Origin of the Detrimental Effect of Lithium Halides on an Enantioselective Nucleophilic Alkylation of Aldehydes

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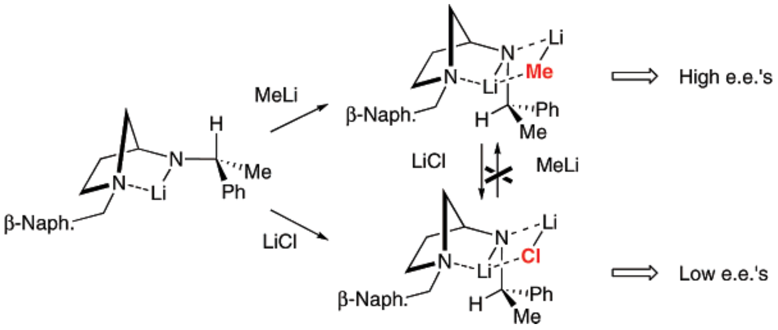

The effect of lithium halides on the enantioselectivity of the addition of methyllithium on *o*-tolualdehyde, in the presence of chiral lithium amides derived from chiral 3-aminopyrrolidines (3APLi), has been investigated. The enantiomeric excess of the resulting 1-*o*-tolylethanol was found to drop upon addition of significant amounts of LiCl, introduced before the aldehyde. The competitive affinity between the lithium amide, the methyllithium, and the lithium halides in THF was examined by multinuclear NMR spectroscopy and DFT calculations. The results showed that the original mixed aggregate of the chiral lithium amide and methyllithium is rapidly, totally, and irreversibly replaced by a similar 1:1 complex involving one lithium chloride or bromide and one lithium amide. While the MeLi/LiX substitution occurs with some degree of epimerization at the nitrogen for the *endo*-MeLi:3APLi complex, it is mostly stereospecific for the *exo*-type arrangements of the aggregate. The thermodynamic preference for mixed aggregates between 3APLi and LiX was confirmed by static DFT calculations: the data show that the LiCl and LiBr aggregates are more stable than their MeLi counterparts by more than 10 kcal·mol^{-1} provided THF is explicitly taken into account. These results suggest that a sequestration of the source of chirality by the lithium halides is at the origin of the detrimental effect of these additives on the ee of the model reaction.

Introduction

Previous results obtained by our group showed that 3-aminopyrrolidine lithium amides (3APLis) are efficient chiral auxiliaries in the enantioselective condensation of halide-free alkyl-,[1,2] aryl-,[3] and vinyllithium[4] derivatives on aromatic aldehydes (Scheme 1). Most of our efforts focused on the influence of parameters such as the structure of the chiral amine,[1] the nature of the nucleophilic organolithium,[2−4] and the solvent[5]

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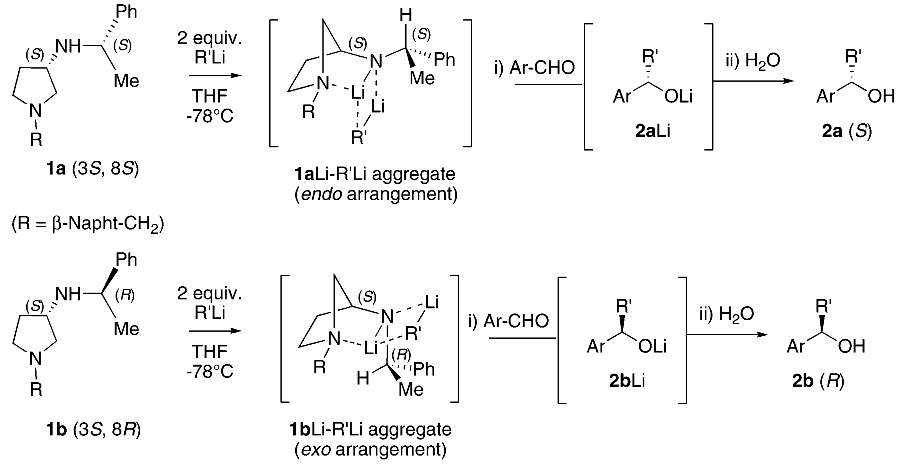
SCHEME 1. Asymmetric Nucleophilic Addition Mediated by 3APLi Chiral Lithium Amide



on the outcome of the reaction. Thus, ee's up to 80% could be obtained in pure THF at reasonably low temperatures (−78 or −20 °C).

Multinuclear (^{1}H, ^{6}Li, ^{13}C, ^{15}N) NMR spectroscopy and theoretical investigations were run in parallel.[2b,6] An azanorbornyl folding of the amide was evidenced in ethers (THF, Et_2O), and the formation of two 1:1 mixed aggregates 3APLi: R′Li, namely the *endo* and *exo* arrangements, was pointed out (Scheme 1). The *endo* arrangements, in which the R′Li lies along the concave face of the norbornyl skeleton, were shown to be obtained with the (3*S*,8*S*) diastereomers of the 3AP (**1a**, Scheme 1). The *exo* complexes correspond to those in which R′Li is oriented toward the convex part of the structure and were observed with the (3*S*,8*R*) diastereomers (**1b**, Scheme 1). These two topologies seem to be closely related to the sense of the induction since the (3*S*,8*S*) amide led to the (*S*) alcohol (**2a**) while its (3*S*,8*R*) counterpart yielded the (*R*) enantiomer (**2b**).

Minor signals on the NMR spectrum were left unassigned after the original investigations on the above structure of the complexes in solution. The synthetic route we followed to prepare the halide-free labeled ^{6}Li alkyllithiums[2b,7,8] led us to think that these unsorted peaks could be due to a contamination by residual amounts of lithium salts, still possible in spite of considerable efforts undertaken to eliminate inorganic salts. We then decided to study in detail the effects of such entities on the induction of a model hydroxyalkylation reaction. The interactions between lithium chloride or bromide and lithium amides,[9,10] alkyllithiums,[11] or lithium enolates[12] have been fathomed on several occasions on chemical, spectroscopic, and theoretical grounds. However, the salt effects have been relatively seldom examined in asymmetric synthesis. A positive role of added salts on the ee's have been noted in the enantioselective protonation[13] and deprotonation[9,14] reactions. The influence of salts on the behavior of lithiated mixed aggregates has also been clearly pointed out as being either beneficial in the case of the 1,4-nucleophilic addition of enolates

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aggregated to lithium amides on nitro olefins studied by Seebach et al.[12b] or unfavorable in the case of the 1,2-condensation of *n*-butyllithium mixed with a chiral lithium aminoalkoxide examined by Jackman and co-workers.[15] Overall, it appears difficult to draw generalities on the structure of the resulting aggregates, even restricting the study to the "popular" lithium amides. It seems that lithium bromide tends to favor mixed dimers (as observed for Ph_2NLi[10a,b] and LiTMP[10c,d]), while lithium chloride rather leads to mixed trimers involving two amide units (with LiTMP[10c,d]).

