Probing the Origins of Asymmetric Induction by 3-Aminopyrrolidine Lithium Amides Complexes: A $^{6}Li/^{1}H/^{13}C$ NMR Study

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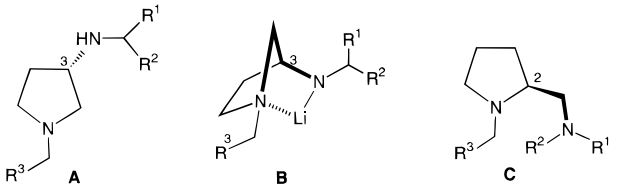
Abstract: The structure of two chiral *N*,*N*′-disubstituted-3-aminopyrrolidine lithium amides **3** and **4** in solution in THF-d_8 has been studied at low temperatures by high-field ^{1}H, ^{13}C, and ^{6}Li NMR spectroscopy. Despite their structural analogy, these two compounds adopt very different conformations in solution: while the amide **3** pyrrolidinic ring undergoes only minor changes with respect to its amino precursor **1**, amide **4** presents a norbornyl-like bridged structure around $^{6}Li^{+}$. When excess Bu^{6}Li is added to both amide solutions, 1:1 amide−Bu^{6}Li complexes arise, and their structures appear, this time, very similar and organized around a parallepipedic N−Li_2−C core, the two lithium cations bridging the amide and the alkyl chain. The **4**−Bu^{6}Li complex appears very tight, with two distinct signals corresponding to each of the diastereotopic α-protons of butyllithium, by contrast with the looser **3**−Bu^{6}Li complex. From all these data, we propose a model to interpret the results obtained using these chiral amides in the asymmetric condensation of butyllithium with aromatic aldehydes.

Introduction

Despite many spectacular results, the efficient enantioselective creation of carbon−carbon bond remains in the forefront of asymmetric synthesis. One of the key reactions in the field, *viz.*, the asymmetric condensation of an organometallic compound onto a carbonyl, has been the focus of many efforts in the 20 past years. The mild organozinc reagents[1] have turned out to be especially suited to this goal, leading to remarkable levels of enantioselectivity when used in the presence of various chiral polydentate ligands. By contrast, a much more limited number of organolithium compounds have been considered, and the enantioselectivities they afford have remained rather disapointing.[2] The latter indeed "suffer" from their generally high reactivity that prevents many subtle enantioface recognition processes from taking place. The best results have been obtained with a few aldehydes and under strictly defined conditions.[3]

Scheme 1



Since their first utilization in asymmetric synthesis,[4] chiral lithium amides have found many applications as chiral inductors for C−C connections (in aldolizations, alkylations, rearrangements, ...)[5] but have only once been used in the asymmetric condensation of an organolithium compound onto an aldehyde.[3c] It thus appeared attractive to explore this latter type of reaction, employing a set of new chiral lithium amides based on the 3-aminopyrrolidine skeleton (Scheme 1A). The relatively rigid tether linking the nitrogen atoms in such a structure could, if a coordination of the lithium cation by the pyrrolidinic nitrogen takes place, fold the pyrrolidinic ring, providing a norbornyl-like bridged conformation (Scheme 1B) with a highly asymmetric topology. Amides with judiciously chosen structures, when used in conjunction with butyllithium, could yield some kind of complex encapsulating, and thus "chiralizing", the alkyllithium. The existence of such a complex would therefore provide a "diastereoisomeric" intermediate to guide an overall enantiomeric phenomenon. Even if the chiral amide could, *a priori*, interact with the aldehyde, the alkyllithium, or both, none of the very few studies dealing with the lithium amide−alkyllithium system[3c,6a] has identified the origin of the asymmetric induction.

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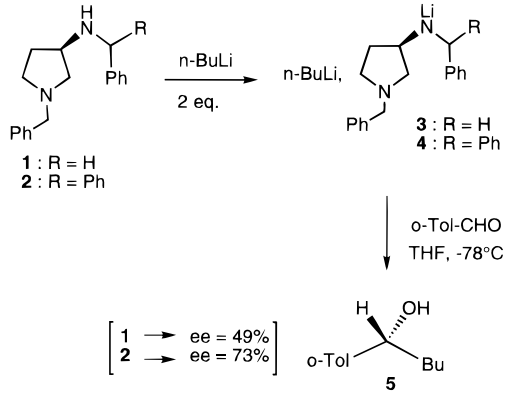
The 3-aminopyrrolidines have been the object of few reports in the literature in which they are mainly used as building blocks in medicinal chemistry.[7] By contrast, the chiral 2-methylaminopyrrolidines[8] (Scheme 1C) and their lithium amides,[5a,8a,9] prepared from L-proline, have been the object of extensive applications as chiral auxiliaries. We have first developed several synthetic routes giving access to a large set of chiral 3-aminopyrrolidines[10,11] (such as **1** and **2**) and have then tested the complex between their lithium amides and butyllithium in the alkylation of aromatic aldehydes.[10b,11] Our results clearly establish that a cumbersome group on the 3-amino moiety is essential to high induction levels, in contrast to those substituting the ring nitrogen. For instance, when *n*-BuLi complexed with 3-benzylaminopyrrolidine lithium amide **3** is condensed with *o*-tolualdehyde at −78 °C, it provides the expected alcohol **5** in 49% ee, while the BuLi−(3-diphenylmethylaminopyrrolidine lithium amide **4**) complex gives, in identical conditions, the same product in 73% ee[10b] (eq 1).



