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ARTICLE TYPE

Probing Solvent Effects on Mixed Aggregates Associating a Chiral Lithium Amide and *n*-BuLi by NMR: From Structure to Reactivity

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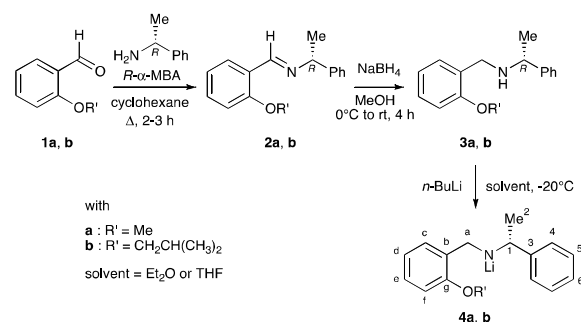
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An NMR study of a 1:1 mix between a chiral lithium amide (4a) and *n*-BuLi shows that, depending on the solvent employed (Et₂O or THF), a mixed aggregate can form in proportions that are directly related to the ee's measured during the enantioselective alkylation of *o*-tolualdehyde by these same species.

Introduction. Chiral lithium amides (CLA) are handy tools for diastereoselective and enantioselective chemical transformations as they can act either as chiral bases,^{1,2} chiral nucleophiles,^{1,3} or chiral ligands.^{1,4,5} With regards to the latter application, the CLA have been mainly associated to highly reactive lithium reactants (RLi) in the perspective of controlling their enantioselective nucleophilic additions.^{4a,b,h,j,p,q,t,u,5a,e,g-j,l-o,t,u} In an effort to understand the interaction between the CLA-ligand and RLi-nucleophile, several studies have been undertaken to get an insight on the structure/reactivity relationship, in particular by NMR. The mixed aggregates studied have been analyzed either directly from the reaction mixture,^{4c-e,i-o,r,s,v,5c,d,h,i,m,n,p-r,t-v,6d,e,g} or after crystallizing the intermediate samples.^{4f,g,6a-c,f} In addition, DFT computations have been undertaken to support and understand the structural observations and, more importantly, to shine some light on the mechanistic aspects (reactivity, stereoselectivity) of the reactions involving such aggregates.^{4g,l,5b,f,h,i,k,m,n,q-w} The theoretical analyses have all highlighted the central role played by the dipole-dipole interactions in the aggregation phenomena.⁷

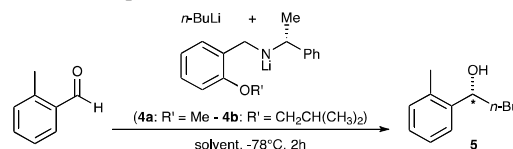
Recently,⁸ we have been working on CLAs **4** (Scheme 1), whose amine precursors (**3**) are easily synthesized through a single reductive amination reacting (*R*)- α -methylbenzylamine ((*R*)- α -MBA) and a 2-alkoxy-benzaldehyde (R' = Me: **1a**,^{9a} R' = CH₂CH(CH₃)₂: **1b**^{9b}). In the retained procedure, the imine intermediates (**2a** and **2b**, respectively) were formed refluxing both starting materials in cyclohexane, and the crude products were directly reduced by NaBH₄. Amines **3a** and **3b** were thus isolated, after distillation, in 99% and 67% yields, respectively. Quantitative deprotonation of **3** by *n*-BuLi in Et₂O or THF at -20°C, afforded lithium amides **4a** and **4b**. The efficiency of CLAs **4a** and **4b** as chiral ligands for nucleophilic *n*-butyllithium toward *o*-tolualdehyde was tested in Et₂O and in THF at -78°C (Table 1). With a 4/*n*-BuLi/ArCHO ratio of 1.5:1.5:1.0, the reactions proceeded in good yield in both ethereal media (>77%), and ee's up to 75%

could be reached. We noticed that the inductions are markedly higher in THF than in Et₂O, with better results for the most hindered CLA **4b**.



Scheme 1 Synthesis of CLAs **4a** and **4b**

Table 1 Enantioselective nucleophilic alkylation of *o*-TolCHO in the presence of **4a**/*n*-BuLi and **4b**/*n*-BuLi.