We present here observations regarding the effects of lithium chloride and bromide on the enantioselective hydroxyalkylation depicted in Scheme 1. Actually, the global system involves four highly polar entities that are the lithium amide, the methyllithium, the lithium halides and the lithium alkoxide formed during the reaction. Considering this latter is progressively accumulating in the medium, the problem is finally to probe the competitive interactions between four partners with time-depending concentrations. This thorny task required us to focus, at least the first time, the investigation on the sole partners present at $t = 0$, i.e., excluding lithium 1-*o*-tolylethoxide, the alkoxide formed during the reaction, from the model system. To analyze the initial course of the reaction, it was indeed essential to have a clear picture of the static composition of the reaction medium before the introduction of the aldehyde, viz. the last reagent introduced according to the procedure presented below. Evaluating the relative affinities between lithium amide, methyllithium, and lithium chloride or bromide was yet relatively complex. A 3-fold study was thus conducted which included a parallel (i) chemical evaluation of the impact of these additives on the enantioselectivity of the known hydroxyalkylation of *o*-tolualdehyde, (ii) description by NMR spectroscopy of the competition between the various aggregates in THF, and (iii) DFT study of the relative (thermodynamic) stabilities of the complexes. A comparable approach has been successfully applied by Gschwind and colleagues to the understanding of the structure into solution of dimethylcuprate mixed with LiI and LiCN.[16]

Results and Discussion

Impact of LiX on the Enantioselectivity of the Model Reaction. The study was conducted for the model reaction depicted in Scheme 1, methyllithium being the nucleophile, 3-aminopyrrolidine lithium amides **1a**Li or **1b**Li the chiral inductors, and *o*-tolualdehyde the electrophile.[1b,2] The selected protocol consisted in preforming the 1:1 lithium amide:MeLi aggregate in THF at −20 °C by mixing **1a**Li or **1b**Li and methyllithium. This solution was then cooled to −78 °C and subjected to the addition of LiX in THF. The aldehyde was then introduced after another 30 min of stirring at −78 °C. The results are summarized in Table 1.

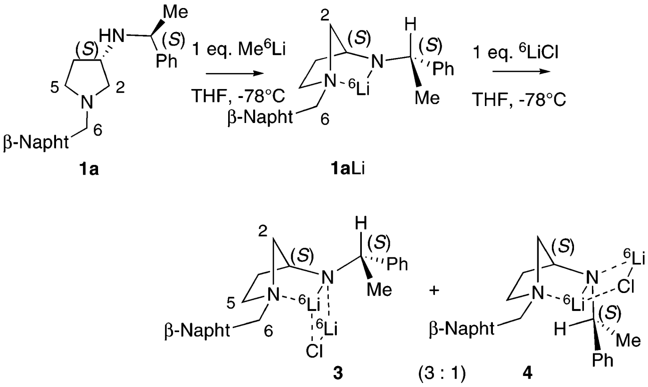
The course of the reaction seems hardly altered upon addition of LiCl on the preformed mixed aggregates **1**Li:MeLi as judged from the little variations undergiven by the conversions. In contrast, the ee's progressively decrease to finally plummet when an excess of LiCl is introduced (entry 3). Interestingly, these ee's are relatively insensitive to the temperature of the introduction of LiCl (entries 1−3). This set of results prompted us to undertake an in depth spectroscopic and theoretical investigation on the state of the solution before the introduction of the aldehyde.

TABLE 1. Influence of LiCl Addition on the Model Reaction of Scheme 1 Using Amide 1aLi or 1bLi

entries	amide **1**Li	MeLi[a] (equiv)	LiCl[b] (equiv)	conv (%)	ee[c] (%)	induction
1	**1a**Li	1.7 (MeLi)	0.0 (LiCl)	96	56 (57)	*S*
2	**1a**Li	1.7 (MeLi)	1.0 (LiCl)	80	37 (25)	*S*
3	**1a**Li	1.7 (MeLi)	2.7 (LiCl)	90	4 (5)	*S*
4	**1b**Li	1.0 (MeLi)	0.0 (LiCl)	94	79	*R*
5	**1b**Li	1.0 (MeLi)	1.0 (LiCl)	70	48	*R*

[a] Equiv/1 equiv of amide. [b] Equiv/1 equiv of complex. [c] Values in parentheses measured when LiCl was added at −20 °C instead of −78 °C.

SCHEME 2



Multinuclear NMR Spectroscopy Characterization of New Aggregates between 3APLi and LiX. The occurrence of noncovalent interactions between lithium halides and lithium amides in solution, leading to robust aggregates of well-defined stoichiometry, has been previously established in many cases, and the fine structure of these species has been studied in detail.[10] With these models in mind, we first examined the putative mixed aggregates arising between amide **1a**Li (3*S*,8*S*) and LiX (X = Cl, Br).

1aLi:LiCl Mixed Aggregate. This aggregate was prepared directly in the NMR tube by first adding, at −78 °C, 1.1 equiv of Me^6Li in THF-d_8 (0.6 M) to a precooled 0.2 M solution of amine in THF-d_8. Then, a 0.9 M solution of ^6LiCl[17] (1.2 equiv) in THF-d_8 was introduced, and the tube was shaken for a few minutes at the same temperature (Scheme 2).

The ^1H spectra (Figure 1S in the Supporting Information) and ^6Li (Figure 1, bottom) recorded from this sample illustrate the evolution of the amide. The monodimensional ^1H spectrum displays, for the main species, a strong splitting of the H^2, H^5, and H^6 proton pairs, characteristic of the folding of the amide **1a**Li.[6a] The ^6Li spectrum exhibits two major singlets of similar intensities (at 1.52 and 2.24 ppm),[18] plus a set of two little singlets (also of comparable intensities, at 1.42 and 1.83 ppm). A broad signal, probably corresponding to an excess of LiCl, was also observed at high field (0.87 ppm). Analogies between this spectrum and those recorded previously[6] for 3APLi:MeLi complexes deserve to be noted. The $\Delta\delta$ measured for each pair of signals (0.72 ppm for the major species and 0.41 ppm for

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(17) ^6LiCl was recovered from the methyllithium synthesis mentioned in ref 7. The 0.9 M solution in THF-d_8 was prepared from a weighted amount of dry ^6LiCl dissolved overnight in this solvent.

(18) All chemical shifts for ^6Li are given with respect to an external reference of 0.3 M ^6LiCl in MeOH-d_4 (δ 0.0).