A key to the understanding of this striking structure−selectivity relationship requires examination of the structure in solution of the complexes between lithium amides **3**/**4** and BuLi. Recent spectacular achievements using ^{6}Li NMR methods[6,12,13] illustrated by the structural study of lithium amides published lately[6,12b,13] prompted us to tackle this problem using the techniques of high-field multinuclear NMR.

Results and Discussion

All experiments described here have been carried out directly in an NMR tube, following experimental conditions transposed from the millimolar scale and providing ee reported in eq 1.[10b,11,14] The Bu^{6}Li has been synthesized in pentane from commercial metallic ^{6}Li and *n*-butyl bromide following the procedure described by Fraenkel *et al.*[15] for propyllithium. After concentration and solvent exchange, a 5 N solution in C_6D_{12} was prepared and stored under dried argon at −20 °C up to several weeks. Chemically and enantiomerically pure amines **1** or **2**[10b,11] in solution in THF-d_8 were loaded into the NMR tube and cooled down to −78 °C. The adjusted volume of the above described *n*-Bu^{6}Li solution was then added dropwise under an ultradry argon atmosphere at this temperature with almost continuous shaking. The tube was then quickly dropped into the precooled NMR probe. It turns out that the resulting lithium amides **3** and **4**, respectively, are reasonably stable under these conditions and can undergo all desired NMR investigations.

We thought the examination of amide structures alone would constitute a reasonable first insight into the problem. Thus, a set of mono- and two-dimensional NMR experiments has been performed after addition of increasing quantities of Bu^{6}Li (up to 1 equiv) to amines **1** and **2**. Comparison of ^{1}H and ^{6}Li NMR spectra of amides **3** and **4** indicates that these closely related compounds adopt drastically different structures in solution. Indeed, amide **3** presents rather intricate spectra consistent with the presence in solution of several species, among which one is dominant. The ^{1}H spectrum of this latter sample exhibits, for all protons, chemical shifts almost identical to those of amine **1**, indicating extremely limited structural changes (Figure 1A). The ^{6}Li spectrum displays one minor singlet at 1.68 ppm[16] together with a broad signal at 1.89 ppm. These δ values are in the range expected for dimeric lithium amides such as isopropylcyclohexylamide in THF at −90 °C (1.89 ppm),[17a] diisopropylamide in THF at −78 °C (1.94 ppm),[17b] or for tetramethylpiperidinamide at −100 °C in a 3:1 THF/pentane mixture (1.48 ppm).[17c] The absence of meaningful cross peaks in a ^{6}Li−^{1}H two-dimensional heteronuclear Overhauser effect experiment (HOESY), a particularly fruitful technique in the field,[12c] imposed severe limitations to further study of **3.** We thus preferred to move forward directly to the lithium amide−butyllithium complex possibly at the origin of the enantioselectivity in the reaction studied and have been nicely rewarded (*vide infra*).

By contrast, amide **4** provides extremely simple spectra probably representative of a single structure in solution. The

