibrium between homoaggregated Li-**1**, homoaggregated *n*BuLi, and Li-**1**/*n*BuLi.

We believe that in order to control the stereoselectivity, the underlying mechanisms for the reactions and the induction of asymmetry must be well understood. Knowledge about the structure of the initial complexes and their dynamics in solution are therefore crucial. We report here our systematic search for new chiral inducers based upon NMR spectroscopy and enantiomeric product distributions in the asymmetric alkylation of benzaldehyde. The structure, dynamics, reactivity, and selectivity of mixed dimers formed from the chiral lithium amides, obtained from the amines **1** to **8**, and alkyllithium reagents were investigated.

Results and Discussion

The structure of lithium amide/alkyllithium complexes in solution: The chiral lithium amide Li-**1** has already been extensively studied by NMR spectroscopy.[8] The addition of one equivalent of *n*Bu^{6}Li to the amines **1**, **2**, **4**, **5**, **6**, **7**, and **8**, respectively, results in the formation of a single species according to ^{1}H and ^{13}C NMR spectra at $-80\,^{\circ}C$ in DEE. The dilithiated species Li-**3** may be prepared from Li-**1** and excess *n*Bu^{6}Li, as previously described.[8] The ^{6}Li NMR spectra of the amides displays two signals in 1:1 ratio, one significantly broader than the other; this indicates a lower coordination number at this lithium.[9] Furthermore, the amides Li-**2** to Li-**8** are all structural analogues of Li-**1** and exhibit similar ^{1}H, ^{13}C, and ^{6}Li NMR spectra. Therefore, it is likely that these chiral lithium amides all form C_2-symmetric dimers with unsymmetrical internal coordination in DEE solution (structure c in Figure 1). However, the ^{6}Li NMR of Li-**4** and Li-**8** displays an additional resonance, indicative of either a monomer or a symmetrical internally coordinated dimer (structures a or b in Figure 1). ^{15}N–^{6}Li NMR coupling studies performed with [^{15}N,^{6}Li]-labeled Li-**4** in our laboratory have shown that Li-**4**, and probably also Li-**8**, forms symmetrical internally coordinated dimers (structure b in Figure 1) in DEE solution. Thus, we conclude that monomers are not observed for any of these chelating lithium amides in DEE solution.

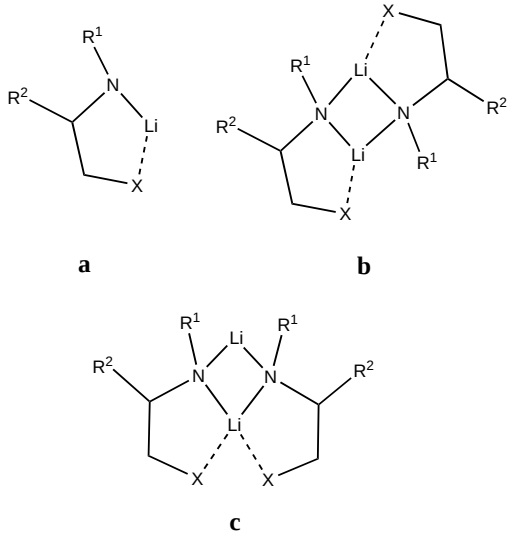

Figure 1. a) Monomer. b) Symmetrical internally coordinated dimer. c) Unsymmetrical internally coordinated dimer.

The formation of new species upon the addition of *n*BuLi to the respective lithium amides is apparent according to NMR. In addition to the signals for the chiral lithium amide dimers, the ^{6}Li NMR spectra show new signals, one for tetrameric *n*BuLi at $\delta = 1.9$ and another two (in a 1:1 ratio) that originate from a mixed complex between a chiral lithium amide and *n*BuLi. The ^{13}C NMR spectra display two sets of resonances for the chiral lithium amides and two sets of resonances for *n*BuLi. This indicates the presence of tetrameric *n*BuLi, lithium amide dimers, and a mixed complex between *n*BuLi and the chiral lithium amide. The mixed complexes are all dimers, since the ^{13}C NMR spectrum displays quintets $^1J(^{13}C,^6Li) \approx 8$ Hz for the α carbons of the complexed *n*BuLi.

In the ^{6}Li NMR spectrum of the homodimer Li-**2** with an additional 1.1 equivalents of *n*BuLi, the mixed dimer of Li-**2**/

*n*BuLi is the predominant species; only traces of the tetrameric *n*BuLi and homodimers of Li-**2** are observed. This indicates a larger preference for Li-**2** to form mixed dimers with *n*BuLi compared with Li-**1**. The lithium amide Li-**6** showed intermediate behavior towards mixed complex formation; the predominant species is the mixed dimer Li-**6**/*n*BuLi, coexisting with small amounts of homodimers of Li-**6** and homotetramers of *n*BuLi (Figure 2).