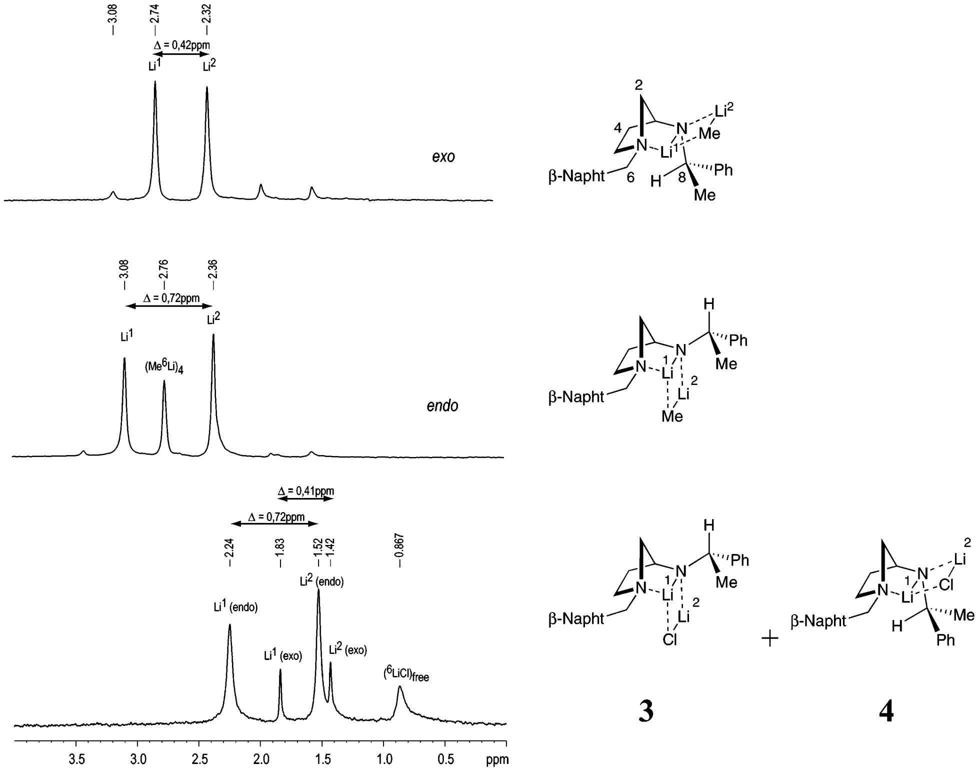

FIGURE 1. ^{6}Li spectra in THF-d_8 at $T = 195$ K of pure *exo* **1a^6**Li:Me^{6}Li (top) and *endo* **1b^6**Li:Me^{6}Li (middle) aggregates plus mixture of putative *endo* and *exo* complexes **1a^6**Li:^{6}LiCl (bottom).

the minor one) are indeed remarkably comparable with those measured from the known *endo*-**1a**Li:MeLi aggregate (0.72 ppm) and *exo*-**1b**Li:MeLi (0.42 ppm), respectively. This, together with the 1:1 peaks, suggest that **1a**Li and LiCl form two 1:1 mixed aggregates, viz. *endo*-**3** and *exo*-**4**, in a ~3:1 ratio (Scheme 2).

The ^{35}Cl atom being a poor nucleus for NMR spectroscopy investigations, the direct determination of the new complex(es) structure was limited to proton, carbon, and lithium spectroscopies. However, the analogies between the spectra obtained for **3** and **4** and those obtained before for comparable aggregates leave little doubt regarding their structures. Thus, the simultaneous correlations between H^2 and H^8 and H$^{6'}$ and H^4 observed in the NOESY experiment (Figure 2S, Supporting Information) are in full agreement with a puckered pyrrolidine core. The structure of the major complex **3** could be evidenced by a ^{6}Li,^{1}H HOESY (Figure 3S, Supporting Information), which exhibits correlations between (i) Li^1 and H^4, H^5 and H$^{6'}$ (other clues of the folding) and (ii) Li^2 and H^3 and H^4 (suggesting LiCl is tightly "bound" along the endo face of the amide). Therefore, it seems that the (*S*,*S*) configuration of amide **1a**Li mainly leads to an *endo* mixed aggregate with LiCl, as in the case of MeLi.

1aLi:LiBr Mixed Aggregate. The above study was repeated with lithium amide **1a**Li, at similar temperature (−78 °C) and concentration in THF-d_8, but adding, this time, a 0.7 M solution of ^{6}LiBr[19] in THF-d_8 (1.6 equiv). The resulting ^{1}H (Figure 4S, Supporting Information) and ^{6}Li (Figure 2) spectra are like those registered with LiCl, suggesting once again the formation of two 1:1 mixed aggregates. The comparable Δδ's (0.70 ppm for the major species and 0.40 ppm for the minor one) led us to regard those as the *endo* and *exo* complexes, formed in this case in a 4:1 ratio. A NOESY experiment (Figure 5S, Supporting Information) supports this hypothesis, at least for the major complex.

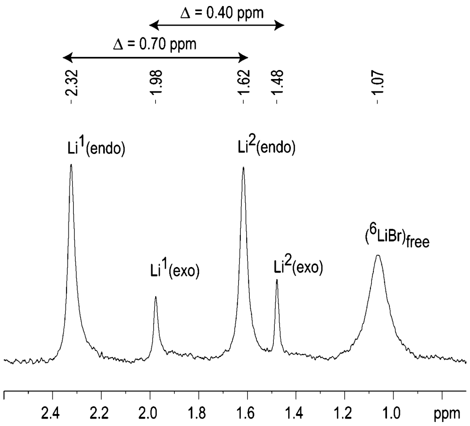

FIGURE 2. ^{6}Li spectrum of **1a^6**Li:^{6}LiBr mixed aggregates in THF-d_8 at $T = 195$ K in the presence of 0.6 equiv of excess of ^{6}LiBr.

Competitive Aggregations of 3APLi, MeLi, and LiCl. Once the LiX mixed aggregates were identified, we turned our attention to the relative affinities between the species possibly competing in solutions contaminated by lithium halides.