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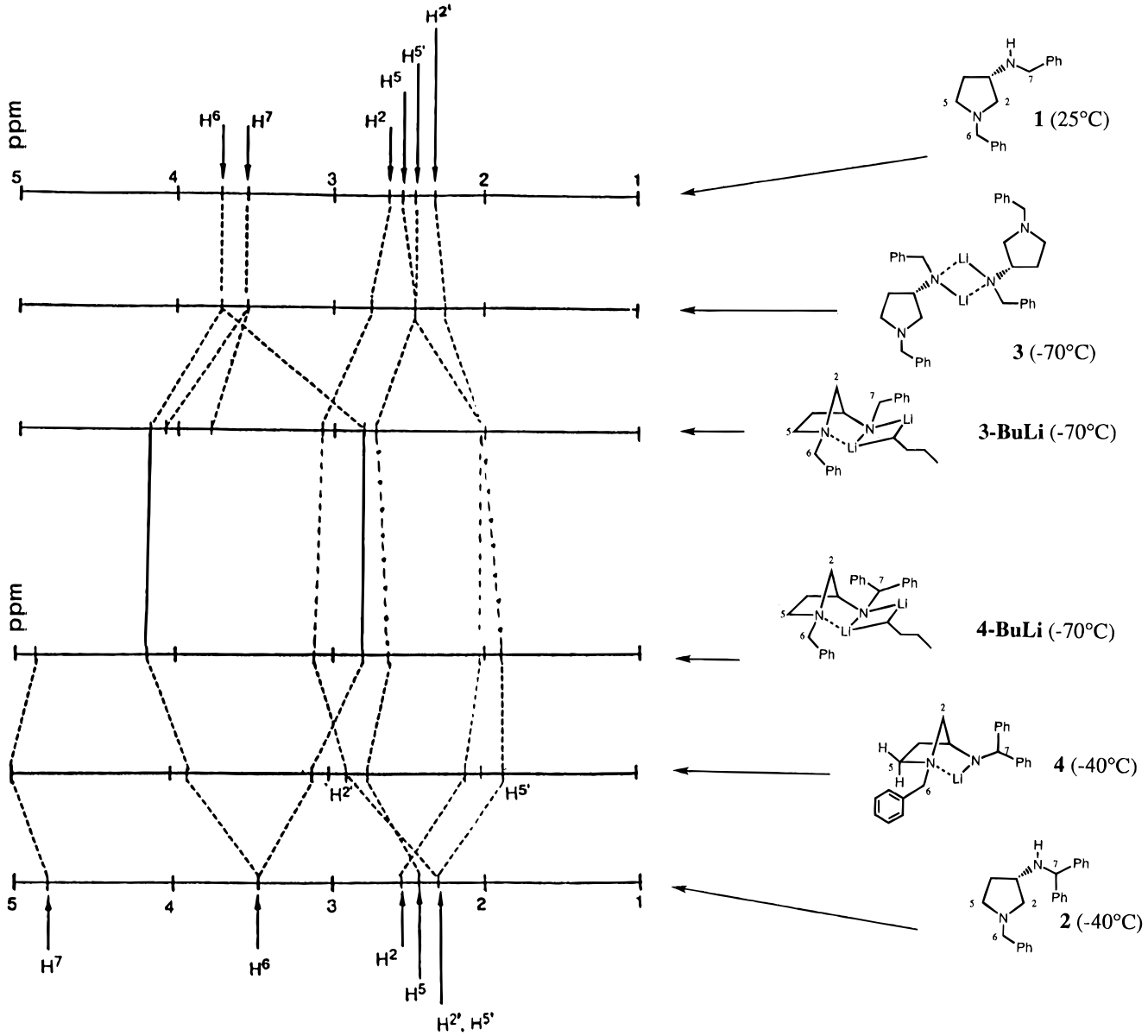
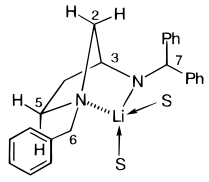


Figure 1. Comparison of selected protons chemical shifts in THF-d_8 for (A) amine **1**, lithium amide **3,** and Bu^{6}Li−**3** complex (0.3 M; −70 °C) and (B) amine **2**, lithium amide **4**, and **4**−Bu^{6}Li complex (0.3 M; −40 °C).

^{1}H NMR data summarized on Figure 1B show that proton pairs 2, 5, and 6 undergo major shifts in opposite directions, indicative of dramatic structural alterations with respect to its amino precursor **2**.[18] In contrast, the ^{13}C spectrum of **4** is similar to that of **2**, except for C^3/C^7 (which undergo 8 ppm downfield shifts due to nitrogen deprotonation) and C^2. In addition, the ^{6}Li spectrum at −70 °C exhibits a sharp singlet at 1.48 ppm, a value which reasonably compares to that for **3**. A HOESY spectrum has also been performed after addition of 0.6 equiv of Bu^{6}Li (Figure 1S of the Supporting Information). The strongest correlation appears between the H^6 of amide **4** and ^{6}Li. Two other cross peaks are also observed between the ^{6}Li singlet and (i) H^2 and H^5 of amine **2**, probably linked to some amide−amine coordination and (ii) a set of unattributed aromatic protons. An intramolecular coordination of the lithium cation by the ring nitrogen leading to a norbornyl-like structure (Figure 2) could account for all these observations.

This conformation explains both the significant nonequivalence[19] of H^2 and H$^{2'}$ and the notable ^{13}C chemical shift on C^2 (7 ppm downfield compared to free amine). The Li$^+$ chelation by the ring nitrogen also stiffens the benzylic moiety rendering H^6 and H$^{6'}$ magnetically unequivalent. This rigidification puts the phenyl ring close to protons H^5 and H$^{5'}$ which now lie in a strongly anisotropic environment. Such a bridged structure relies on the intramolecular coordination of the amide's lithium by the ring's nitrogen. Other intramolecular lithium amide coordinations by heteroatoms have already been proposed in several cases,[6,13a−c,e] albeit leading to apparently less strained



^{1}H NMR 500 MHz (d$_8$-THF, 203 K) δ (ppm)
H^2: 2.91, 2.15; H^5 2.77, 1.91; H^6: 3.93, 3.12

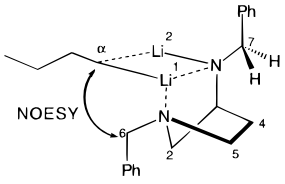
^{13}C NMR 125 MHz (d$_8$-THF, 203 K) δ (ppm)
C^2: 68.3; C^3: 61.5; C^7: 74.4

^{6}Li NMR 74 MHz (d$_8$-THF, 203 K) δ (ppm)
1.48

Figure 2. Proposed conformation for lithium amide **4** in THF-d_8 solution.

(18) Aromatic protons also undergo major shifts that are not discussed here since the complexity of this 15 proton-multiplet impedes attributions.