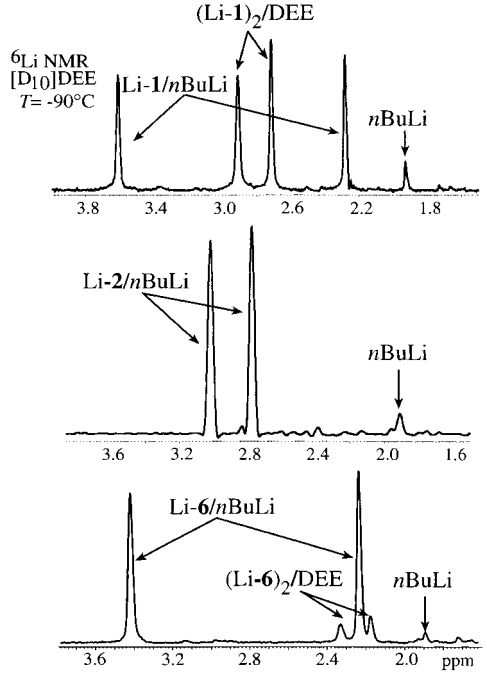

Figure 2. The ^{6}Li NMR spectra ($-90\,^\circ$C) of mixtures of *n*BuLi with (Li-**1**)$_2$, (Li-**2**)$_2$, and (Li-**6**)$_2$ showing the formation of mixed complexes.

The equilibrium constants between the lithium amide homodimers, (*n*BuLi)$_4$, and lithium amide/*n*BuLi mixed dimers were estimated from ^{6}Li NMR intensities and the known concentrations of added *n*BuLi and chiral amine at $-90\,^\circ$C (Table 1).

Table 1. Equilibrium constants for formation of mixed *n*BuLi/lithium amide dimers from tetrameric *n*BuLi and dimers of the various lithium amides.[a]

Equilibrium	K [mol l^{-1}]
$(n\text{BuLi})_4 + 2\,(\text{Li-}\mathbf{1})_2 \overset{K}{\rightleftharpoons} 4\,(\text{Li-}\mathbf{1})/n\text{BuLi}$	4
$(n\text{BuLi})_4 + 2\,(\text{Li-}\mathbf{2})_2 \overset{K}{\rightleftharpoons} 4\,(\text{Li-}\mathbf{2})/n\text{BuLi}$	10000
$(n\text{BuLi})_4 + 2\,(\text{Li-}\mathbf{6})_2 \overset{K}{\rightleftharpoons} 4\,(\text{Li-}\mathbf{6})/n\text{BuLi}$	800
$(n\text{BuLi})_4 + 2\,(\text{Li-}\mathbf{8})_2 \overset{K}{\rightleftharpoons} 4\,(\text{Li-}\mathbf{8})/n\text{BuLi}$	0.14

[a] Determined from the relative ^{6}Li NMR intensities.

The ability of the various chiral lithium amides to complex *n*BuLi is evidently very different. A reason for this could be differences in steric interactions within the lithium amide/*n*BuLi complexes and the corresponding lithium amide homodimers. Compound (Li-**8**)$_2$ with intramolecular pyrrolidine coordination, showed only a weak tendency to coordinate *n*BuLi.

Difference in complexation ability of lithium amides towards different alkyllithium compounds: Is the size of the alkyl group in the alkyllithium important for the formation of mixed complexes with lithium amides? The tendency for Li-**1** to form mixed complexes with alkyllithiums of differing bulkiness was investigated. A series of NMR experiments was performed starting with the alkyllithium reagent with the least steric hindrance, MeLi, followed by the more congested alkyllithium compounds *n*BuLi, *s*BuLi, and *t*BuLi. In DEE solution at $-80\,^\circ$C, homoaggregates of MeLi, *n*BuLi, and *s*BuLi are predominantly tetrameric, whereas for *t*BuLi they are predominantly dimeric. The equilibrium complexation constants were determined from the relative ^{6}Li NMR intensities at $-80\,^\circ$C (Table 2). From the equilibrium constants in Table 2, it is clear that *s*BuLi is superior to the other alkyllithium reagents in the formation of mixed dimers with the chiral lithium amide Li-**1**.

Table 2. The equilibrium constants between alkyllithium (R–Li)$_x$ aggregates, (Li-**1**)$_2$ dimers, and mixed dimers R-Li/Li-**1**.[a]

Equilibrium	K [mol l^{-1}]	δG [kJ mol^{-1}]
$(\text{MeLi})_4 + 2\,(\text{Li-}\mathbf{1})_2 \overset{K}{\rightleftharpoons} 4\,(\text{Li-}\mathbf{1})/\text{MeLi}$	0.001 ± 0.0009	11
$(n\text{BuLi})_4 + 2\,(\text{Li-}\mathbf{1})_2 \overset{K}{\rightleftharpoons} 4\,(\text{Li-}\mathbf{1})/n\text{BuLi}$	1.22 ± 0.41	-0.32
$(s\text{BuLi})_4 + 2\,(\text{Li-}\mathbf{1})_2 \overset{K}{\rightleftharpoons} 4\,(\text{Li-}\mathbf{1})/s\text{BuLi}$	150 ± 70	-8.0
$(t\text{BuLi})_2 + (\text{Li-}\mathbf{1})_2 \overset{K}{\rightleftharpoons} 2(\text{Li-}\mathbf{1})/t\text{BuLi}$	0.4 ± 0.3[b]	1.5

[a] Determined from the relative ^{6}Li NMR intensities. [b] This equilibrium constant has no units.

