

Internal coordination and solvent effects upon hetero- and homocomplexation of chiral lithium amides: structure reactivity effects

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Received 27 December 1999; accepted 9 May 2000

Abstract

The two chiral lithium amides prepared from (*R*)-(2-*N,N*-dimethylamine-ethyl)-(1-phenyl-2-pyrrolidin-1-yl-ethyl)amine (**1**) and (*R*)-(2-methoxyethyl)-(1-phenyl-2-pyrrolidin-1-yl-ethyl)amine (**2**) and *n*-BuLi, were found to form symmetrically solvated dimers in diethylether (DEE). The addition of tetrahydrofuran (THF) and of 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU) did not affect the ⁶Li-NMR chemical shift due to a very strong internal coordination. Their reactivity as chiral bases in the desymmetrization of cyclohexenoxide was very low due to this strong entropy driven internal coordination. However, they were found to easily form mixed complexes with *n*-BuLi which was verified by ¹³C-NMR and ⁶Li, ¹H-HOESY NMR. One molecule of *n*-BuLi and one molecule of the chiral lithium amide Li-**1** respectively Li-**2** constituted the mixed complexes. In this mixed dimer at least one coordination site is available on lithium for coordination of the substrate. The alkylation of benzaldehyde using Li-**1**/*n*-BuLi gave 40% and Li-**2**/*n*-BuLi gave 30% enantiomeric excess of the (*S*)-1-phenyl-1-pentanol in very high chemical yields. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Chiral lithium amides; HOESY-NMR; Internal coordination; Mixed complexes; Alkylation; Deprotonation

1. Introduction

Nucleophilic addition to carbonyl carbon atoms using organometallic reagents, e.g. R₂Zn, RMgX, RCu, and the use of organolithium bases in deprotonation reactions are central reactions in organic synthesis today [1]. The addition reactions provide a reliable route to optically active secondary alcohols, when chiral auxiliaries or ligands are used. Despite the wide use of organolithium reagents in organic synthesis, only a few examples of asymmetric alkylation reactions using alkylolithium reagents and non-covalently bound chiral additives have been reported, compared to the more investigated asymmetric deprotonation reactions [2]. One reason for the limited exploration of organolithium reagents in addition reactions could be their high reactivity and propensity to form homo- and hetero-aggre-

gates [3]. To the best of our knowledge there exist only a few X-ray crystallographic studies [4] and NMR spectroscopic studies [5] on chiral *n*-BuLi complexes. Recently it has been shown that mixed complexes between chiral lithium amides and alkylolithium reagents can be used with great success in the formation of stereogenic carbon atoms [6]. The molecular design of chiral auxiliaries and ligands for use in asymmetric synthesis is one important task of modern organic chemistry. A variety of chiral ligands have been designed for catalytic or stoichiometric chirality transfer in various reactions [7].

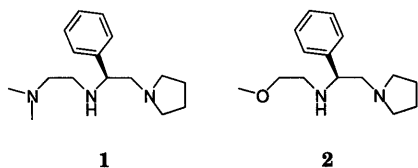
2. Result and discussion

In our development of chiral ligands to be used in both asymmetric additions and deprotonation reactions we obtained some intriguing results with respect to solvent effects and the importance of internal coordination upon reactivity and selectivity. Previous studies of

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chiral lithium amides with one internal coordinating group gave dimers in diethylether (DEE) and tetrahydrofuran (THF). By the introduction of an additional internal coordinating group we expected to obtain monomers in DEE and THF which would result in a more reactive reagent [8]. The chiral amines (*R*)-(2-*N,N*-dimethylamine-ethyl)-(1-phenyl-2-pyrrolidin-1-yl-ethyl)amine (**1**) and (*R*)-(2-methoxy-ethyl)-(1-phenyl-2-pyrrolidin-1-yl-ethyl)amine (**2**) were prepared using the method developed by O'Brien [9].



The ^6Li -NMR spectra of the mixture of **1** (0.24 mmol) and *n*-BuLi (0.24 mmol) in 0.7 ml diethylether (DEE- d_{10}) at -60°C showed the presence of one major signal at δ 2.35. Two very small peaks were also observed in a 1:1 ratio at δ 2.15 and 2.54, respectively (Fig. 1a).

The addition of tetrahydrofuran (THF- d_8) to the above solution did not alter the chemical shift for the large peak at δ 2.35 even if up to five equivalents of THF were added. Addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (DMPU) [10], up to 3.5 equivalents,

was also found to have no effect upon the chemical shift of the signal at δ 2.35. The same observation, lack of solvent effects upon chemical shifts, was also found for the two signals at δ 2.15 and 2.54. There was no difference in intensity observed between the three signals upon addition of THF or DMPU. The absence of solvent effects upon chemical shifts is not in concordance with our previous studies on chiral lithium amides with internal coordination, where large chemical shift ranges in the ^6Li -NMR spectra were observed. Instead we observed large chemical shift changes in the ^6Li -NMR spectra when e.g. THF was added. In our previous studies of chiral lithium amides we obtained symmetrically and unsymmetrically solvated dimers if DEE and THF were used [11]. We interpret the observation of one large signal at δ 2.35 for the lithium salt of **1** (Li-**1**) to be due to the formation of an internal symmetrically coordinated dimer.