(19) Li$^+$ induced splitting of bridge protons in a norbornane derivative has already been observed: Paquette, L. A.; Bauer, W.; Sivik, M. R.; Bühl, M.; Feigel, M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1990**, *112*, 8776−8789.

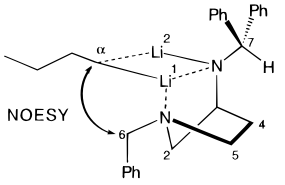


^{1}H NMR 500 MHz (d_8-THF, 203 K) δ (ppm)
H^2: 3.07, 2.02; H^5: 2.71, 2.02; H^6: 4.22, 2.84; Hα: -0.89

^{13}C NMR 125 MHz (d_8-THF, 203 K) δ (ppm)
C^2: 65.8; C^3: 60.0; Cα: 13.4

^{6}Li NMR 74 MHz (d_8-THF, 203 K) δ (ppm)
Li^1: 2.23; Li^2: 2.06

Figure 3. Proposed conformation for **3**−Bu^{6}Li complex in THF-d_8 solution.



^{1}H NMR 500 MHz (d_8-THF, 203 K) δ (ppm)
H^2: 3.22, 1.99; H^5: 2.68, 1.99; H^6: 4.23, 2.79
Hα: -0.72, -0.81

^{13}C NMR 125 MHz (d_8-THF, 203 K) δ (ppm)
C^2: 65.8; C^3: 60.5; C^7: 71.6; Cα: 13.4

^{6}Li NMR 74 MHz (d_8-THF, 203 K) δ (ppm)
Li^1: 2.57; Li^2: 2.19

Figure 4. Proposed conformation for **4**−Bu^{6}Li complex in THF-d_8 solution.

situations. The difference of behavior between **3** and **4** may be due to the bulky diphenylmethyl group in **4** which would disfavor a dimerization such as that apparently occurring in **3**. The intermolecular Li−N coordination in **3** would thus be replaced by an intramolecular[20] norbornyl-like one in **4**. However, one has to keep in mind that both a monomeric situation and a symmetric dimer would match our NMR spectra. Nevertheless, we think bulky **4** is likely to be monomeric[13a−c,e] such as established in comparable cases wherein ^{15}N labeling experiments have been carried out.[13,20]

Our goal being a better understanding of the enantioselectivity brought about by butyllithium complexed with these lithium amides, we moved to those species. When adding an excess of *n*-Bu^{6}Li to amides **3** and **4** solution at −70 °C, a new complex arises in each case. Let us first consider the case of amide **3** at this temperature. Spectacular simplifications of both ^{1}H and ^{6}Li spectra take place, probably characteristic of the formation of a single species which would now adopt a norbonyl-like structure such as proposed above. Compared to **3**, the most spectacular splitting concerns benzylic protons H^6 and, to a lesser extent, H^2, H^5, and H^7. The ^{1}H spectrum of the amide moiety in the **3**−Bu^{6}Li complex (Figure 1A), analyzed via a ^{1}H−^{1}H COSY experiment that allows almost total assignment,[21] is thus very similar to the one of **4** alone. In addition, a new set of multiplets appears which are attributed to the butyl chain. The one at −0.89 ppm is characteristic of the Bu^{6}Li methylene α, and the comparison of its integration with that of any signal belonging to the amide part of the **3**−Bu^{6}Li complex indicates that we are dealing with a 1:1 stoichiometry. A ^{1}H−^{1}H NOESY experiment has then been performed to locate these two partners with respect to each other (Figure 2S). In addition to the expected intramolecular correlations between protons of the pyrrolidine ring as well as between the α- and β-CH$_2$ of the butyl chain, an interesting set of cross peaks appears between the α-CH$_2$ (−0.89 ppm) and benzylic H^6 (4.22 ppm) and H$^{6'}$ (2.84 ppm), the former being much stronger than the latter (Figure 3S). Other significant correlations are also observed between the same α-CH$_2$ and H^2 (3.07 ppm), on the one hand, and aromatic protons attributed to the pyrrolidino benzyl group, on the other hand. This array of interactions is consistent with the structure depicted on Figure 3 and is fully supported by the set of spectra described hereafter. The ^{13}C spectrum displays new signals for butyllithium among which the α-methylene carbon appears at 13.4 ppm as a quintet (J = 7.7 Hz), indicating its coupling to two lithiums (I = 1) as expected from Figure 3. Both chemical shifts and the coupling constant are in good accord with values found in literature,[12c,d,22] and J roughly follows the empirical rule $^1J(^{13}C,^6Li) = 17/n$ (Hz), n being the number of ^{6}Li nuclei bonded to the observed ^{13}C.[12c,d]