Addition of MeLi on 1aLi:LiCl. The stability of the main **1a**Li:LiCl complex toward methyllithium was first evaluated by adding a solution of Me^{6}Li (0.2 M in THF-d_8) to a solution of **1a**Li:LiCl prepared as above (see the top spectrum of Figure 3; the large signal at ~1.0 ppm is due to an excess of LiCl). The ^{1}H and ^{6}Li spectra did not show significant alteration of the signals associated with the two isomers of **1a**Li:LiCl. Only the singlets corresponding to the Me and ^{6}Li signals of free

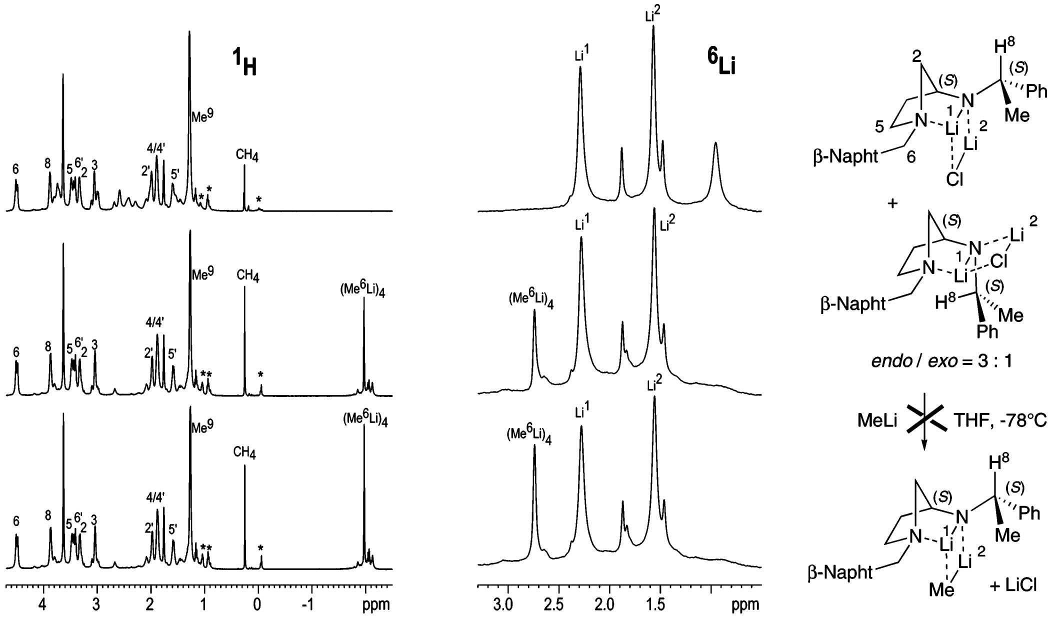

FIGURE 3. Evolution of the ^{1}H and ^{6}Li spectra, in THF-d_8 at T = 195 K, of **1a^6**Li:^{6}LiCl main complex **(**top**)** upon progressive addition of 0.6 equiv **(**middle**)** and 1.3 equiv **(**bottom**)** Me^{6}Li. *Unidentified peaks. The signal at 0.23 ppm has been assigned to methane according to: Lampert, H.; Mikenda, W.; Karpfen, A.; Ka1hlig, H. *J. Phys. Chem. A* **1997**, *101*, 9610−9617.

Me^{6}Li increased progressively upon addition of up to 1.3 equiv, simultaneously with the disappearance of the free LiCl signal (Figure 3). These results indicate that LiCl aggregated to the lithium amide is not substituted by the methyllithium, whatever the topology of the complex. Note that a broad signal progressively superimposes over the baseline. It corresponds to the formation of (MeLi)$_x$(LiCl)$_y$ aggregates that we are currently studying.

Addition of LiCl on 1aLi:MeLi. The effect of the reverse addition of LiCl on the **1a**Li:MeLi complex was probed next. The **1a**Li:MeLi mixed aggregate was prepared directly in THF-d_8 by adding, at −78 °C (195 K), 1.2 equiv (deprotonation) then 1.2 equiv (aggregation) of a 0.2 M solution of Me^{6}Li in THF-d_8 on a solution of **1a**, also in THF-d_8. A control by NMR spectroscopy showed that the resulting sample consisted in the expected **1a**Li:MeLi aggregate,[6] together with some free methyllithium (about ≈14%) and a small amount of the *endo*/*exo* mixture of the **1a**Li:LiCl aggregates. The formation of this latter at this stage can be explained by a contamination of the labeled MeLi, despite all the care paid to eliminate LiCl by centrifugation.[20] A solution of ^{6}LiCl in THF-d_8 (1.0 equiv of a 0.8 M) was slowly introduced at −78 °C. The NMR spectra exhibits a total disappearance of the signals of the original **1a**Li:MeLi mixed aggregate, both on the high field region of the ^{1}H spectra (the rest of the spectrum being hardly altered) and on the ^{6}Li one. Complementarily, the singlets corresponding to the **1a**Li:LiCl aggregates raised up (Figure 4). Thus, the pure *endo*-methyllithium complex fully transforms into the **1a**Li:LiCl complexes. It is, however, difficult to determine if the substitution of the alkyllithium takes place with some degree of epimerization of the chiral nitrogen as both *endo*- and *exo*-**1a**Li:LiCl complexes were already present in the starting sample. The final *endo*/*exo* ratio, as measured by the integration (after deconvolution) of the peaks on the bottom spectrum of Figure 4 (2 equiv LiCl), can only be evaluated as ∼5:1.

Addition of LiCl on 1bLi:MeLi. The next step consisted of examining the stability of the *exo* aggregate, obtained upon mixing amide **1b**Li (3*S*,8*R*) and methyllithium, toward lithium chloride. Here again, the addition of LiCl was responsible for a dramatic attrition of the induction process. Indeed, the salt-free reaction led to 79% ee (in favor of the *R* enantiomer **2b**), while in the presence of LiCl, this value dropped to 48% (1 equiv). An NMR spectroscopy experiment similar to the previous one was performed starting from a 0.13 M solution of the **1b**Li:MeLi complex in THF-d_8, which was prepared following the above protocol. After quickly checking that the known[6] mixed aggregate was obtained, successive aliquots of a 0.66 M solution of ^{6}LiCl in THF-d_8 were added at −78 °C. Two representative ^{1}H and ^{6}Li spectra are given below (Figure 5) to illustrate the progressive fading of the MeLi aggregate in favor of a major new complex.

The top spectra of Figure 5 show the starting point consisting of the **1b**Li:MeLi complex, contaminated by an excess methyllithium and another species characterized by two (1:1) ^{6}Li singlets at high field. These latter signals increase dramatically upon addition of ^{6}LiCl as they remain in the same 1:1 ratio (middle spectra). Simultaneously, the original peaks assigned to Li^1 and Li^2 of the **1b**Li:MeLi aggregate vanish, and the ^{6}Li singlet of the free methyllithium (at 2.74 ppm, superimposed to the Li^1 signal) increases. Finally (bottom spectra), the new complex and tetrameric methyllithium become, by far, the main species in solution. The above data suggest that a 1:1 complex involving LiCl was already present in the starting sample and accumulated in the medium. The structure of this entity was characterized through the usual NOESY (Figure 6S, Supporting

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[19] ^{6}LiBr is a byproduct of the ^{6}Li *n*-butyllithium synthesis; see: Fraenkel, G.; Henrichs, M.; Hewitt, J. M.; Su, B. M.; Geckle, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 3345−3350. The 0.7 M solution in THF-d_8 was prepared by dissolving overnight a weighted amount of dry ^{6}LiBr in this solvent.