Entry	CLA	Solvent	Yield (%)	Ee (%) ^{a,b}
1	4a	Et ₂ O	79	11
2	4a	THF	88	30
3	4b	Et ₂ O	81	27
4	4b	THF	77	75

^adetermined by chiral HPLC; ^bmajor alcohol: **5-R**

This significant solvent effect, albeit observed in several other cases,^{4c,5i,10} led us to examine the intermediates formed in diethyl ether and THF. We undertook this structural study by NMR, and decided to focus on amide **4a**, whose spectra were expected to be easier to decipher, in particular in the perspective of monitoring low concentration species. All the samples examined were ⁶Li-labeled because the weak quadrupolar relaxation of this nucleus generates sharp NMR signals and renders possible the fine analyses of organolithiums in solution.

Characterization of 4a in Et₂O and THF. CLA **4a** was studied first, in deuterated Et₂O. Thus, a \approx 0.15 M Et₂O-*d*₁₀-solution of ⁶Li-labeled **4a** was prepared directly in an NMR tube by addition, at -20°C and under argon, of one equiv of

$n\text{-Bu}^6\text{Li}^{5\text{p}}$ on amine **3a** in the same solvent. The comparison of the monodimensional ^1H spectra of **4a** and **3a** registered at 195K (-78°C) evidenced the complete fading of the NH signal at 2.16 ppm (see Figure S1, top and middle, in Sup. Info. Section). The **4a** and **3a** ^{13}C NMR analyses run at the same temperature (complemented by bidimensional $^1\text{H},^{13}\text{C}$ -HMQC, $^1\text{H},^{13}\text{C}$ -HMBC and $^1\text{H},^1\text{H}$ -COSY experiments run on **4a**, see Figures S2-S5 in Sup. Info. Section), allowed the complete H and C assignments of the signals of the amide. One can note, for both **4a** ^1H and ^{13}C spectra, a strong splitting of the signals attributed to the CH_2^a benzylic group, as well as those corresponding to the aromatic protons. These changes suggest a relatively constrained arrangement that could soundly result from an intramolecular coordination between the oxygen of the OMe group and the lithium atom. The ^6Li spectrum also obtained at 195K displays one singlet at 2.18 ppm (see Figure S6 in Sup. Info. Section). An intriguing shoulder on this peak led us to vary the temperature from 195K to 273K. A gradual split of the original singlet into two signals (Fig. 1) was noticed, and a base-line separation was observed at 250K. At this temperature, two peaks with similar integration values at δ 2.16 ppm and 2.11 ppm suggested the presence of two distinct lithium atoms. By contrast, decreasing the temperature from 195 to 170K (not shown) did not alter the chemical shifts and led only to a slight broadening of the signals, probably due to the expected increased viscosity of the medium. Note that the ^1H spectrum at 250K did not show much changes (see Figure S1, bottom spectrum compared with middle one, in Sup. Info. Section), indicating that the structure of the amide is little sensitive to temperature.

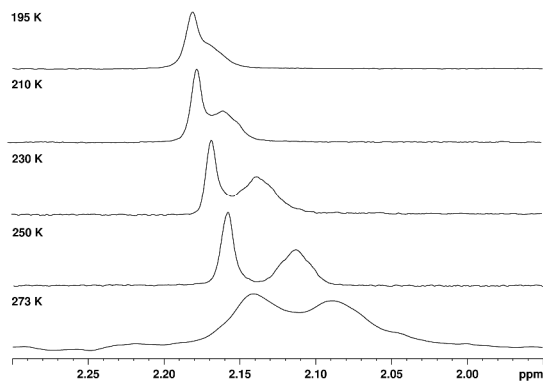


Fig. 1 ^6Li NMR spectra of **4a** in $\text{Et}_2\text{O}_{d10}$ at 195-273K.

Complementary information extracted from both the ^1H and ^6Li spectra, as well as a $^6\text{Li},^1\text{H}$ -HOESY one, showed that the two ^6Li signals are related to the same molecule. First, the ^1H spectrum exhibits only the signals corresponding to the lithium amide (no excess $n\text{-BuLi}$). This species that seems to be the only one in solution, would then incorporate two distinct lithium atoms. On the other hand, the use of the resolution enhancement by gaussian multiplication before Fourier transform of the 250K ^6Li NMR data resolved the broad singlet at 2.11 ppm into a triplet ($^3J_{\text{Li-H}} = 0.7$ Hz, see Figure S7, top, in Sup. Info. Section). Irradiation of CH^1 suppressed this coupling (see Figure S7, bottom, in Sup. Info. Section). Thus, the triplet at 2.11 ppm is due to a coupling between one ^6Li and two equivalent H^1 , which suggests that **4a** could be a dimer. Taking into account the expected intramolecular Li-OMe interaction, two dimeric arrangements (C_1 or C_2 symmetrical) organized around a same N-Li-N-Li quadrilateral, but differing by the coordination sites of the