The ^{6}Li spectrum of **3**−Bu^{6}Li at −70 °C displays two singlets at 2.25 and 2.07 ppm (called respectively Li^1 and Li^2 in the following) while no peak corresponding to the original amide **3** is observed. Warming up the sample to −40 °C causes these two signals reversibly to coalesce at 2.19 ppm. A ^{6}Li−^{1}H HOESY spectrum has been recorded at −70 °C; as expected, strong correlations are observed between both lithiums (and especially Li^1) and Bu^{6}Li α-methylene. In addition, both ^{6}Li−^{6}Li COSY (Figure 4S) and EXSY (Figure 5S) experiments indicate that there is a small scalar coupling, not detected by 1D, between the two chemically nonequivalent lithium positions (which thus belong to a same complex) and exchange between these two lithium sites, respectively. On further addition of Bu^{6}Li to this complex at −70 °C, one major new signal appears for ^{1}H (broad, at −1.10 ppm) and ^{6}Li (at 1.28 ppm). Those δ values are characteristic of the Bu^{6}Li tetramer in THF, *viz*., the oligomeric form expected in this solvent at this same temperature.[12,22a,23a]

We have next considered the Bu^{6}Li−amide **4** complex. Comparison of ^{1}H NMR chemical shifts in the isolated amide with those for this new species indicates that H^6 and H$^{6'}$ are nonequivalent as already observed in the amide but not in the free amine. Similarly, H^2 drifts further downfield, while H$^{2'}$ remains almost unchanged (Figure 1B). Compared to **4**, new signals at −0.86 and 1.56 ppm (at −40 °C) appear that are, as above, attributed to the butyl chain α- and β-methylene groups, respectively. The integration of the signals for Bu^{6}Li α-CH$_2$ with respect to amide's H^7, for instance, indicates that once more a 1:1 complex is formed. When the temperature is lowered to −70 °C, H^2 further shifts from 3.08 to 3.21 ppm. More interesting in relation with the complex derived from amide **3** is the splitting of the −0.86 ppm signal into two multiplets at −0.73 and −0.83 ppm (Figure 6S). We interpret this phenomenon as a rigidification of the complex at −70 °C revealing the diastereotopicity of the two protons of the butyllithium α-methylene due to inherent chirality in the neighborhood and/or slow rotation about the C$_\alpha$−C$_\beta$ bond. A complementary ^{1}H−^{1}H NOESY experiment has also been achieved on **4**−Bu^{6}Li (Figure 7S). Many of the expected intramolecular correlations between the pyrrolidine ring protons are observed together with a set of intermolecular cross peaks (Figure 8S) between (i) Bu^{6}Li α-methylene proton at −0.83 ppm and amide's H$^{6'}$ at 2.78 ppm and H^2 at 3.21 ppm and (ii) both protons of Bu^{6}Li α-methylene and H^6 at 4.22 ppm and one set of aromatic protons. All these data, and their striking similarity with those obtained for the amide **3** complex (Figure 1A,B), prompt us to propose a structure closely related to the previous one, as displayed on Figure 4.

As previously, the ^{13}C spectra of amide **4** and the complex **4**−*n*-Bu^{6}Li are very similar apart from the appearance of four peaks belonging to the butyl chain at 13.4 (α), 15.1 (δ), 35.9

(20) For a discussion about intra- and intermolecular chelation of amino lithiated compounds, see: Reich, H. J.; Gudmunsson, B. Ö. *J. Am. Chem. Soc.* **1996**, *118*, 6074−6075, and ref 3 therein.

(21) Attribution of the signals for benzylic protons H^6 and H^7 requires comparison to spectra of complexed amide **4** and is confirmed by the NOESY experiment.

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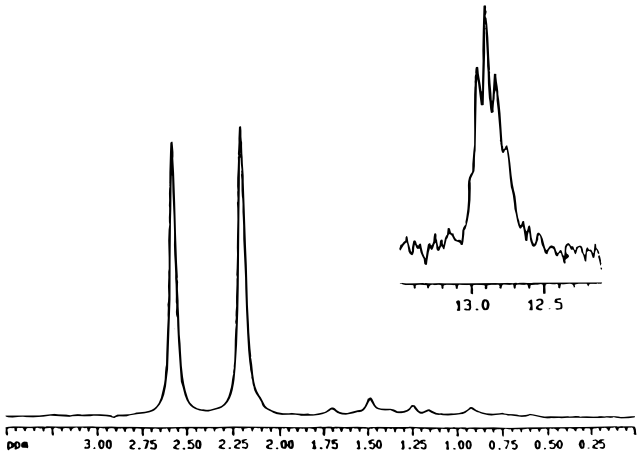

Figure 5. ^{6}Li and ^{13}C NMR spectra of **4**−Bu^{6}Li complex in THF-d_8 solution at −70 °C.