The equilibrium constant between homo- and heterocomplexes is determined by the steric requirements of the substituents on the α carbon. The introduction of branching on the carbanion carbon, as found in *s*BuLi, adds substantial steric requirements for the carbanion close to the lithium atoms, which disfavors *s*BuLi homotetramers compared with the Li-**1**/*s*BuLi mixed dimer. However, *t*BuLi is only sparingly found in these mixed complexes. We suggest that this unpredictable behavior is due to the fact that *t*BuLi is homodimeric in DEE. This will result in an equilibrium between homodimers and mixed dimers. This is in contrast to the previously used alkyllithiums where there is an equilibrium between homotetramers and mixed dimers. Thus, the interactions are different and comparisons of the equilibrium constants are, therefore, complex.

Diastereotopic α protons on *n*BuLi and diasteromeric *s*BuLi complexes: The α protons of *n*BuLi in the mixed complexes Li-**2**/*n*BuLi (Figure 3) and Li-**6**/*n*BuLi display different chemical shifts. Such large differences in chemical shifts are not observed with Li-**1**/*n*BuLi, although this complex also gives high enantioselectivity in the alkylation of benzaldehyde. We interpret this as a rigidification of the mixed complexes Li-**2**/*n*BuLi and Li-**6**/*n*BuLi relative to Li-**1**/*n*BuLi, which reveals the diastereotopicity of the two methylene α protons on *n*BuLi due to nearby inherent chirality and/or slow rotation about the C_α–C_β bond in *n*BuLi.

The ^{13}C NMR spectrum of the Li-**1**/*s*BuLi complex showed the presence of two Li-**1**/*s*BuLi complexes in a 2:1 ratio at low temperatures. This indicates a difference in the stability of the two diastereomeric Li-**1**/*s*BuLi complexes, and corresponds to a free energy difference of ≈ 1.7 kJ mol^{-1} (Scheme 2 and Figure 4).

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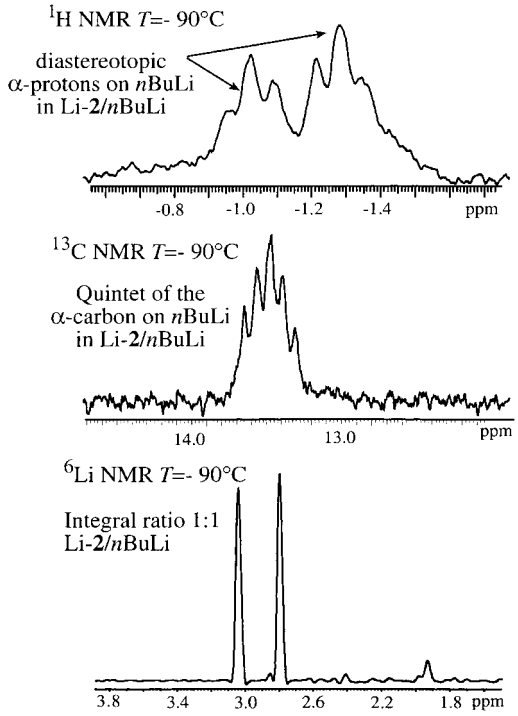
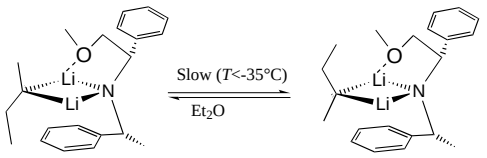


Figure 3. ^{1}H, ^{13}C, and ^{6}Li NMR spectra of Li-**2**/nBuLi.



Scheme 2. The two diastereomeric complexes of Li-**1**/sBuLi.

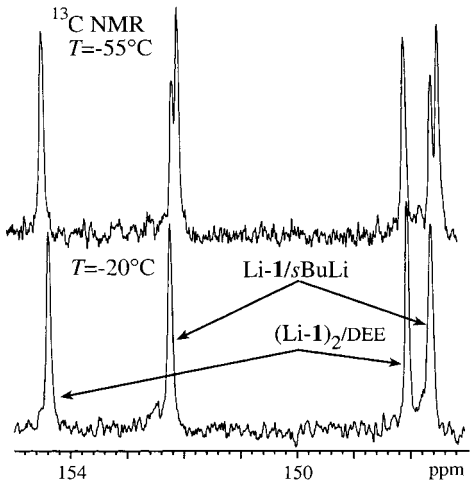


Figure 4. ^{13}C NMR spectra of selected carbons from the two diastereomeric complexes, Li-**1**/sBuLi, showing the intensity ratio 2:1.

However, the activation energy for racemization, estimated from the coalescence of the NMR signals at $-35\,^{\circ}C$, is much larger ($\approx 50\,kJ\,mol^{-1}$). We ascribe this behavior of the complexed sBuLi to the inherent chirality of the environment.