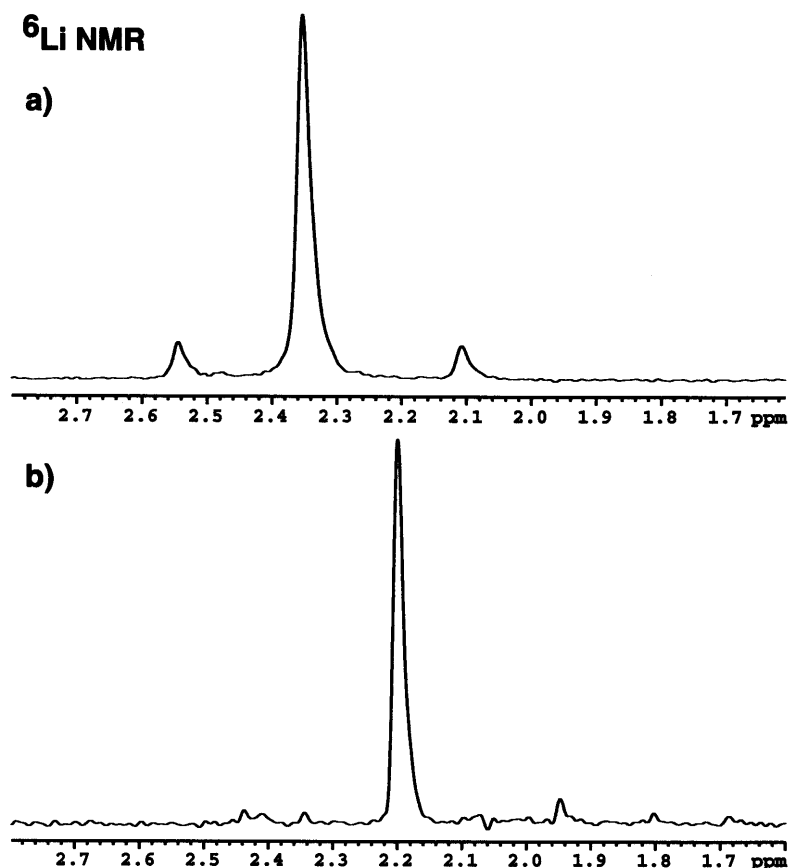
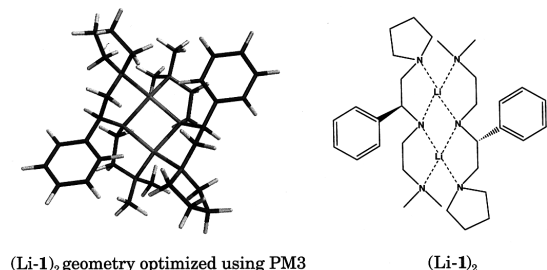
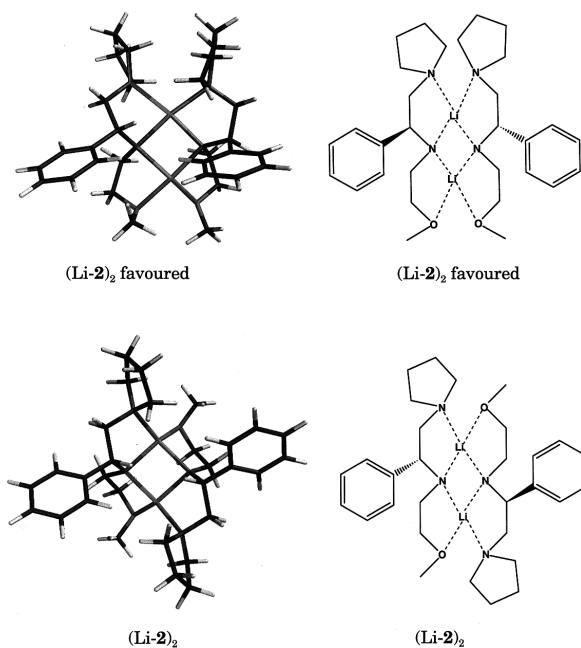


Fig. 1. ^6Li -NMR in DEE- d_{10} at -60°C of (a) Li-**1**, (b) Li-**2**.

The internal coordination results in two tetracoordinated lithiums in the dimer, which is the most favorable coordination state for lithium cations. The formation of a monomer would result in three-coordinated lithium, which would be more accessible for coordination of an external coordinating solvent. Furthermore, the T_1 relaxation of the ^6Li -NMR peak at δ 2.35 of 7.9 s is in the range for a dimeric complex rather than a monomer or higher aggregates such as trimers and tetramers [12]. The two small peaks at δ 2.15 and 2.54 with T_1 relaxation times of 9.5 and 10.3 s, respectively, appearing in a 1:1 ratio, we interpret as originating from an internal non-symmetrically solvated dimer. However both lithiums are still tetra-coordinated.

Geometry optimization calculations of Li-1 and Li-2 using the semi-empirical PM3 method showed that the most stable geometry, by 15 kcal mol $^{-1}$, was the one where each lithium in the dimer coordinates one pyrrolidin nitrogen and one methoxy oxygen in Li-2 [13]. The difference in energy between the dimer where each lithium coordinates one pyrrolidin and one dimethyl nitrogen compared to the dimer where one lithium coordinates two pyrrolidin nitrogens and the other coordinates two dimethyl nitrogens was only 9 kcal mol $^{-1}$ in favor of the first. This also explains why a small amount of the non-symmetrically solvated dimer is observed in the ^6Li -NMR spectra.