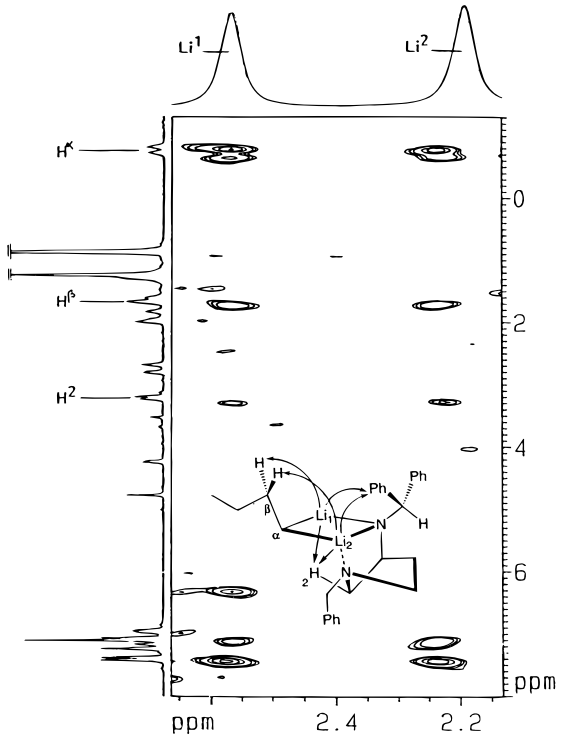

Figure 6. Two-dimensional ^{6}Li−^{1}H HOESY (mixing time: 2 s) contour plot of **4** and Bu^{6}Li (1:1.2) mixture (0.3 M in THF-d_8 at −70 °C) in the **4**−Bu^{6}Li complex in THF-d_8 solution.

(γ or β), and 37.3 (β or γ) ppm. There again, the signal at 13.4 ppm (Figure 5) is a quintet (J = 7.9 Hz), as expected for the reasons discussed above. Two singlets at 2.56 (Li^{1}) and 2.48 (Li^{2}) ppm appear on the ^{6}Li spectra at −40 °C (2.57 and 2.19 ppm at −70 °C, Figure 5), concomitantly with the disappearance of the original amide **4** signal. The ^{6}Li−^{1}H HOESY spectrum (Figure 6) displays strong correlations between the two lithium cations and both Bu^{6}Li α- and β-methylenes. Also, a slightly stronger correlation can be noticed between ^{6}Li^{1} and the proton signal at −0.83, on the one hand, and between Li^{2} and that at −0.73 ppm, on the other hand. Another set of cross peaks is observed between only one pyrrolidine-H^{2} and both lithiums, but the intensities of those correlations are very different: while the signal for Li^{1} is extremely weak, the one for Li^{2} is significantly more intense. Lastly, several cross peaks appear between the aromatic protons and both lithiums. These numerous correlations (Figure 6), not observed in the complex derived from **3**, are probably characteristic of a somewhat more compact situation. Finally, and as already established for **3**, both ^{6}Li−^{6}Li COSY (Figure 9S) and EXSY (Figure 10S) experiments indicate that both lithium cations belong to a same complex and mutually exchange internally. On further addition of Bu^{6}Li to this complex, new signals appear identical to those observed in the case of the complex derived from **3** (see above). These are also attributed to *n*-Bu^{6}Li tetrameric form. Noteworthy is the stable stoichiometry of the complex itself that seems to be preserved, at low temperature, up to 6 equiv extra of Bu^{6}Li.

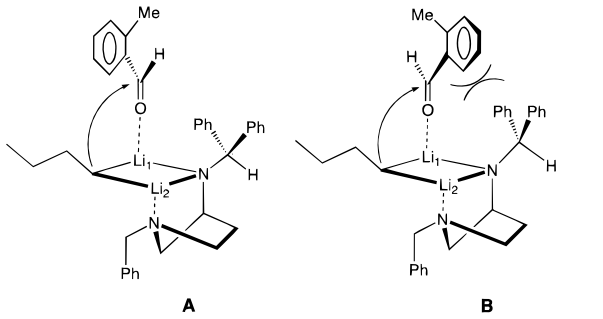

Figure 7. Proposed models for tolualdehyde docking on Bu^{6}Li−**3**/**4** complexes.

Better understanding of the phenomena driving the enantioselectivity would require the addition of the aromatic aldehyde onto the amide−BuLi complex. However, the condensation reaction is extremely rapid, even at −70 °C,[11] and the resulting alkoxide would probably be the main species observed by NMR.[24] The structure for the complex we have characterized thus constitutes, within the framework of an early transition state hypothesis, one of the best starting points for a further analysis of the following steps. It is indeed generally claimed in the litterature[1,25] that upon addition of a carbonyl compound to an organometallic complex there is first a coordination between the metal cation and the carbonyl oxygen. This has been proposed by Schleyer, Houk *et al*. to develop along the pathway of the reaction between formaldehyde and dimeric methyllithium.[25] When disymmetric dimers presenting different coordination spheres for the two metals are involved, Noyori[1] suggests that as the carbonyl coordination becomes chemioselective, the docking takes place at the cation with the highest Lewis acid character. In our case, the difference between lithium acidities is probably small enough to render the steric interactions more important; according to molecular models, Li^{1} is clearly favored over Li^{2}. More than likely, the topology of this coordination determines the enantioselectivity of the transfer of the butyl anion onto the carbonyl. Two modes of approach for tolualdehyde, allowing a concerted transfer of the butyl chain, can be considered and are represented in Figure 7.