Solvent dependence upon complex formation: Addition of THF to a DEE solution of the mixed complex Li-**1**/nBuLi showed that the equilibrium between homo and hetero complexes is solvent dependent (Scheme 3). The addition of small amounts of THF to (Li-**1**)$_2$ in DEE results in dramatic changes in the ^{6}Li NMR chemical shifts.[9] The ^{6}Li NMR spectra in Figure 5 shows the effect of THF addition to the mixture of (Li-**1**)$_2$, Li-**1**/nBuLi, and (nBuLi)$_4$ in DEE. In agreement with our previous observations, addition of 5% THF

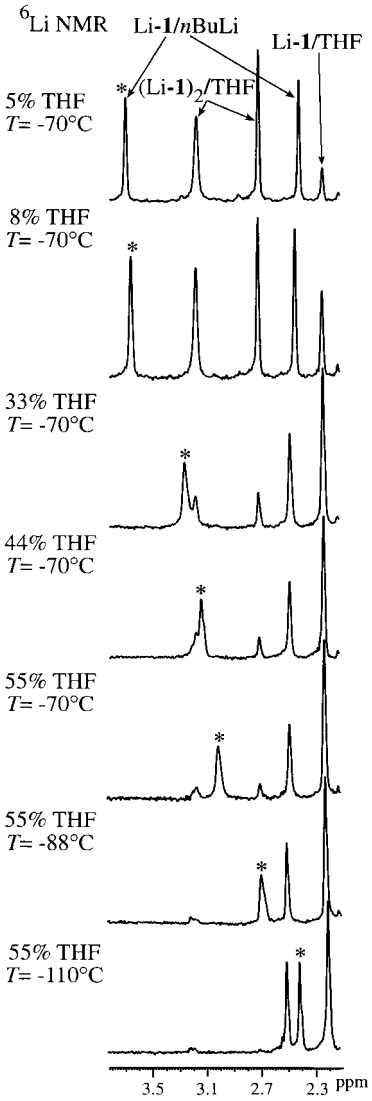
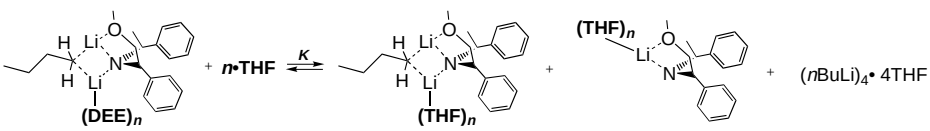


Figure 5. The ^{6}Li NMR spectra of Li-**1**/nBuLi in DEE with increasing concentration of THF.

causes the DEE-solvated (Li-**1**)$_2$ ($\delta = 2.72$ and 2.90) to disappear, while the THF-solvated (Li-**1**)$_2$ ($\delta = 2.70$ and 3.14) is formed together with the THF-solvated monomer ($\delta = 2.28$). The signals for Li-**1**/nBuLi at $\delta = 2.40$ and 3.68



Scheme 3. The solvent dependence of the equilibrium between homo- and heterocomplexes.

were also affected by THF; the most downfield ^{6}Li NMR signal at $\delta = 3.68$ was observed to shift slightly further downfield, possibly caused by the replacement of one DEE molecule by one THF molecule in the solvated Li-**1**/*n*BuLi mixed complex.

At THF concentrations above 8 %, the ^{6}Li signals from the THF-monosolvated Li-**1**/*n*BuLi shifted upfield towards that of Li-**1**/*n*BuLi in pure THF (Figure 5). At 55 % THF in DEE, no homodimers of $(\text{Li-}\mathbf{1})_2$ were observed. The most downfield ^{6}Li resonance from Li-**1**/*n*BuLi (originally at $\delta = 3.68$) was observed at ≈ 0.5 ppm upfield (now at $\delta = 3.14$). These changes in the chemical shifts are likely to be caused by an increase in the coordination number for one of the lithium atoms in Li-**1**/*n*BuLi. This signal also showed a large temperature dependence in the ^{6}Li NMR spectra. Upon lowering the temperature from $-70\,^\circ$C to $-110\,^\circ$C, the ^{6}Li NMR signal at $\delta = 3.14$ shifted upfield to $\delta = 2.42$. The chemical shift for this ^{6}Li NMR signal seems to merge with the ^{6}Li NMR chemical shift of the tetra-coordinated lithium in Li-**1**. The second ^{6}Li NMR signal at $\delta = 2.40$ from Li-**1**/*n*BuLi in DEE showed only small THF concentration-dependent variations, which implies a preserved coordination sphere around this lithium atom. This indicates that the lithium is solvated by the oxygen in the methoxy group and that this coordination also persists in THF.

Addition of THF to a mixture of Li-**8** and *n*BuLi in DEE increases the fraction of mixed dimers, because of the increase in the complexation constant in THF. The unsymmetrical internally coordinated dimer $(\text{Li-}\mathbf{8})_2$ (structure c in Figure 1) decreased upon formation of the symmetrical internally coordinated dimer (structure b in Figure 1). Mixed dimers Li-**8**/*n*BuLi are strongly favored in solutions of DEE containing traces of THF, as compared with a pure solution of DEE.

Fast ligand exchange (DEE and THF) was observed for Li-**1**/*n*BuLi at all accessible temperatures (down to $-110\,^\circ$C). Addition of TMEDA to a DEE solution of Li-**1**/*n*BuLi, $(\text{Li-}\mathbf{1})_2$, and $(n\text{BuLi})_4$ resulted in a large fraction of TMEDA-solvated monomers of Li-**1**, namely, Li-**1**/TMEDA and TMEDA-solvated *n*BuLi dimers (Figure 6).