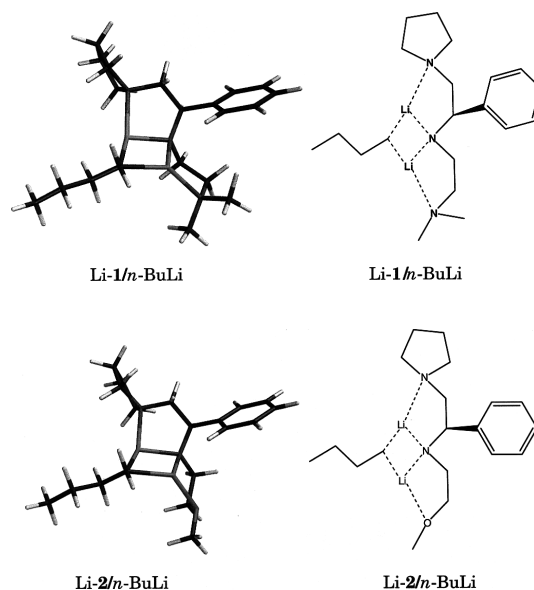


The use of Li-1 in the desymmetrization of cyclohexene oxide also showed that the internal coordination is strong. In a sample constituted of 0.126 mmol of Li-1 and 0.180 mmol of cyclohexenoxide in DEE, the yield of the corresponding allylic alcohol was found to be less than 5% after 200 h and no enantiomeric excess

was obtained. This shows that the cyclohexene oxide does not or hardly coordinates to Li-1. The ^6Li -NMR spectra of the mixture of **2** (0.24 mmol) and *n*-BuLi (0.24 mmol) in 0.7 ml diethylether (DEE) at -60°C showed the presence of only one large signal at δ 2.20 (Fig. 1). The effect on the ^6Li -NMR spectra upon addition of THF and DMPU was the same as found for Li-1. The desymmetrization reaction using the lithium salt of **2** (Li-2) gave a similar result as found for Li-1 with less than 5% conversion after 48 h and no enantiomeric excess was obtained. All these observations are in agreement with our NMR studies showing that additives, solvents and consequently substrates do not coordinate to the lithiums in Li-1 or Li-2 and therefore the reaction rate is slow with no stereoselectivity. The ^{13}C -NMR spectrum showed only one set of ^{13}C -NMR signals indicating that only one species is present in the solution.

The addition of an excess of *n*-BuLi to a sample of Li-1 and Li-2, respectively, in DEE at -60°C gave rise to three new signals in each case. The ^6Li -NMR of Li-1 and *n*-BuLi in excess (two equivalents) gave two signals at δ 2.26 and 2.53 with T_1 relaxation times of 9.5 and 10.3 s, respectively. These two signals were found to appear in a 1:1 ratio. The ^6Li -NMR of Li-2 and *n*-BuLi in excess (three equivalents) also gave two new signals at δ 2.03 and 2.46. These two signals were found to appear in a 1:1 ratio (Fig. 2).

Based upon observed T_1 relaxation times of the two signals at δ 2.26 and 2.53, from Li-1 with an excess of *n*-BuLi added, we tentatively assigned these to originate from the heterocomplex Li-1/*n*-BuLi. The same interpretation was also made for Li-2 with an excess of *n*-BuLi added.



A third signal was also observed at δ 1.90 with a T_1 relaxation time of 14 s. The signal at δ 1.90 was

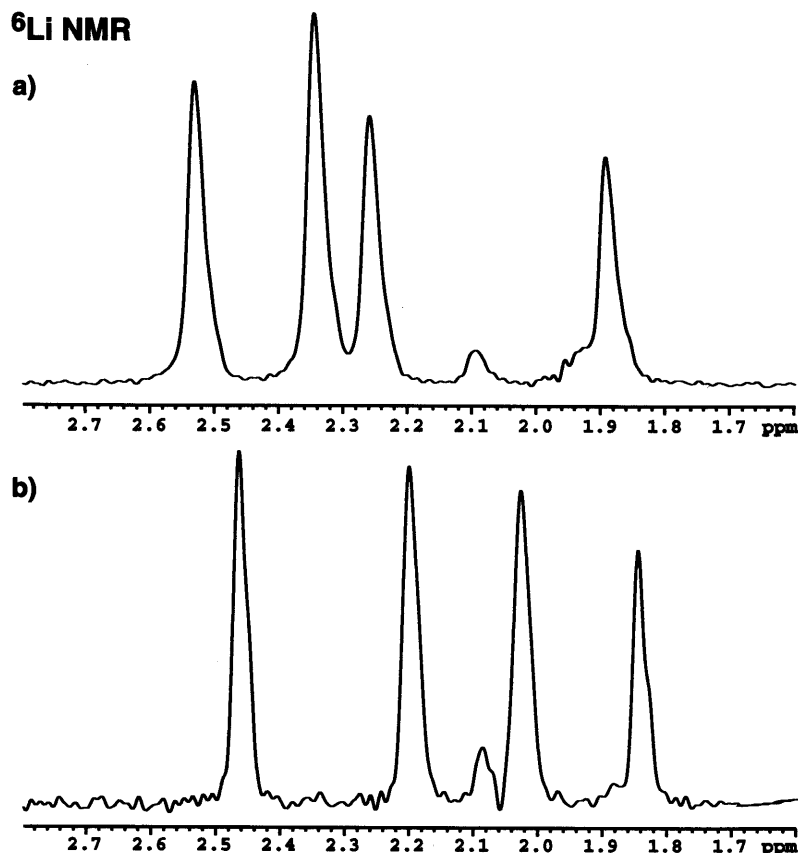


Fig. 2. ${}^6\text{Li}$ -NMR in $\text{DEE-}d_{10}$ at -60°C of (a) Li-1 with two equivalents of $n\text{-BuLi}$ in excess, (b) Li-2 with three equivalents of $n\text{-BuLi}$ in excess.

tentatively assigned to the homocomplex $[n\text{-BuLi}]_4$ based upon T_1 relaxation time and the fact that this signal increased upon addition of $n\text{-BuLi}$. The ${}^6\text{Li}$, ${}^1\text{H}$ -HOESY spectra of the above solution unequivocally showed that the two new signals, trace at δ 2.26 and 2.53, indeed originate from the heterocomplex Li-1/ $n\text{-BuLi}$ as NOE effects were observed between both the Li-1 and the methylene α -protons at δ -1.1 and -1.2 in $n\text{-BuLi}$ (Fig. 3).