It is clear that in Figure 7B, unfavorable steric interactions arise between aromatic moieties upon complexation of the aldehyde onto Li^{1}. The *gem*-diphenyl group indeed adopts a conformation close to the one represented in Figure 4 as demonstrated by a significant NOESY correlation between H^{7} and H^{4}/H^{5} (Figure 7S). The approach depicted on Figure 7A, which would thus be relatively favored, accounts for the induction experimentally observed in the condensation of

(24) Except if resorting to the Rapid-Injection NMR (RINMR) technic employed by McGarrity et al.[23b] We are also aware of the likely alcoholate−butyllithium complexation taking place after introduction of the aldehyde. We have checked however that the amide−Bu^{6}Li complex survives in presence of important amounts of lithium butylate. In addition, BuLi−alcoholate complexes are known to be less nucleophilic species: Tanaka, F.; Node, M.; Tanaka, K.; Nizuchi, M.; Hosoi, S.; Nakayama, M.; Taga, T.; Fuji, K. *J. Am. Chem. Soc.* **1995**, *117*, 12159−12171.

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butyllithium on *o*-tolualdehyde ((*S*)-3-aminopyrrolidine → (*R*)-1-tolyl-1-pentanol). This model also explains the drop in selectivity observed with amide **3**, in which the *gem*-diphenyl group is replaced by a benzyl.

Conclusion

We have examined the structure in THF solution of chiral lithium amides **3** and **4**, alone and complexed with butyllithium. The set of mono- and two-dimensional ^{6}Li, ^{1}H and ^{13}C NMR spectra obtained on these samples indicates that the two closely related compounds behave very differently: while conformation of **3** remains almost identical to that of its parent amine **1**, cumbersome highly substituted **4** adopts a norbornyl-like rigid structure in which a lithium cation is chelated, as expected, by both nitrogen atoms of the molecule, imposing a considerable folding in the pyrrolidine ring. We have not used these amides alone yet, but we are currently trying to take advantage of this rigidity and of the participation of the lithium cation in a five-membered ring[8] to apply **4** to asymmetric deprotonation reactions, for instance.

Our results also indicate that, by contrast, the butyllithium−amide complexes derived from **3** and **4** both adopt a 1:1 stoichiometry. The structure of these species presents a norbornyl-type arrangement organized around a Li_2 core linking the aminopyrrolidine and the butyl moiety. Minor spectral differences suggest that the Bu^{6}Li−**4** complex is somewhat tighter than the Bu^{6}Li−**3** complex. From this observation as well as the derived structures, we propose an interpretation for the different degree of asymmetric induction observed for these complexes in their interaction with aromatic aldehydes. The selective docking of the carbonyl compound on one specific lithium site would be responsible for a steric differentiation between the two faces of the prochiral center. Our model, one of the first one to be built on experimental grounds, accounts for the sense of induction observed experimentally. Furthermore, we think this work provides a unique example of a diastereoselective scheme to interpret an enantioselective process.

We hope such a model will be helpful in further improving the induction potential of 3-aminopyrrolidines in the generation of asymmetric centers in C−C bond formation. Other studies trying to take advantage of this chelation-controlled folding of the lithium amide as well as structural modifications of the 3-amino substituent,[10b,11] more extended mechanistic discussions,[11] and theoretical investigations[26] on the nature of these complexes are in progress and will be reported in due course.

Experimental Section

General Considerations. Argon was dried and deoxygenated by bubbling through an hexane solution of butyllithium. Commercial tetrahydrofuran-d_8 was distilled over a few drops of a C_6D_6 solution of butyllithium. ^{6}Li (95%) has been purchased from Aldrich, and 1,3-dibenzylaminopyrrolidine (**1**) and 1-benzyl-3-diphenylmethylaminopyrrolidine (**2**) have been prepared as described elsewhere.[10,11]

[^{6}Li]−Lithium Amides 3 or 4 and Their Complex with *n*-Butyllithium. Amine (**1** (40 mg) or **2** (51.3 mg); 0.15 mmol) was transferred into a dry 5-mm NMR tube, which was fitted with a septum and flushed under argon. Freshly distilled THF-d_8 (0.5 mL) was introduced by a syringe. To this solution, at −78 °C, was added dropwise 5 M [^{6}Li]-*n*-butyllithium in C_6D_{12} (35 μL, 0.17 mmol) with a syringe. The tube was then quickly dropped in the precooled (−40 °C) NMR probe. All the spectra of the corresponding amide **3** or **4** were recorded at this temperature or at −70 °C. The complexes between amides **3** and **4** and butyllithium have been prepared in a similar way, using an excess of Bu^{6}Li.

1-Benzyl-3-benzylaminopyrrolidine 1: ^{1}H-NMR (25 °C, 200 MHz) δ 7.35−7.10 (m, 10H), 3.68 (s, 2H), 3.55 (s, 2H), 3.31−3.19 (m, 1H), 2.68 (dd, 1H, J_1 = 9.0 Hz, J_2 = 6.6 Hz), 2.56 (td, 1H, $J_1 = J_2$ = 8.6 Hz, J_3 = 6.1 Hz), 2.45 (td, 1H, $J_1 = J_2$ = 8.3 Hz, J_3 = 5.9 Hz), 2.35 (dd, 1H, J_1 = 9.1 Hz, J_2 = 5.0 Hz), 2.11−1.94 (m, 1H), 1.71 (br s, NH), 1.65−1.50 (m, 1H).