No TMEDA-solvated Li-**1**/*n*BuLi mixed complexes were obtained. Similar results were found upon the addition of THF or TMEDA, respectively, to the other mixed-dimer complexes in DEE. This shows that the coordination at the most solvent-sensitive lithium cation in Li-**1**/*n*BuLi has a lower energy barrier to coordination. Structurally, this implies that the internal methoxy-oxygen coordination has to be very strong, as it persists even in the presence of a strong polar solvent, such as THF. Tentatively, this suggests that solvents, as well as substrates, initially coordinate to the nonmethoxy-coordinated lithium cation. A further consequence of the strong internal methoxy coordination is that the substituents at the methylene carbons between the amide nitrogen and the methoxy group will be locked in a well-defined spatial arrangement. Consequently, this will result in favorable and unfavorable diastereomeric transition states upon substrate complex formation.

The reported improved stereoselectivity obtained in the asymmetric alkylation of benzaldehyde in a 1:1 solvent mixture of DEE and DMM encouraged us to investigate the

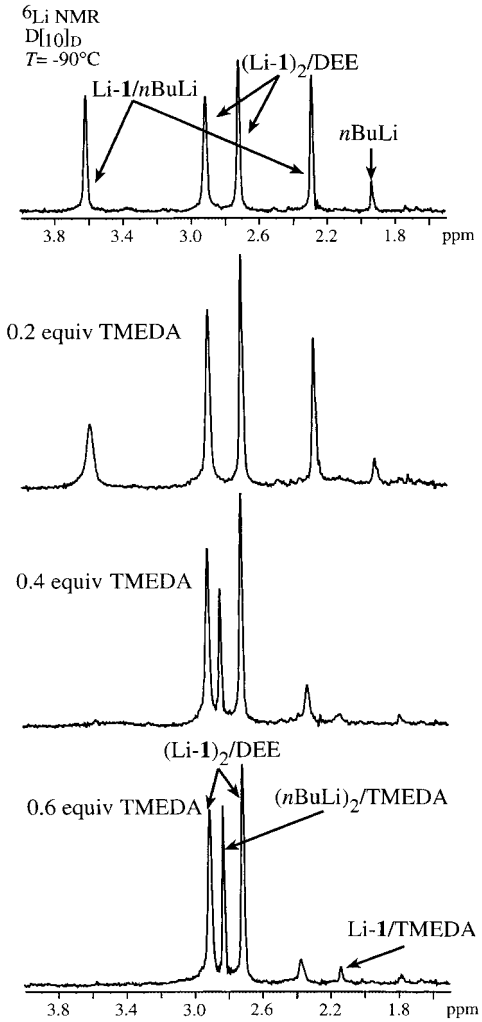


Figure 6. The ^{6}Li NMR spectra of Li-**1**/*n*BuLi in DEE with increasing concentrations of TMEDA.

effect of DMM on the equilibrium between Li-**1**, *n*BuLi, and Li-**1**/*n*BuLi. However, we did not observe any structural changes in the ^{6}Li NMR spectra for Li-**1**/*n*BuLi upon addition of 50 % (v/v) DMM to the DEE solution.

However, the addition of DMM to a DEE solution of *n*BuLi and Li-**6** resulted in the disappearance of the signal from the unsymmetrical internally coordinated dimer $(\text{Li-}\mathbf{6})_2$ and a single ^{6}Li NMR resonance was observed instead (either from a symmetrical internally coordinated dimer or monomer of Li-**6**). The signals from Li-**6**/*n*BuLi showed no indication of specific solvation by DMM. This indicates that DMM only has a marginal effect on the above equilibrium and structures.

Nucleophilic asymmetric addition of *n*BuLi to benzaldehyde: Most of the asymmetric alkylation reactions were performed in DEE solutions. This solvent does not give the highest possible enantioselectivity in the asymmetric alkylation reactions; however, it did enable us to use the information obtained from the NMR studies of the reaction mixtures to partially explain the selectivity in the reactions.

In order to test our method, we reproduced the experiment of Hogeveen and Eleveld;[3a] however, we used GC on a chiral stationary phase, instead of optical rotation, to accurately

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determine the products' *ee*. The chiral lithium amides (Li-**1** to Li-**8**) were generated by the addition of *n*BuLi (1.45 equiv) to the respective amine precursors (1.0 equiv). After 30 minutes, the mixtures were cooled down to $-116\,^{\circ}C$ and benzaldehyde (0.25 equiv) was added. The reaction mixture was quenched at $-116\,^{\circ}C$ with MeOH and analyzed by GC. We obtained the product (*S*)-1-phenyl-1-pentanol in $\leq 82\,\%$ *ee* (Table 3).

Table 3. Enantiomeric excess of 1-phenyl-1-pentanol, obtained by asymmetric addition of *n*BuLi to benzaldehyde in the presence of the chiral lithium amides Li-**1** to Li-**8**.[a]

Amide	R^1	R^2	X	*ee* % (GC)
Li-**1**		Ph	OMe	72 (*S*)
Li-**2**		Ph	OMe	75 (*S*)
Li-**3**		Ph	OMe	8 (*S*)
Li-**4**	Me	Ph		7 (*R*)
Li-**5**	Me	*i*propyl		7 (*R*)
Li-**6**	*i*propyl	Ph	OMe	82 (*S*)
Li-**7**	Me	Ph	OMe	2 (*S*)
Li-**8**	*i*propyl	Ph		26 (*S*)

[a] The following molar ratios were used: lithium amide (1 equiv), *n*BuLi (0.45 equiv), and benzaldehyde (0.25 equiv). The reactions were carried out at $-116\,^{\circ}C$ in DEE. See Figure 1 for definition of the substituents R^1, R^2, and X.