Interestingly the two methylene α -protons from the complexed $n\text{-BuLi}$ display different chemical shifts. They are diastereotopic, due to nearby inherent chirality. In contrast the trace at δ 2.35, previously assigned to originate from the homodimer Li-1, only showed NOE effects to Li-1 protons. Finally the trace at δ 1.90 assigned to homocomplexed $n\text{-BuLi}$ tetramer only showed NOE effects to one set of methylene α -protons on $n\text{-BuLi}$ at δ -1.0 and not to any Li-1 protons. The same pattern was also seen using Li-2 and an excess of $n\text{-BuLi}$ (three equivalents) where the traces at δ 2.03 and 2.46 showed NOE effects to both the Li-2 protons and to two diastereotopic methylene α -protons at δ -1.0 and -1.2 from $n\text{-BuLi}$ (Fig. 4).

The trace at δ 1.83 showed NOE effects to the α -protons in $n\text{-BuLi}$ at δ -1.1 but not to any Li-2 protons and finally the trace at δ 2.20 showed only

NOE effects to Li-2 protons. A ${}^6\text{Li}$, ${}^6\text{Li}$ -EXSY NMR spectrum also showed an exchange between the lithium signals at δ 2.03 and 2.46 indicating that they originate from one and the same complex. No other correlations were observed (Fig. 5).

By using the ${}^6\text{Li}$, ${}^1\text{H}$ -HOESY experiment we were able to assign all new species formed and to assign which lithium is coordinated to which internal coordinating group. The trace at δ 2.26 from Li-1/ $n\text{-BuLi}$ shows a strong NOE to the phenyl ring protons; this NOE correlation is not seen in the trace at δ 2.53. Based upon geometries obtained from semiempirical PM3 calculations we are able to assign the lithium signal appearing at δ 2.26 to be internally coordinated with the $-\text{N}(\text{CH}_3)_2$ nitrogen. The phenyl proton lithium distances are 2.5 Å to the lithium coordinating with the $-\text{N}(\text{CH}_3)_2$ nitrogen and 3.7 Å to the lithium coordinating with the pyrrolidin nitrogen. The mixed complex Li-2/ $n\text{-BuLi}$ also showed significant differences in NOE correlations to the phenyl ring protons. The phenyl proton lithium distances are 2.8 Å to the $-\text{OCH}_3$ oxygen coordinated lithium and 3.9 Å to the pyrrolidin nitrogen coordinated lithium. Based upon the semiempirical PM3 calculated geometries we are able to assign the lithium signal appearing at δ 2.03 to the lithium that is internally coordinated with the $-\text{OCH}_3$ oxygen.

In an analogous manner the pyrrolidin ring protons for the complex $\text{Li-2}/n\text{-BuLi}$ have distances of 5.0 Å to lithium at δ 2.26 and 2.8 Å to the lithium at δ 2.53.

The ^{13}C -NMR spectrum also showed that a mixed dimer was formed, as two sets of carbon signals were seen, one set from the chiral lithium amide homodimer