[20] The formation of a mixed aggregate between MeLi and LiCl is not easily evidenced by NMR at 195 K since the ^{6}Li NMR spectrum shows a broad singlet, due to the coalescence of the signals characteristics of the species in solution. Therefore, a simple spectroscopic assay of small quantities of LiCl is currently impossible at this temperature.

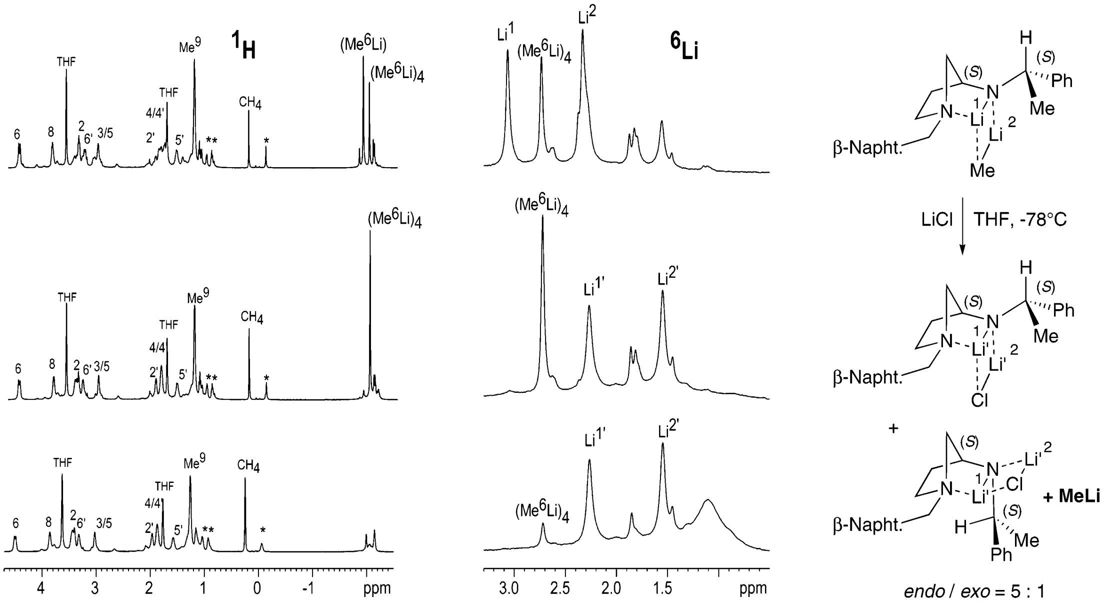

FIGURE 4. ^{1}H and ^{6}Li spectra, recorded at $T = 195$ K, of **1a^6**Li:Me^{6}Li complex in THF upon addition of 1 (middle) and 2 (bottom) equiv of ^{6}LiCl. The top spectrum corresponds to a **1a^6**Li:Me^{6}Li sample containing an excess Me^{6}Li. *Unidentified peaks.

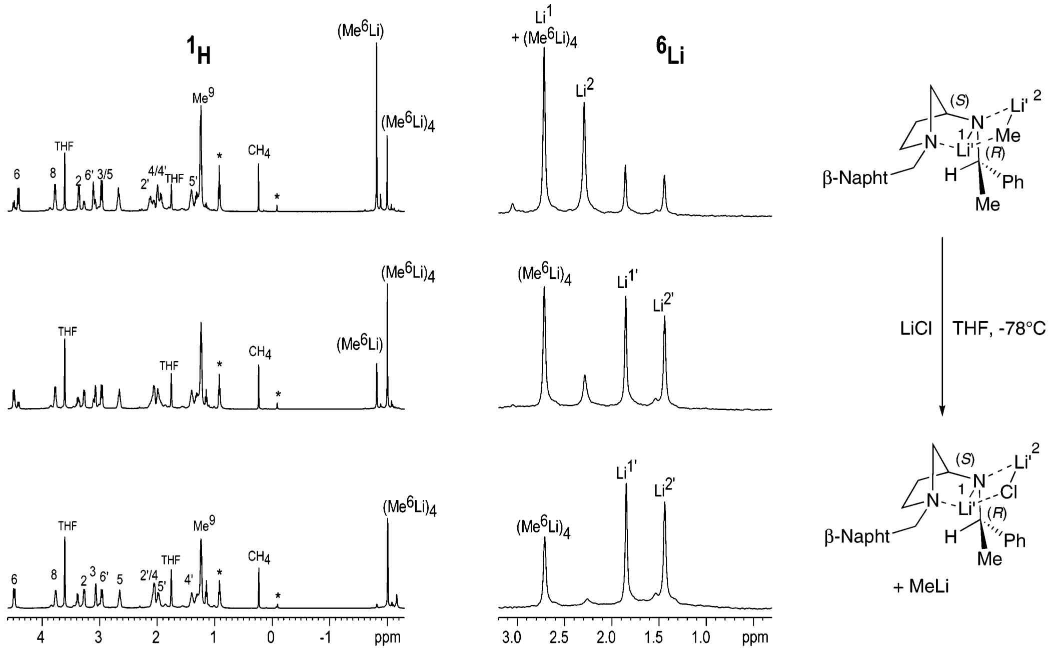

FIGURE 5. Evolution of the ^{1}H and ^{6}Li spectra, recorded at $T = 195$ K, of **1b^6**Li:Me^{6}Li complex in THF upon addition of ~0.5 (middle) and 1 (bottom) equiv of ^{6}LiCl. The top spectra correspond to a **1b^6**Li:Me^{6}Li sample containing an excess of Me^{6}Li. *Unidentified peaks.

Information) and HOESY (Figure 7S, Supporting Information) bidimensional experiments. All of the information made available from these spectra are in favor of an *exo* arrangement of a **1b**Li:LiCl. This time, it thus seems that the MeLi−LiCl substitution is more or less stereospecific.

Comparing the HOESY spectrum recorded for the latter *exo* complex to that obtained at the beginning of our study from the **1a**Li:LiCl mixture of isomers (Figure 6) shows that excellent correlations are found between the minor species formed in the latter case and the main *exo*-**1b^6**Li:^{6}LiCl complex. This further supports the hypothesis of an *endo*/*exo* mixture for **1a**Li:LiCl.

Competitive Aggregations of 3APLi, MeLi, and LiBr. The competitive aggregation phenomena were extended to the case of LiBr, although this salt is not supposed to contaminate methyllithium. However, trace amounts of LiBr are likely to contaminate *n*-Bu^{6}Li, which could play a comparable part in the competitive aggregations.