From the results in Table 3, some important structural factors in the lithium amide, which controls the enantioselectivity of the alkylation reactions, can be identified. The steric requirements of the R^1 substituent are crucial for the reaction, that is, the stereoselectivity is dependent on a large bulky group at R^1, a methyl group is too small (see the entries with compounds Li-**4**, Li-**5**, and Li-**7** in Table 3). Sterically demanding R^1-groups, such as those in Li-**1**, Li-**2**, and Li-**6**, gave high enantioselectivities. Furthermore, compound Li-**6**, in which one of the chiral centers of Li-**1** has been removed, did not result in a decrease in stereoselectivity; instead, the product *ee* increased to 82 %. This observation shows that the asymmetric induction is controlled by the chiral center between the R^2 and the chelating group.

The enantioselectivity decreased and the configuration of the 1-phenyl-1-pentanol was reversed when amides Li-**4** and Li-**5** were used. Obviously, the pyrrolidine group forces the benzaldehyde into a different geometry in the transition state. Two factors are important, as seen for Li-**8**. The large *iso*-propyl group in R^1 would imply a good selectivity for the (*S*)-alcohol; however, this effect is biased by the large pyrrolidine group, which favors a transition state that results in the (*R*)-alcohol. The effects controlling the enantioselectivities are, evidently, not very large for the different conformations and a net cancellation of the different effects occurs.

Hogeveen and Eleveld reported in their paper that a 1:1 solvent mixture of DMM/DEE in the alkylation reaction results in a 90 % *ee* of the chiral (*S*)-alcohol. However, after repeating this experiment several times we conclude that the (*S*)-alcohol is formed at best in 72 % *ee*, indicating that DMM has a limited effect, not only on the equilibrium and structure, but also on the stereoselectivity in the addition reaction. Hogeveen and Eleveld determined the *ee* from the optical rotation, whereas we have determined the *ee* from GC. Surprisingly, the addition of DMM to the reaction performed with Li-**6** as a chiral inducer resulted in a large increase in stereoselectivity; (*S*)-1-phenyl-1-pentanol was formed in 91 % *ee*. The reason for this improved stereoselectivity was not determined unambiguously; however, it is probably an effect of increased solvation of the transition state with DMM.

It should also be mentioned that the alkoxide product may affect the *n*BuLi aggregation. A study by Alberts and Wynberg has shown that mixed chiral alkoxide/EtLi complexes are capable of stereoselective autoinduction.[10] However, since the bidentate chiral lithium amides in this study are better complexation agents for *n*BuLi than monodentate alkoxides, stereoselective autoinduction is likely to be of minor importance.

Conclusions

Mixed 1:1 complexes between *n*BuLi and chiral lithium amides are formed in solution, as shown by low-temperature NMR spectroscopy. The equilibrium constants for these complexes were determined by ^{6}Li NMR spectroscopy. These findings allowed a systematic investigation of the factors controlling the stereoselectivity in the addition of *n*BuLi to benzaldehyde. Addition of *n*-butyllithium to benzaldehyde in the presence of Li-**1** gave the product (*S*)-1-phenyl-1-pentanol in 72 % *ee*. From rational design, partially based on multinuclear NMR studies of mixtures of alkyllithium and lithium amides, the optimum chiral lithium amide Li-**6** was synthesized. The use of this new ligand for the asymmetric alkylation of benzaldehyde gave the same product in 91 % *ee* (GC). Thus, the optimum chiral inducer in this system is Li-**6**/*n*BuLi. We are currently investigating other asymmetric alkylation reactions with Li-**6**/*n*BuLi.[11]

Experimental Section

General: All glassware used in the syntheses was dried overnight in an oven (120 °C) when necessary. Glassware and syringes used for the NMR studies and alkylation reactions were dried at 50 °C in a vacuum oven before transfer into a glove box (Mecaplex GB 80 equipped with a gas-purification system to remove oxygen and moisture) and stored under a nitrogen atmosphere. Typical moisture content was < 0.5 ppm. Most manipulations for the alkylation reactions were carried out in the glove box by means of gas-tight syringes. Ethereal solvents, distilled under nitrogen from sodium and benzophenone, were kept over 4 Å molecular sieves in septum-sealed flasks inside the glove box. The concentrations of commercially available *n*BuLi solutions (*n*BuLi, 1.6 or 2.5 M solution in hexanes,

Aldrich) were determined by titration with biphenylmethanol.[12] The enantiomeric purity of the synthesized chiral amines were verified to be >95% *ee*, based on ^{1}H NMR in the presence of (*R*)-1-phenyl-2,2,2-trifluoroethanol.[13]