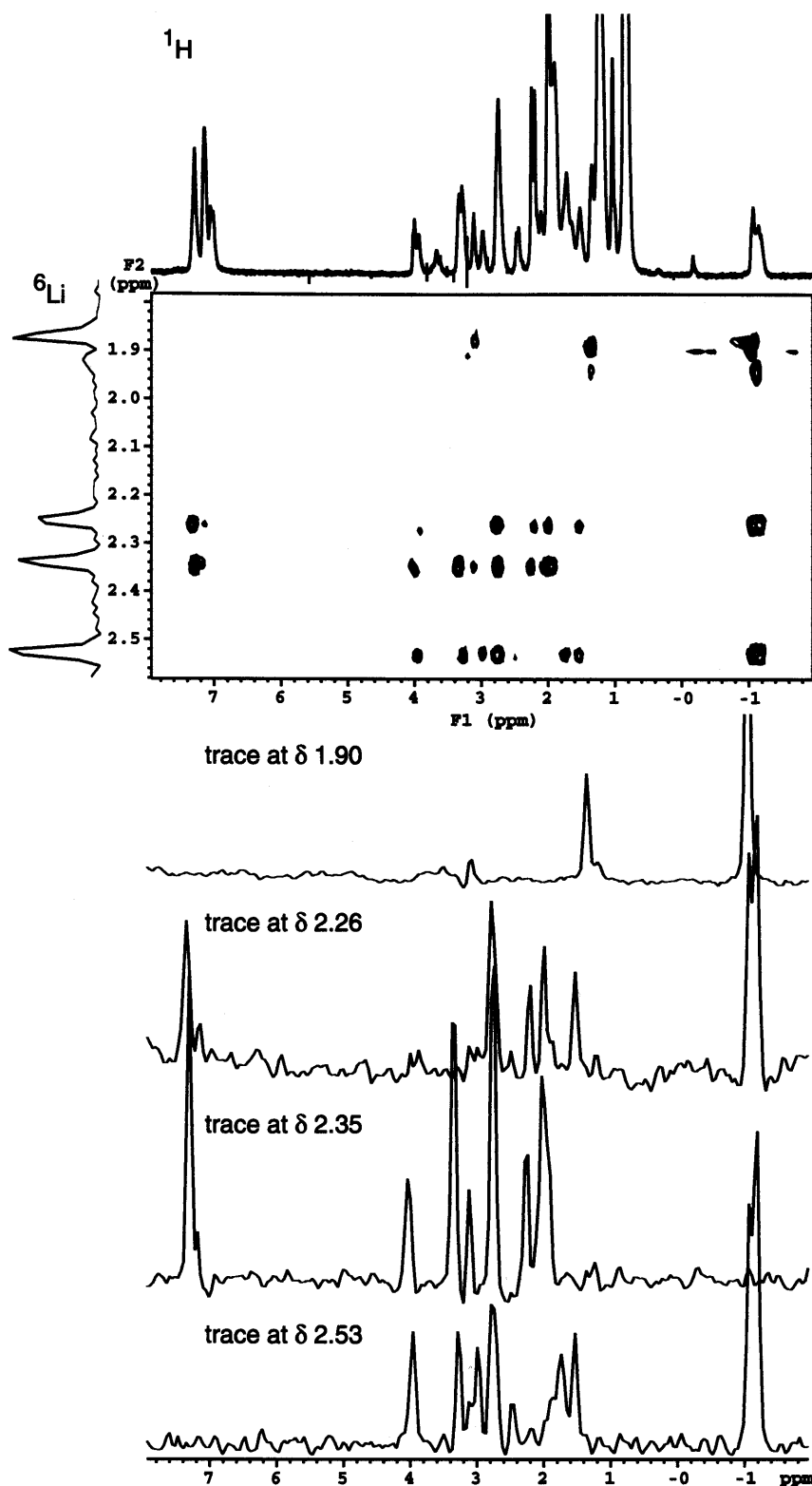


Fig. 3. ^6Li , ^1H -HOESY NMR in $\text{DEE-}d_{10}$ at -60°C for Li-1 with two equivalents of $n\text{-BuLi}$ in excess showing the ^6Li -NMR traces at δ 1.90, 2.26, 2.35, and 2.53 ppm.

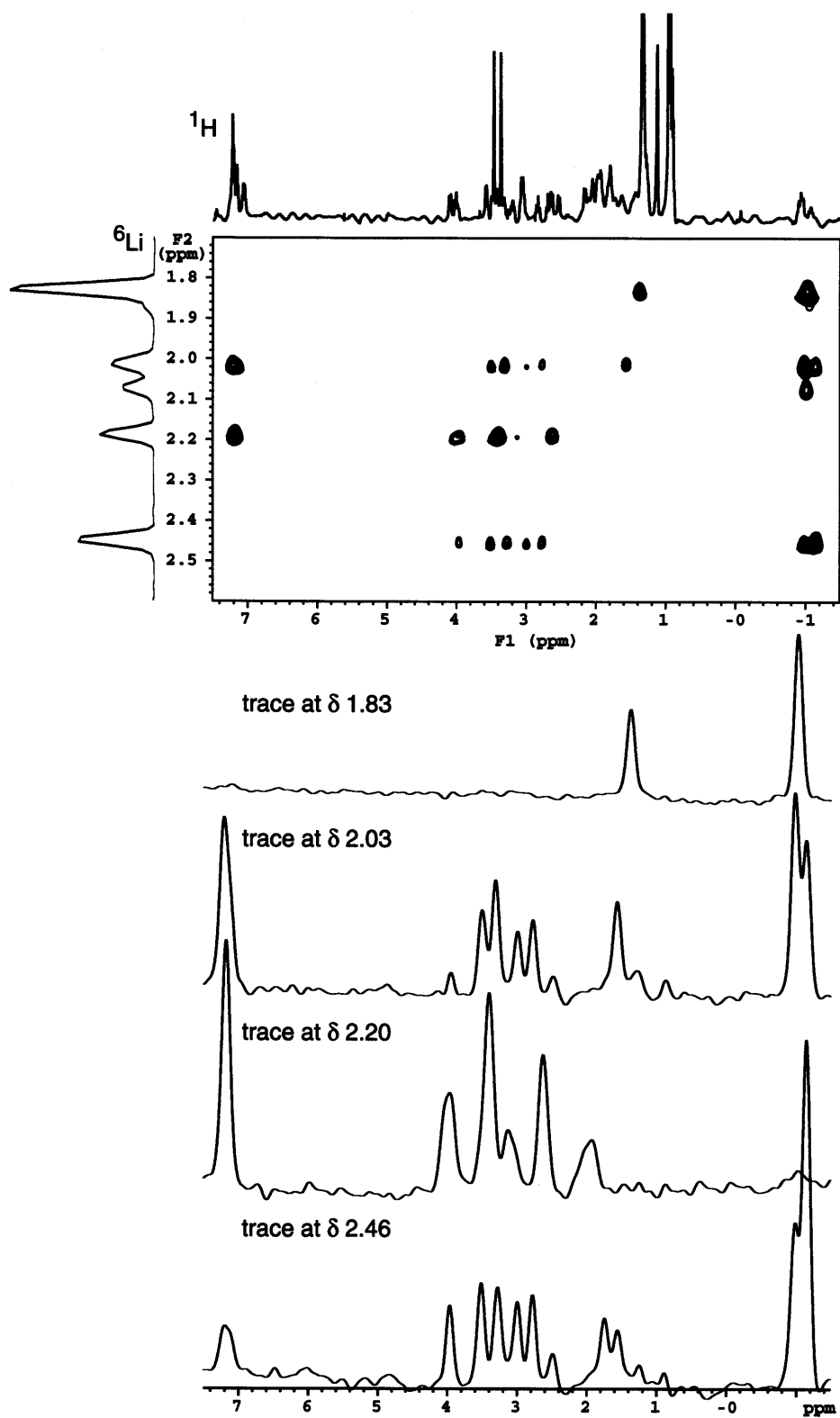


Fig. 4. ${}^6\text{Li}$, ${}^1\text{H}$ -HOESY NMR in $\text{DEE-}d_{10}$ at -60°C for Li-2 with three equivalents of $n\text{-BuLi}$ in excess showing the ${}^6\text{Li}$ -NMR traces at δ 1.83, 2.03, 2.20, and 2.46 ppm.

and one set from the chiral lithium amide/*n*-BuLi heterocomplex.