Only the substitution of MeLi by LiBr was studied in this case. Thus, a 0.20 M solution of amine **1a** in THF was reacted two times with 1.2 equiv of Me^{6}Li (0.67 M in THF) to yield the expected **1a**Li:MeLi complex. Increasing amounts of a 0.70 M solution of LiBr in the same solvent were then added at −78 °C, and the corresponding ^{1}H and ^{6}Li spectra were recorded (Figure 8S, Supporting Information). The same complete displacement of methyllithium by lithium bromide was observed, leading to a 5:1 mixture of the two *endo*- and *exo*-

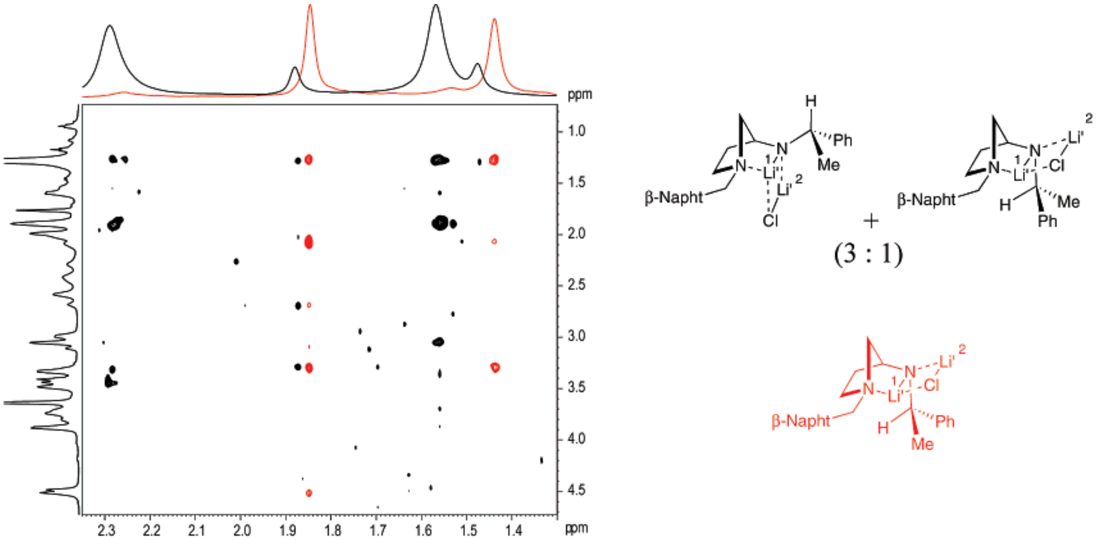

FIGURE 6. Superimposition of HOESY spectra (recorded at 195 K) of **1a**^{6}Li:^{6}LiCl *endo* + *exo* (black) and **1b**^{6}Li:^{6}LiCl *exo* (red) complexes in THF-d_8. A good match between the correlations of both *exo* isomers can be noted.

1aLi:LiBr complexes. However, the presence of residual LiCl in the methyllithium used to form the initial mixed aggregate, affording the corresponding *endo* and *exo* aggregates with **1a** in the starting sample, did not permit an accurate determination of the stereospecificity of the exchange.

In conclusion, to this part of the NMR spectroscopy study, the data presented above show that the amides **1a**Li and **1b**Li aggregate with lithium chloride and bromide in THF, to provide robust 1:1 complexes, characterized by ^{1}H and ^{6}Li mono- and bidimensional NMR spectra. These complexes arise either by direct association between the "naked" lithium amide and the lithium halide or by substitution of methyllithium out of a preformed lithium amide:methyllithium mixed aggregate. This latter substitution (i) is complete and irreversible, as demonstrated in the case of **1a**Li:LiCl, (ii) is stereospecific for the *exo* complexes, (iii) could partly epimerize the chiral nitrogen N^7 for the *endo* arrangements. Note that these observations match extremely well those reported by Collum et al. for diphenyllithium amide.[10a,b]

These results hint that the lithium amide:methyllithium aggregates supposed to be at the origin of the induction phenomenon during the reaction displayed in Scheme 1, are destabilized, in the presence of lithium halides, to the benefit of the lithium amide:lithium halide complexes. The source of chirality would thus be sequestrated into a chemically irrelevant entity, leaving the tetrameric methyllithium almost free to add on the aldehydes in the absence of a closely associated inductor. However, the fact that a significant excess of LiCl is necessary for the ee to plummet (Table 1, entry 3) suggests another parameter has to be taken into account. The interference between the above complex and the alcoholate progressively formed in the reaction media could be involved in this phenomenum. We are currently examining this point.

Theoretical Study of the Competitive Aggregations of 3APLi, MeLi, and LiX. It was next tempting to evaluate the relative stabilities of the various aggregates formed between the 3APLi and MeLi, LiCl, and LiBr. The aggregation of organolithium compounds has been the object of many theoretical investigations.[21] The large size of the systems considered here led us to restrict our computations to the DFT level. The B3P86 functional and the 6-31G** basis set, which behaved satisfactorily in related situations,[22] were retained. All of the calculations have been performed using the Jaguar 4.1 software.[23] Note that the basis set superposition errors (BSSE), the zero-point energy (ZPE) corrections, and the entropic contribution have not been included in our results. We preferred dedicating our computational resources to the explicit treatment of the three THF molecules in the first solvation shell. The BSSE and ZPE are probably of lesser importance[6c,d] since they are not expected to modify the relative order of the complex stabilities or that of the activation barriers.

We have first considered the complexes involving the lithium amides **1a**Li and **1b**Li and the three additives in vacuo. The full optimizations (B3P86, 6-31G**) led to folded aggregates similar to those described previously for the MeLi aggregates. The aggregation energies were calculated according to

$$E_{\mathrm{aggr}} = E_{\mathrm{complex}} - E_{\mathrm{3APLi}} - E_{\mathrm{LiX}}\ (-\ 3E_{\mathrm{THF}})$$

where E_{complex} is the total energy of the optimized aggregate, E_{3APLi} the energy of the isolated lithium amide optimized in a conformation similar to that it adopts within the complex, E_{LiX} the energy of the additive (MeLi, LiCl, or LiBr), and E_{THF} the energy of THF, this latter being taken into account for the solvated species only. The corresponding values are displayed in Tables 2 and 3.