1-Benzyl-3-diphenylmethylaminopyrrolidine 2: ^{1}H-NMR (25 °C, 500 MHz) δ 7.34−7.30, 7.22−7.04 (2m, 15H), 4.77 (s, 1H), 3.48 (AB, 2H, J_1 = 13.0 Hz), 3.12−3.07 (m, 1H), 2.52 (td, 1H, $J_1 = J_2$ = 8.7 Hz, J_3 = 5.4 Hz), 2.51 (dd, 1H, J_1 = 9.2 Hz, J_2 = 6.7 Hz), 2.41 (dd, 1H, J_1 = 9.1 Hz, J_2 = 4.8 Hz), 2.31 (td, 1H, $J_1 = J_2$ = 8.4 Hz, J_3 = 6.3 Hz), 1.96 (dddd, 1H, J_1 = 12.8 Hz, $J_2 = J_3$ = 8.3 Hz, J_4 = 5.4 Hz), 1.89 (br s, NH), 1.59 (dddd, 1H, J_1 = 12.8 Hz, J_2 = 8.3 Hz, J_3 = 6.2 Hz, J_4 = 4.6 Hz).

^{1}H-NMR (−40 °C, 500 MHz) δ 7.40−7.37, 7.25−7.12, 7.08 (m, 15H), 4.78 (s, 1H), 3.47 (AB, 2H, J_1 = 13.4 Hz), 3.06 (br s, 1H), 2.55 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.0 Hz), 2.46 (pseudo-q, 1H), 2.37−2.31 (m, 2H), 2.24 (br s, NH), 1.97 (m, 1H), 1.61 (m, 1H).

^{13}C-NMR (−40 °C, 125 MHz) δ 146.0, 145.9, 140.8, 129.4, 129.2, 129.1, 128.2, 127.72, 127.66, 66.2, 61.5, 61.3, 55.5, 54.0, 32.9.

Instrumental Considerations. All NMR experiments were performed on a Bruker Avance DMX 500 spectrometer equiped with a Bruker Station 1 computer. An indirect 5 mm ^{1}H {BB} gradient probehead was used. Spectra were processed on a Bruker Station 1 computer using UXNMR and Aurelia softwares (Bruker Inc.).

Measuring frequencies were 500 MHz (^{1}H), 125 MHz (^{13}C), and 73 MHz (^{6}Li). ^{1}H and ^{13}C chemical shifts were referenced to the solvent THF-d_8 signals at δ 1.73 and δ 25.37, respectively. Lithium spectra were referenced to external 0.3 M ^{6}LiCl in MeOH-d_4 (δ 0.0). Proton and carbon one-dimensional experiments were recorded with standard parameters. Lithium spectra were recorded with and without proton Waltz-16 decoupling.

2D NMR Measurements. All 2D spectra were acquired using nonspinning 5 mm samples with deuterium field-frequency locking. All experiments involving ^{6}Li nuclei as well as the ^{1}H, ^{1}H-COSY experiments were processed in the absolute value mode. In no case were symmetrization procedures carried out.

Two-dimensional ^{1}H, ^{1}H-NOESY spectra were obtained with quadrature detection in both dimensions using the hyper complex method in the f_1 dimension.[27] The relaxation delay was fixed generally to 1 s.

For the ^{6}Li, ^{6}Li-COSY spectra,[28] the following parameters were used: 256 experiments with 1024 data points and four scans each were recorded; no proton decoupling was used; one time zero filling in f_1; pure sine bell window function was applied before fourier transformation.

For the ^{6}Li, ^{1}H-HOESY spectra,[29] the following parameters were used: 128 experiments with 1024 data points and four scans each were recorded; mixing time 2.0 s; one time zero filling in f_1; $\pi/2$ and $\pi/4$ shifted sine square window functions were applied to f_2 and f_1 dimension, respectively, before fourier transformation.

For the ^{6}Li, ^{6}Li-EXSY spectra,[30] the following parameters were used: 256 experiments with 1024 data points and four scans each were recorded; no proton decoupling was used; mixing time 4.0 s; one time zero filling in f_1; $\pi/2$ shifted sine bell window function was applied before fourier transformation.

For the ^{1}H, ^{1}H-COSY spectra, the following parameters were used: 256 experiments with 1024 data points and 16 scans each were recorded; one time zero filling in f_1; pure sine bell window function was applied before fourier transformation.

For the ^{1}H, ^{1}H-NOESY spectra, the following parameters were used: 256 experiments with 1024 data points and 16 scans each were

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recorded; mixing time 600 ms; relaxation delay 2 s; one time zero filling in f_1; $\pi/2$ and $\pi/4$ shifted sine square window functions were applied to f_2 and f_1 dimension, respectively, before fourier transformation.

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Supporting Information Available: Most important mono- and two-dimensional spectra of amines **1** and **2** and their ^{6}Li amides **3** and **4** as well as their complexes with *n*-Bu^{6}Li (20 pages). See any current masthead page for ordering and Internet access instructions.

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