Furthermore, the ^{13}C -NMR spectrum of the above solutions of Li-1 and Li-2 displayed two carbanionic carbons each, for Li-1 at δ 15.9 and 14.0 and for Li-2 at δ 15.5 and 14.0. Different coupling patterns were observed as different coupling magnitudes (Fig. 6).

The signals at δ 15.9 and 15.5 displayed a pentet with a carbon–lithium coupling of 8.2 and 8.3 Hz, respectively. The two signals at δ 14.0 displayed a septet with a carbon–lithium coupling around 5.3 Hz. Both the magnitudes and the multiplicities of the lithium–carbon couplings show that the carbon signals at δ 15.9 and 15.2 originate from the mixed complexes Li-1/*n*-BuLi and Li-2/*n*-BuLi, respectively. The two carbon signals at δ 14.0 originate from *n*-BuLi homotetramers.

The ability of Li-1 and Li-2 to coordinate *n*-BuLi was determined by measuring the relative ^6Li -NMR intensities. The equilibrium complexation constant for Li-1 to coordinate *n*-BuLi was found to be $K = 1.8 \text{ M}^{-1}$ and for Li-2 $K = 49 \text{ M}^{-1}$ at -60°C . The higher complexation constant for Li-2 to *n*-BuLi is also reflected in the ^{13}C -NMR spectra (Fig. 6).

The butylation of benzaldehyde was investigated using Li-1 and Li-2 with a slight excess of *n*-BuLi (1.4 equivalents) with respect to amine. The mixed complex Li-1/*n*-BuLi gave, upon reaction with benzaldehyde, an enantiomeric excess of 40% of the (*S*)-1-phenyl-1-pentanol and Li-2/*n*-BuLi gave an enantiomeric excess of 30% of the (*S*)-1-phenyl-1-pentanol. These observations are all in agreement with our NMR studies showing that a mixed complex is formed that transfers its chirality in the reactions to give enantiomeric enriched products.

3. Summary

With this study we have shown that the role of internal coordination, and the coordination number obtained, largely affects the reactivity of the reagent. In the case of using the amines as chiral bases one should avoid using amines exhibiting two potentially internal coordinative groups. The reason for this is that there will be no coordination site available for the substrate, the two lithiums are tetracoordinated. The internal coordination seems to be very strong probably due to favorable entropy. The mixed dimer has at least one coordinating site available at each lithium for coordination of benzaldehyde. This is reflected in the enantiomeric excess and chemical yield obtained. The enantiomeric excess is not as high as in previous reports but we see a large potential in using these amines as two chirality centers can be introduced, one at each lithium internal coordinating link.

4. Experimental

4.1. General

All glassware used for synthesis was dried overnight in a 120°C oven 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 that removes oxygen and moisture) containing a nitrogen atmosphere. Typical moisture content was less than 0.5 ppm. Most manipulations concerning the alkylation reactions were carried out in the glove box using gas-tight syringes. Ethereal solvents, distilled under nitro-

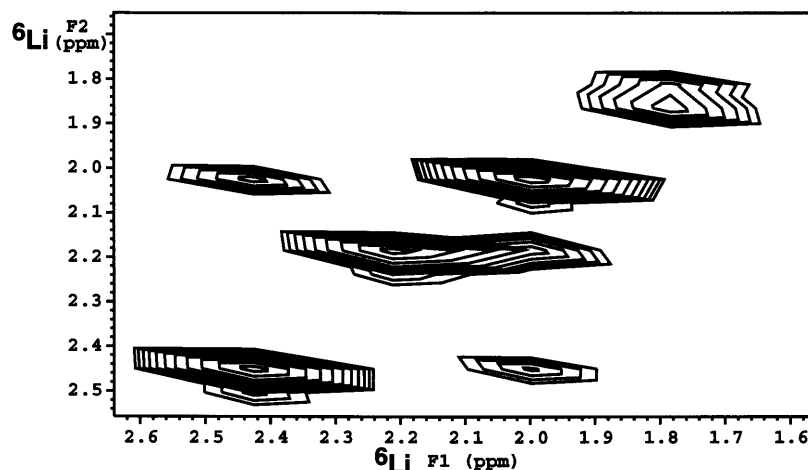


Fig. 5. ^6Li , ^6Li -EXSY NMR in $\text{DEE-}d_{10}$ at -60°C for Li-2 with three equivalents of *n*-BuLi in excess showing the correlations between signals at δ 2.03 and 2.46 ppm from the *n*-BuLi/Li-2 mixed complex.