The data in Table 2 show that the *endo* and *exo* arrangements are more or less isoenergetic, as noted before.[6b] The conforma-

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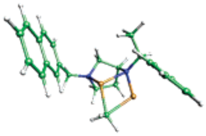
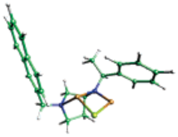
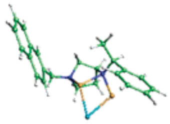
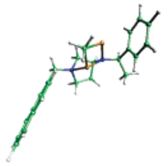
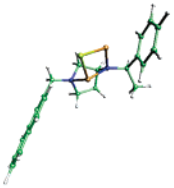
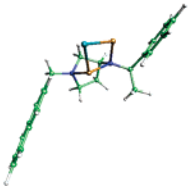
[21] Sapse, A.-M.; Jain, D. C.; Raghavachari, K. In *Lithium Chemistry: A Theoretical and Experimental Overview*; Sapse, A.-M., Schleyer, P. v. R., Eds.; J. Wiley & Sons: New York, 1995. For a recent paper dealing with this problem, see: Matito, E.; Poater, J.; Bickelhaupt, F. M.; Sola, M. *J. Phys. Chem. B* **2006**, *110*, 7189−7198.

[22] See, for instance: (a) Pratt, L. M.; Streitwieser, A. *J. Org. Chem.* **2000**, *65*, 290−294. b() Fressigné, C.; Maddaluno, J.; Marquez, A.; Giessner-Prettre, C. *J. Org. Chem.* **2000**, *65*, 8899−8907. (c) Pratt, L. M.; Nguyên, N. V.; Ramachandran, B. *J. Org. Chem.* **2005**, *70*, 4279−4283. (d) Fressigné, C.; Lautrette, A.; Maddaluno, J. *J. Org. Chem.* **2005**, *70*, 7816−7828.

[23] Jaguar 4.1, release 53, Schrödinger, LLC., Portland, OR, 2000.

TABLE 2. Aggregation Energies (B3P86, 6-31G) of the Unsolvated Complexes between 1aLi and 1bLi and LiX (*X* = Me, Br, Cl)**

Complex	Optimum	$E_{complex}$ [a,b]	$E_{aggr.}$ [c]	$\Delta E_{aggr.}$ [c]
endo **1a**Li : MeLi		-1059.525159	-48.85	0.0
endo **1a**Li : LiCl		-1480.085359	-56.13	-7.3
endo **1a**Li : LiBr		-1032.895656	-55.54	-6.7
exo **1b**Li : MeLi		-1059.524919	-49.71	0.0
exo **1b**Li : LiCl		-1480.083746	-56.13	-6.4
exo **1b**Li : LiBr		-1032.894810	-54.66	-5.0

[a] E(MeLi) = −47.613361 au; *E*(LiBr) = −20.973194 au; E(LiCl) = −468.161964 au. [b] Values in au. [c] Values in kcal·mol^{-1}.

TABLE 3. Variation of the Differences between Aggregation Energies (B3P86, 6-31G) of the Unsolvated Complexes 1aLi:MeLi or 1bLi:MeLi and 1aLi:LiX or 1bLi:LiX (X = Cl, Br) with the Aggregation State of the Reacting (LiX)$_n$**

X	*n*	**1a**Li:LiMe ΔE (kcal·mol^{-1})	**1b**Li:LiMe ΔE (kcal·mol^{-1})
Cl	1	−7.28	−6.42
	2	−4.46	−3.60
	4	−3.68	−2.82
Br	1	−6.69	−7.67
	2	−6.38	−7.36
	4	−6.39	−7.37

tion of the complexes is hardly altered upon substitution of MeLi by LiCl or LiBr. This explains the high similarity between the ^{1}H NMR spectra of **1a,b**Li:MeLi and of **1a,b**Li:LiX. In contrast, the energy values indicate that the substitution is thermodynamically favored: the aggregates with the lithium halides are preferred by 6.4 to 7.3 kcal·mol^{-1} for LiCl and by 5.0 to 6.7 kcal·mol^{-1} for LiBr, in line with the data from the NMR spectroscopy. The energy gain is slightly larger for the *endo* complexes.

In the above calculations, neither the degree of aggregation of LiX nor the solvation of the interacting species were taken into account. We thus decided to study the respective influence of these two parameters on the thermodynamics of the exchange.

The influence of the aggregation state of (LiX)$_n$ on the energy balance of the equilibrium was evaluated by computing the ΔE values for the following reaction

$$\mathbf{1a}\text{Li:LiMe} + (\text{LiX})_n = \mathbf{1a}\text{Li:LiX} + (\text{LiX})_{n-1}(\text{LiMe})$$

with an associated $\Delta E = (E_{\text{II}} + E_{\text{n}-1}) - (E_{\text{I}} + E_{\text{n}})$, where E_{II} is the energy associated to **1a**Li:LiX, E_{I} that associated with **1a**Li:LiMe, E_{n} that of (LiX)$_n$, and $E_{\text{n}-1}$ that of (LiX)$_{n-1}$(MeLi). The results are shown Table 3, LiCl and LiBr being considered as monomers, dimers, or tetramers (n = 1, 2, or 4).

In the two topologies, the two halides behave quite differently: the aggregation has little impact on LiBr aggregation energy while it changes considerably that of LiCl. In this latter case, the **1a,b**Li:LiCl energy formation decreases significantly (by∼50%) when the aggregation of LiCl increases. This difference is probably due to the homogeneous aggregation energy of LiCl and LiBr. This assumption was confirmed by comparing the dissociation energy of (LiCl)$_2$ to that of (LiBr)$_2$ and the aggregation energy of **1a**Li:LiCl to that of **1a**Li:LiBr. While the dissociation [(LiX)$_2$ → 2 LiX] favors LiBr over LiCl

TABLE 4. Aggregation Energies (B3P86, 6-31G) of the Complexes between 1aLi, 1bLi and LiX (X = Me, Br, Cl) Solvated by Three THF**

complex	E^a	E_{aggr}^{b,c}	ΔE_{aggr}^{b}
endo-**1a**Li:MeLi−3THF	−1759.123499	−80.3	0.0
endo-**1a**Li:LiCl−3THF	−2179.692188	−93.0	−12.6
endo-**1a**Li:LiBr−3THF	−1732.504632	−93.7	−13.4
exo-**1b**Li:MeLi−3THF	−1759.122528	−77.9	0.0
exo-**1b**Li:LiCl−3THF	−2179.688705	−89.7	−11.8
exo-**1b**Li:LiBr−3THF	−1732.501999	−90.3	−12.3

^{a} Energies in au. ^{b} Energies in kcal·mol^{-1}. ^{c} E(THF) = −233.183081 au.