Routine ^{1}H and ^{13}C 1D-NMR spectra were recorded on a Varian Unity 400 MHz instrument. Optical rotations were measured on a Perkin Elmer 341LC polarimeter. Melting points were measured on a Büchi B-545 melting point apparatus. Chromatographic analyses were carried out on a Varian Star 3400 CX gas chromatograph. All GC analyses were run on a chiral stationary phase column (CP-Chirasil-DEX CB, 25 m, 0.32 mm) from Chrompack. All analyses were performed at 135 °C (injector: 225 °C; detector: 250 °C) with He (2 mL min^{-1}) as the carrier gas. Mass spectra (MS) were recorded on a Varian Saturn 2000 GC-MS/MS operating in the electronic ionization (EI) or chemical ionization (CI) mode. Methane was used as the reagent gas for CI operation. The GC column connected to the mass analyzer was a DB-5MS (J and W Scientific).

Preparations: The following compounds were synthesized according to literature methods: (*R*)-*N*-2-methoxy-1-phenyl-(*S*)-α-methylbenzylamine (**1**),[10] (*R*)-*N*-2-methoxy-1-phenyl-(*R*)-α-isopropylbenzylamine (**2**),[10] (*R*)-*N*-methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine (**4**),[14] and (*R*)-*N*-methyl-1-isopropyl-2-(1-pyrrolidinyl)ethanamine (**5**).[16]

(*R*)-*N*-Isopropyl-*O*-methylphenylglycinol (6):[15] A solution of (*R*)-phenylglycinol (10.1 g, 73.8 mmol), acetone (5.9 mL, 80 mmol), and a catalytic amount of *p*-toluenesulfonic acid in benzene (150 mL) was refluxed for 3 days, while water was removed by means of a Deans–Stark trap. Upon cooling, the reaction mixture was washed with Na_2CO_3 (100 mL, 5% aqueous solution) and brine (100 mL), dried ($MgSO_4$), and concentrated under vacuum to yield the imine as an oil, which slowly crystallized into pale yellow crystals. Yield: 13.1 g (100%).

Without further purification, the imine crystals (12.5 g, 71.0 mmol) were dissolved in dry THF (200 mL) and catalytically hydrogenated for 12 h in a Parr apparatus with H_2 (4 atm) and with Pd/C (10%) as the catalyst. The mixture was filtered through Celite, dried ($MgSO_4$), and the solvent evaporated under vacuum to give the amino alcohol as white acicular crystals. Yield: 11.7 g (93%).

Sodium hydride (3.1 g, 55% dispersion in oil, 71 mmol) was added to a round-bottomed flask equipped with a magnet, a dropping funnel, a thermometer, and a nitrogen inlet. The dispersing oil was removed by successive washing with hexane, and dry THF (20 mL) was added. The amino alcohol (11.5 g, 64.2 mmol) dissolved in dry THF (100 mL) was added over a period of 15 min to the hydride suspension. The mixture was then heated to 40 °C for 30 min. Upon cooling to 5 °C, methyl iodide (4.0 mL, 64.2 mmol) dissolved in dry THF (40 mL) was added to the gelatinous, pale greenish-yellow solution. The reaction mixture was kept at room temperature overnight. Slow addition of water (20 mL) gave a yellow solution, which was extracted with DEE (3 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, and evaporated under vacuum to yield an yellow oil. The oil was dissolved in aqueous HCl (100 mL, 1M) and washed with DEE (150 mL). The aqueous layer was made alkaline by addition of NaOH and was extracted with DEE (3 × 150 mL). The combined extracts were again dried and evaporated. The resulting pale yellow oil was distilled at reduced pressure (65 °C, 1 × 10^{-3} mbar) to give (*R*)-*N*-isopropyl-*O*-methylphenyl glycinol as a clear oil. Yield: 9.83 g (76%); $[\alpha]_D^{23} = -79.1$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (d, 3H), 1.04 (d, 3H), 1.62 (br, 1H), 2.64 (sept, 1H), 3.36 (s, 3H), 3.39–3.47 (m, 2H), 4.02 (dd, 1H), 7.30–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.2$, 24.6, 45.9, 59.0, 60.1, 78.2, 127.4, 127.8, 128.5, 141.7; MS (CI): *m*/*z*: 194 [M^++1].

(*R*)-*N*-Methyl-1-phenyl-2-methoxyethanamine (7): The method described by Rossiter et. al.[16] for the synthesis of the enantiomer of this compound was followed with some modifications: (*R*)-Phenylglycinol (5.0 g, 36.5 mmol) and ethyl formate (3.8 mL, 45.6 mmol) was refluxed for 18 h. Evaporation of the excess ethyl formate under vacuum resulted in a clear oil. This oil was stripped with DEE (10 mL) to afford white crystals, which were filtered and dried under a vacuum to give *N*-formyl-2-amino-2-phenylethanol. Yield: 5.7 g, (95%); m.p. 100.6 °C.