OMe on the lithium atoms, can be proposed (Fig. 2).¹¹ In the C_1 -dimer, each Li cation is coordinated to a methoxy appendage, while both OMe groups are linked to a same Li atom in the C_2 -dimer. On the $^6\text{Li},^1\text{H}$ -HOESY spectrum at 250K (Fig. 3), only the Li-signal at 2.16 ppm correlates with that of the OMe-protons. The C_2 -dimer is the sole to fit this observation.

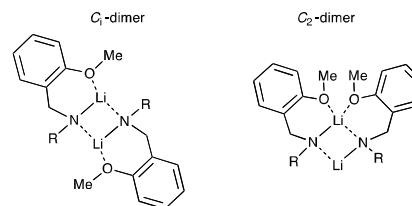


Fig. 2 Possible C_1 and C_2 dimers for **4a** ($R = (R)\text{-CH}(\text{Me})\text{Ph}$)

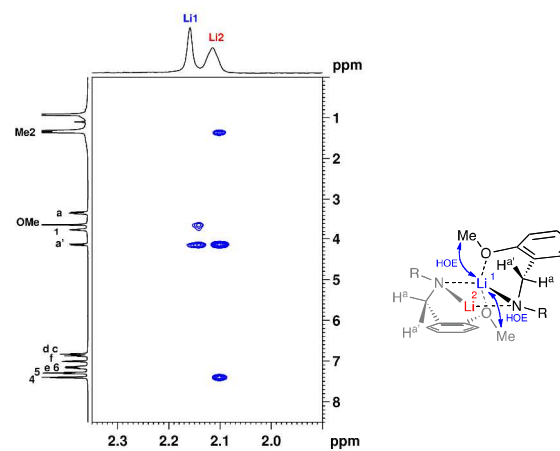


Fig. 3 $^6\text{Li},^1\text{H}$ -HOESY NMR spectrum of **4a** in $\text{Et}_2\text{O}_{d10}$ at 250K ($R = (R)\text{-CH}(\text{Me})\text{Ph}$)

A converging series of NMR $^6\text{Li},^1\text{H}$ -HOESY (Fig. 3, left) and $^1\text{H},^1\text{H}$ -NOESY (see Figure S8 in Sup. Info. Section) correlations then allowed to determine the arrangement of the $R = (R)\text{-CH}(\text{Me})\text{Ph}$ and the $o\text{-MeOC}_6\text{H}_4\text{CH}_2$ appendages around the N-Li¹-N-Li² quadrilateral of C_2 -dimer **4a**. The key ones are reported on Fig. 4. Note that the two nitrogen atoms in the dimer are chiral and that their absolute configuration (R) is controlled by the two stereogenic (R) C^1 carbons in the supramolecule. Therefore, only one ($\text{C}^{1R}\text{-N}^R$)₂ structure, in which the Me^2 point toward the N-Li¹-N-Li² quadrilateral, is observed in the solution.

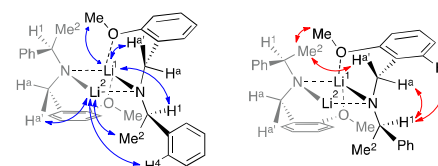


Fig. 4 $^6\text{Li},^1\text{H}$ -HOESY (left) and $^1\text{H},^1\text{H}$ -NOESY (right) NMR correlations observed on C_2 -dimer **4a** in $\text{Et}_2\text{O}_{d10}$ at 250K.

A ^1H -DOSY NMR experiment further confirmed the structure of **4a** in Et_2O (see Figures S9-S10 and Table S1 in Sup. Info. Section). Registered in the presence of three internal references (cyclooctene, hexamethyldisilane and squalene) at 195K, the data led to $\text{MW} = 480$, a value consistent with an unsolvated C_2 -dimer (calc. $\text{MW} = 494$). The thermal variation of the chemical shifts comes to support

this measurement: $\delta(\text{Li}^1)$ is relatively insensitive to temperature as the intramolecular coordination by the two MeO is little altered, while $\delta(\text{Li}^2)$ drifts from high fields at 273K to a value similar to $\delta(\text{Li}^1)$ at 195K,⁵ⁱ probably because of changes in the Li^2 surrounding induced by lateral chain movements and/or changes in the solvation. The little solvation of Li^2 is most likely due to its poor availability: based on the NOESY and HOESY data, it is clear that the two lateral chains encircle Li^2 , leaving almost no room for bulky ether molecules to complete the solvation sphere.