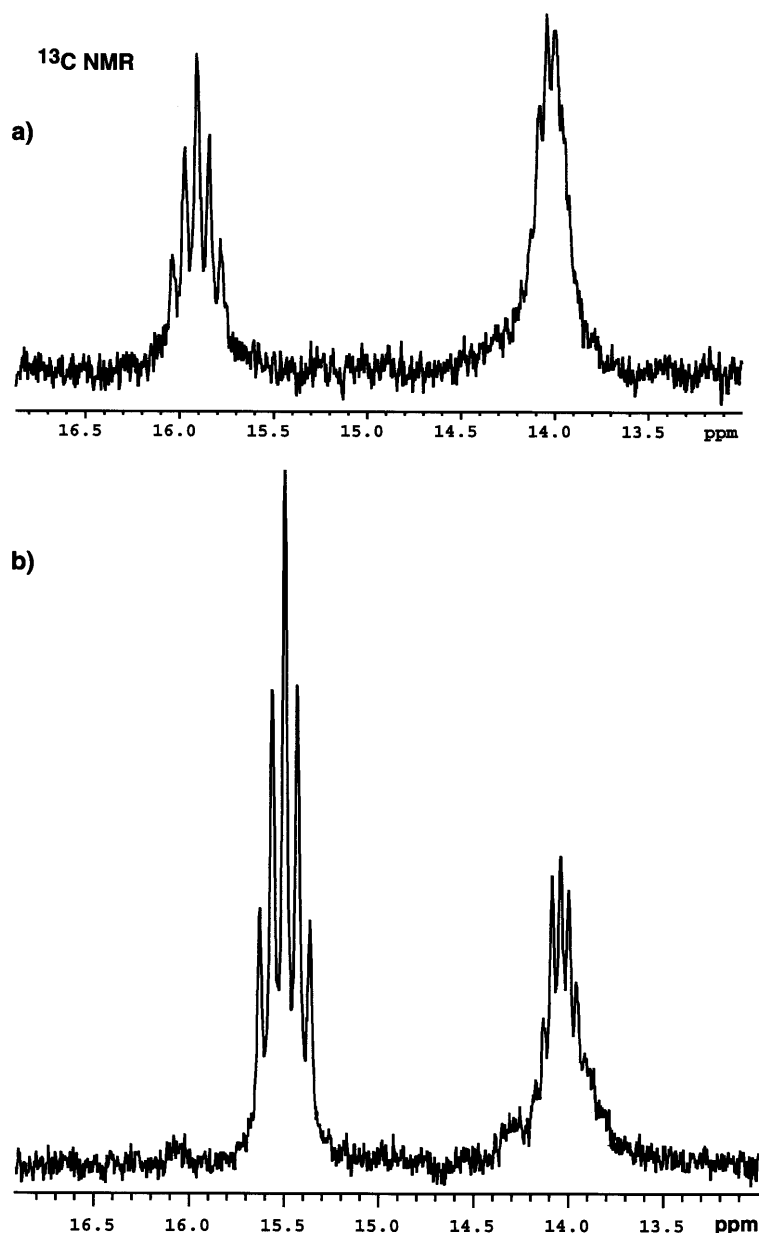


Fig. 6. ^{13}C -NMR in $\text{DEE-}d_{10}$ at -60°C of (a) Li-1 with two equivalents of $n\text{-BuLi}$ in excess showing the α -carbon signals from complexed $n\text{-BuLi}$, at δ 15.9 ppm (pentet, $^1J_{\text{CLi}} = 8.2$ Hz), and free $n\text{-BuLi}$, at δ 14.0 ppm (septet, $^1J_{\text{CLi}} = 5.3$ Hz), respectively. (b) Li-2 with two equivalents of $n\text{-BuLi}$ in excess showing the α -carbon signals from complexed $n\text{-BuLi}$, at δ 15.5 ppm (pentet, $^1J_{\text{CLi}} = 8.3$ Hz), and free $n\text{-BuLi}$, at δ 14.0 ppm (septet, $^1J_{\text{CLi}} = 5.2$ Hz), respectively.

gen from sodium and benzophenone, were kept over 4 Å molecular sieves in a septum sealed flask inside the glove box. The concentrations of commercially available $n\text{-BuLi}$ solutions ($n\text{-BuLi}$ 1.6 M or 2.5 M solution in hexanes, Aldrich) were determined by double Gilman titration [14]. The enantiomeric purities of the synthesized chiral amines were $>95\%$ enantiomeric excess.

Routine 1D ^1H and ^{13}C -NMR spectra were recorded using a Varian Unity 400 MHz instrument. 1D ^6Li and 2D ^6Li , ^1H -HOESY and ^6Li , ^6Li -EXSY spectra were recorded using a Varian Unity 500 MHz instrument.

Chromatographic analyses were carried out using 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 done at 135°C (injector 225°C , detector 250°C) using He (2 ml min^{-1}) as carrier gas. Alkylation reaction analyses were performed at 125°C and the epoxide opening reaction analyses at 90°C . Mass spectra (MS) were recorded on a Varian Saturn 2000 GC-MS/MS operating in electronic ionization (EI) or chemical ionization (CI) mode.

Methane was used as reagent gas for CI operation. The GC column connected to the mass analyzer was a DB-5MS (J&W Scientific).