Sodium hydride (3.3 g, 55% dispersion in oil, 76 mmol) was added to a round-bottomed flask equipped with a magnet, a thermometer, and a nitrogen inlet. The dispersing oil was removed by successive washing with hexane. Dry THF (60 mL) and methyl iodide (5.1 mL, 81.8 mmol) was added. A suspension of *N*-formyl-2-amino-2-phenylethanol (4.5 g, 27.3 mmol) in THF was added, and the resulting mixture was refluxed for 6 h. The mixture now had a white appearance and contained a lot of solid material. Saturated Na_2SO_4 was added to the suspension, which dissolved after the addition of water. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 150 mL). The combined organic layers were dried (Na_2SO_4), and the solvent evaporated under a vacuum. The resulting oil, which contained a mixture of mono- and dimethylated *N*-formyl-2-amino-2-phenylethanol, was purified by flash chromatography [silica gel, EtOAc/hexane 8:2; $R_f = 0.54$ (monomethylated) and 0.25 (dimethylated)]. Yield of *N*-formyl-*N*-methyl-1-phenyl-2-methoxyethanamine: 3.6 g (69%).

Attempts to hydrolyze the amide with KOH (101%) failed, even after long reaction times (>12 h). Instead, the *N*-formyl-*N*-methyl-1-phenyl-2-methoxyethanamine (3.6 g, 18.7 mmol) was refluxed in a mixture of EtOH (10 mL) and KOH (20 mL, 50% aqueous solution) for 12 h. The reaction mixture was cooled and then extracted with DEE (3 × 100 mL). The combined ether extracts were dried (Na_2SO_4), and evaporation of the solvent under vacuum gave an orange oil, which was purified by distillation (b.p. 45 °C, oil bath 73 °C, 2.9 × 10^{-2} mbar), to give (*R*)-*N*-methyl-1-phenyl-2-methoxyethanamine as a clear oil. Yield: 1.76 g (62%); $[\alpha]_D^{23} = -97.5$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.95$ (br, 1H), 2.28 (s, 3H), 3.36 (s, 3H), 3.38–3.48 (m, 2H), 3.75 (dd, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.6$, 59.9, 65.0, 77.9, 127.6, 127.7, 128.5, 140.5; MS (CI): *m*/*z*: 166 [M^++1].

(*R*)-*N*-Isopropyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine (8): This compound was prepared from (*R*)-styrene oxide following the general method of O'Brien et al:[17] (*R*)-styrene oxide (1.5 mL, 13.1 mmol) and pyrrolidine (1.8 mL, 21.5 mmol) dissolved in EtOH (45 mL, 95%) was refluxed for 3 h. The solvent was removed under vacuum and the flask, which contained a slightly beige oil, was put under high vacuum (5 × 10^{-2} mbar). Light beige crystals had formed after 10 min. These crystals were dried for 1 h (vacuum), before introduction of a dry nitrogen atmosphere. Dry DEE (60 mL) and triethylamine (5.5 mL, 39.6 mmol) were added and the flask was cooled to 0 °C. Methane sulfonyl chloride (1.23 mL, 15.9 mmol) was added dropwise over a period of 40 min, during which time the suspension turned yellow. Triethylamine (3.7 mL, 26.4 mmol) was added, and the mixture was allowed to warm to room temperature before addition of 2-aminopropane (12.3 mL, 144 mmol) and water (7.5 mL). The two-phase reaction mixture was vigorously stirred for 16 h. The mixture was transferred to a separating funnel, and the layers separated. The yellow aqueous layer was extracted with DEE (3 × 100 mL). The combined organic extracts were washed with aqueous sodium hydrogen carbonate (5%, 100 mL) and water (100 mL). The mixture was dried (Na_2SO_4), and evaporation of the solvent under reduced pressure followed by Kügelrohr distillation (100 °C, 7 × 10^{-3} mbar) gave a very pale yellow oil. Yield: 2.18 g (72%); $[\alpha]_D^{23} = -60.8$ ($c = 1.2$ in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (d, 3H), 1.04 (b, 3H), 1.64 (br, 1H), 1.78 (m, 4H), 2.25 (dd, 1H), 2.42 (m, 2H), 2.60 (m, 3H), 2.80 (t, 1H), 3.85 (dd, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.2$, 23.8, 24.9, 46.2, 54.1, 59.4, 64.3, 127.1, 127.5, 128.4, 144.2; MS (CI): *m*/*z*: 233 [M^++1].

Preparation of NMR samples: For the preparation of ^{6}Li-labeled lithium amides and details of the NMR sample preparations, see previously published papers.[18]

Quantitative ^{6}Li NMR measurements: All quantitative ^{6}Li NMR data for the calculations of equilibrium constants were obtained from single transient experiments on ^{6}Li-labeled compounds. The signal-to-noise ratio was typically ≈200 or better. The spectral widths were 2000 Hz.

Asymmetric alkylation of benzaldehyde: A septum-sealed flask containing a magnet, the amine (0.30 mmol), and dry DEE (1.6 mL) was assembled inside the glove box. The flask was taken out of the box and directly fitted with a dry argon inlet. The flask was cooled to 0 °C and *n*BuLi (0.435 mmol) was added with a syringe. After stirring for 15 minutes at 0 °C, the flask was moved to a DEE/N_2(l) bath (−116 °C) and the temperature was allowed to equilibrate at −116 °C for 45 min. Benzaldehyde (0.075 mmol) was added with a syringe. The reaction was quenched after 1 h by the addition of methanol (0.5 mL). The crude mixture, which contained the alkylation product, was analyzed by chiral stationary-phase GC.

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