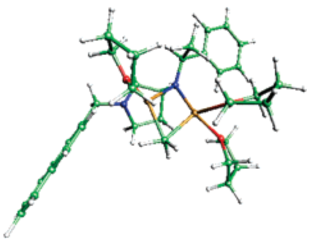


FIGURE 7. *Endo*-**1a**Li:MeLi−3THF-optimized aggregate.

by 3.8 kcal·mol^{-1}, the aggregation [**1a**Li + LiX → **1a**Li:LiX] favors LiCl over LiBr but by only 0.6 kcal·mol^{-1}. To conclude on the influence of the aggregation, it is worth emphasizing that LiBr which appears, when considering only the monomers, to be equivalent to LiCl actually has a higher affinity for lithium amide **1a**Li than LiCl for both the *endo* and *exo* topologies. Note finally that these figures are to be taken with some caution since only the **1a,b**Li:MeLi + (LiX)$_2$ → **1a,b**Li:LiX + MeXLi$_2$ reactions are isodesmic.

We next considered the influence of THF in trisolvated[5] complexes.[24] The data show that the *endo* and *exo* bicyclic cores of the complexes are preserved upon solvation. For the sake of space economy, only the *endo* **1a**Li:MeLi−3THF-optimized aggregate is illustrated in Figure 7. Note that (i) the THF−lithium interactions impose steric constraints on the lateral substituents which rotate out of their original position, (ii) the aggregation energies are considerably increased upon solvation since the calculation now incorporate the interactions between the two lithium and the three THF, and (iii) the thermodynamic preference for the complexes with lithium halides is amplified by the solvation (>11 kcal·mol^{-1}), the lithium bromide leading to complexes more stable than LiCl. The aggregation energy of the *endo* complexes remains slightly larger than for the *exo* ones. Similar calculations run for the 3APLi bearing an α-naphthyl appendage led to comparable conclusions, but for the orientation of the lateral chain bearing the naphthyl appendage.[25]

Overall, the theoretical data computed for the solvated complexes are in good agreement with the above results from NMR spectroscopy, the large energy differences calculated (>10 kcal·mol^{-1}) warranting the irreversibility of the MeLi → LiX substitution. Note that these conclusions are perfectly in line with previous results obtained by Williard, Schleyer, and colleagues[10d] on different systems.

Conclusions

A drop of the enantiomeric excess of the 1-*o*-tolylethanol resulting from the addition of methyllithium on *o*-tolualdehyde in the presence of chiral lithium amides derived from chiral 3-aminopyrrolidines (3APLi) was observed upon addition of LiCl to the medium. The formation of the various possible aggregates between the LiX, the lithium amide, and the methyllithium was thus examined by multinuclear NMR spectroscopy in THF. The results show that the initial mixed aggregate of the chiral lithium amide and methyllithium is rapidly, totally, and irreversibly replaced by a 1:1 complex involving one lithium chloride or bromide and one lithium amide. The overall conformation of these new aggregates is similar to the original ones. However, the MeLi/LiX substitution occurs with some degree of epimerization at the nitrogen for the *endo*-MeLi:3APLi complex. In contrast, the substitution is more or less stereospecific for the *exo* arrangements of the aggregate. DFT calculations confirm the thermodynamic preference for the 3APLi:LiX mixed aggregates (by more than 10 kcal·mol^{-1} when THF is explicitly taken into account). This phenomenon can explain the detrimental effect of these additives on the ee of the model reaction.

Experimental Section

Under an argon atmosphere, MeLi (0.75 mmol, 1.6 M in ether) was added to a solution of **1a** (0.75 mmol) in THF (15 mL) at −20 °C. After the solution was stirred for 20 min, a second aliquot of MeLi (1.25 mmol, 1.7 equiv against **1a**Li, 1.6 M solution in ether) was added dropwise to the **1a**Li, and the resulting mixture was stirred 30 min at −20 °C. The mixture was then cooled to −78 °C and aged 30 min at the same temperature. LiCl (0−2.7 equiv against **1a**Li, 0.3 M in THF) was added dropwise at −78 °C, and the resulting mixture was aged for 30 min. A solution of *o*-tolualdehyde (0.5 mmol) in THF (2 mL) was added at −78 °C over a 5 min period, and the mixture was stirred at −78 °C for 2 h. The medium was quenched at −78 °C with a 3 M aqueous HCl solution (3 mL) and extracted with ether (3 × 10 mL) after reaching room temperature. The combined organic layers were washed with NaHCO$_3$ (10 mL) and brine (10 mL), dried (MgSO$_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (Et$_2$O/cyclohexane 30:70) to give 1-*o*-tolylethanol as a colorless oil.

General Aspects for the NMR Study. Argon was dried and deoxygenated by bubbling through a commercial solution of *n*-butyllithium in hexane. Commercial tetrahydrofuran-d_8 was distilled over sodium and benzophenone. ^{6}Li (95%) washed in freshly distilled pentane. All NMR experiments were performed on a 500 MHz spectrometer, equipped with *z*-gradient unit and a 5 mm {^{1}H, ^{6}Li, ^{13}C, and ^{15}N} quadruple-resonance probe. 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 25.37, respectively. Lithium spectra were referenced to external 0.3 M ^{6}LiCl in MeOH-d_4 (d 0.0). Processing of NMR data was performed on SGI O2 computer, using the manufacturer's program Xwinnmr 2.1 (Bruker).

1D NMR Measurements. Proton and lithium one-dimensional experiments were recorded with standard parameters.

2D NMR Measurements. ^{1}H/^{1}H NOESY. The following parameters were used for acquiring and processing the spectra in phase sensitive−sensitive mode: 256 experiments with 2048 data points and 16 scans each were recorded; pure phase line shapes were obtained by using time proportional phase incrementation phase cycling, variable mixing times, depending on the sample, were used; one time zero filling in f1; p/2 shifted sine square window functions were applied to f2 and f1 dimension before FT.

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(24) For a very recent paper dealing with the theoretical solvation of alkyllithiums, see: Pratt, L. M.; Truhlar, D. G.; Cramer, C. J.; Kass, S. R.; Thompson, J. D.; Xidos, J. D. *J. Org. Chem.* **2007**, *72*, 2962−2966.

(25) Paté, F. Ph.D. thesis, Université de Rouen, 2006.

^{6}Li/^{1}H HOESY. The following parameters were used for acquiring and processing the spectra in phase sensitive−sensitive mode: 128 experiments with 1024 data points and 16 scans each were recorded; pure phase line shapes was obtained by using time proportional phase incrementation phase cycling; variable mixing times, depending on the sample, were used; one time zero filling in f1; p/2 and p/3 shifted sine square window functions were applied to f2 and f1 dimension respectively before FT.

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Supporting Information Available: Detailed experimental protocols and copies of mono- and bidimensional ^{1}H and ^{6}Li NMR spectra for **1a** alone and **1a**Li:LiCl, **1a**Li:LiBr, and **1a**Li:MeLi aggregates. This material is available free of charge via the Internet at http://pubs.acs.org.

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