4.2. Synthesis

4.2.1. (*R*)-(2-*N,N*-Dimethylamine-ethyl)-(1-phenyl-2-pyrrolidin-1-yl-ethyl)amine (**1**)

Pyrrolidine (7.26 g, 0.1 mol) was added to a 500 ml round-bottled flask with ethanol (150 ml). (*R*)-styrene oxide (5.7 g, 47.51 mmol) was added to the solution and the solution was heated to reflux for 3 h. The solvent was evaporated and the crude product was dried for 1 h under high vacuum. The crude product was solvated in dry DEE (100 ml) and triethyl amine (14.42 mg, 0.143 mol) was added. The solution was cooled in an ice-bath and methanesulfonyl chloride (6.56 g, 57.2 mmol) was added dropwise via a syringe. The solution was stirred for 30 min and then triethylamine (9.62 g, 95 mmol) was added. The solution reached room temperature and 25 equivalents of *N,N*-dimethylethylenediamine (105 g, 1.18 mol) and water (25 ml) were added. The solution was stirred for 3 days. More water (50 ml) was added until the two-layer solution became clear. The solution was swirled for 5 h. The organic phase was removed and the water-phase was extracted three times with DEE (3 × 50 ml). The combined ether phases were washed with NaHCO₃ (5%, 50 ml) and water (50 ml) and dried over Na₂SO₄. The solvent was evaporated. The product, a clear light yellow oil, was purified by distillation under high vacuum at 103°C at 3.3×10^{-2} mBar at a yield of 62% (7.7 g, 29.5 mmol).

(500 MHz; DEE-*d*₁₀); ¹H-NMR (293 K) δ 7.36 ppm (2H, d, Ph), 7.22 ppm (2H, t, Ph), 7.13 ppm (1H, t, Ph), 3.69 ppm (1H, dd, CH), 2.70 ppm (1H, t, CHCH₂N), 2.62 ppm (4H, m, pyrrolidine), 2.48 ppm (4H, m, pyrrolidin), 2.42 ppm (2H, dd, NHCH₂CHN(CH₃)₂), 2.23 ppm (2H, dd, NHCH₂CH₂N(CH₃)₂), 2.16 ppm (1H, t, CHCH₂N), 2.14 ppm (6H, s, N(CH₃)₂), 1.74 ppm (4H, dd, pyrrolidine).

4.2.2. (*R*)-(2-Methoxy-ethyl)-(1-phenyl-2-pyrrolidin-1-yl-ethyl)amine (**2**)

To a stirred solution of pyrrolidine (5.6 ml, 68.1 mmol) in ethanol (100 ml), was added (*R*)-styrene oxide (4.9 ml, 41.6 mmol) and the mixture was refluxed for 2 h. After cooling, the solvent was evaporated under reduced pressure. The crude product was given as slightly yellow oil, which was dried under vacuum, and the product crystallized. The crystals were dissolved in dry ether (100 ml) and triethyl amine (17.4 ml, 124.8 mmol) was added and the mixture was cooled to 0°C. Methanesulfonyl chloride (3.9 ml 49.9 mmol) was added dropwise and a white precipitate was formed. After 1 h triethylamine (11.6 ml, 83.2 mmol) was added and the mixture was allowed to warm to room temperature. 2-Methoxyethylamine was

added together with ethanol (50 ml) and water (5 ml). The resulting mixture was vigorously stirred. After 48 h, water (100 ml) was added, and the layers were separated. The yellow aqueous layer was evaporated under reduced pressure and was then extracted with ether (4 × 50 ml). The combined organic phases were washed with 5% aqueous sodium hydrogen carbonate (200 ml) and water (200 ml), dried over sodium sulfate, filtrated. The solvent was evaporated under reduced pressure to give the crude product as a yellow oil which was purified by distillation to give the pure product (4.01 g, 39%) as a colorless oil, b.p. 120–125°C at 0.1 mmHg.

(400 MHz; CDC13); ¹H-NMR (293 K) δ 7.30–7.16 ppm (5H, m, Ph), 3.65 ppm (1H, dd, PhCHNH₂), 3.41–3.35 ppm (2H, m, CH₂OCH₃), 3.26 ppm (3H, m, OCH₃), 2.77 ppm (1H, t, CH₂N), 2.62–2.51 ppm (4H, m, NHCH₂O, CH₂N), 2.60–2.54 ppm (2H, in, CH₂N), 2.20 ppm (1H, dd, CH₂N), 1.77–1.69 ppm (4H, m, CH₂CH₂).

4.2.3. Epoxide opening

THF (803 μl) was added to a reaction vessel followed by addition of the amine (32.9 μl, 0.126 mmol) under nitrogen atmosphere. A solution of *n*-BuLi in hexane (74 μl, 0.17 mmol) was added and the reaction was maintained at 20°C for 15 min. A solution of cyclohexene oxide in THF (90 μl, 0.18 mmol) was added and the reaction started. The reaction was monitored by extracting a small portion of the reaction mixture. The samples were quenched as follows. To a vial a sample of the reaction mixture (100 μl) was added and the vial was filled with dry DEE (0.5 ml). NH₄Cl (0.5 ml) was added to the vial and the lower phase was extracted. Brine (0.5 ml) was added and the lower phase was extracted. The organic phase was dried over NaSO₄, and the organic phase was transferred to a new vial equipped with septa. The products were analyzed using chiral stationary phase GC.

4.2.4. Alkylation of benzaldehyde

A reaction flask containing a magnet, a dry 1:1 DMM:DEE solution (1.6 ml) and amine (0.20 mmol) was prepared inside the glovebox. The flask was taken out and fitted with a dry nitrogen inlet. The flask was cooled to 0°C and *n*-BuLi (0.28 mmol) was added via a syringe to the stirred solution. After 15 min the flask was moved to an ether/N₂ (l) bath (−116°C). Benzaldehyde (0.05 mmol, as a 25% solution in DMM:DEE 1:1) was added via a syringe and after 15 min the reaction was quenched with methanol (0.5 ml). The crude mixture was analyzed using chiral stationary phase GC.

Acknowledgements

The authors are most grateful to Dr Gunnar Stenhagen, Chalmers University Organic Chemistry, for mass spectral analyses and the Swedish Natural Science Research Council and Carl Trygger for financial support.

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