The above experiments were next repeated in THF_{ds}. In this solvent, the monodimensional ¹H spectra of **4a** registered at 195K showed two imbalanced sets of signals (see Figure S11 in Sup. Info. Section). Complementarily, the monodimensional ¹³C and bidimensional ¹H,¹³C-HMQC, ¹H,¹³C-HMBC and ¹H,¹H-COSY spectra (see Figures S12-S15 in Sup. Info. Section), recorded at the same temperature, suggested also the co-existence of two forms for **4a**. The monodimensional ⁶Li spectrum (Fig 5, middle), still at 195K, highlighted three peaks at 2.34 ppm (singlet), 1.94 ppm (doublet, $J = 0.4$ Hz), and 1.25 ppm (broad singlet) in a 1:1:1 ratio.

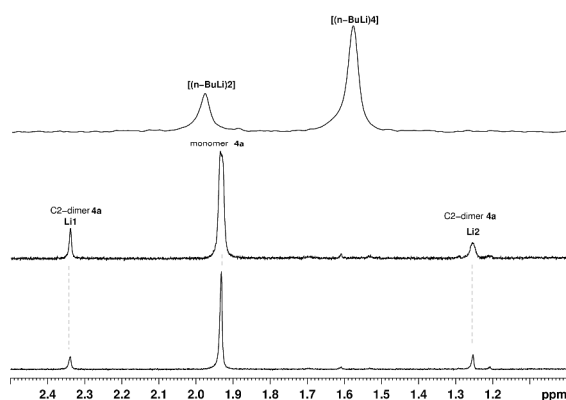


Fig. 5 ⁶Li NMR spectra of *n*-BuLi (top) and **4a** (middle) in THF_{ds} at 195K. Bottom line: ⁶Li spectrum of **4a** with proton H¹ selective decoupling at 3.85 ppm.

An irradiation of the CH¹ of the two entities, of which signals superimpose at 3.85 ppm in the ¹H spectrum, transformed the ⁶Li doublet at 1.94 ppm into a singlet, and the broad singlet at 1.25 ppm in a finer peak (Fig 5, bottom). At this stage, we hypothesized that the two 1:1 minor ⁶Li peaks (2.34 and 1.25 ppm) belonged to a sole entity, actually similar to the one depicted in Et₂O, *i.e.* a C₂-dimer. The ⁶Li broad signal at lower chemical shift (1.25 ppm) would indeed correspond to a poorly resolved triplet, transformed into a singlet upon decoupling of H¹. This signal could thus be assigned to Li² in the C₂-dimer **4a**, distinct from the intramolecularly coordinated Li¹ (at 2.34 ppm).

Going further into this analysis suggests that the major ⁶Li peak at 1.94 ppm belongs to a second lithiated compound bearing only one type of lithium atom. The doublet to singlet transformation upon irradiation of H¹ calls for a ³J_{Li-H} coupling between this ⁶Li atom and a sole H¹ proton. From this observation, one can deduce that the major species is necessarily monomeric (monomer-**4a**, Fig. 6, left). Indeed, a dimer with two equivalent lithium atoms would have to be fully symmetrical, imposing that each Li cation is not only equally coordinated to one OMe group, but also that the two Li-OMe coordinations lie on the same side of the quadrilateral

plane (Fig. 6, right). In such a context, each Li atom would be coupled to two equivalent H¹ protons, and its ⁶Li signal would appear as a triplet.

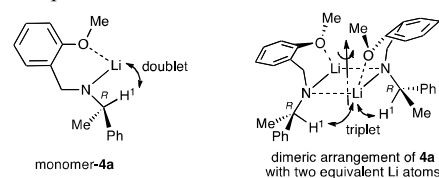


Fig. 6 Monomer-**4a** in THF_{ds} at 195K (left) and putative dimer containing two equivalent Li atoms (right)

The ¹H and ¹³C monodimensional and bidimensional ⁶Li,¹H HOESY and ¹H,¹H-NOESY spectra (see Figures S16 and S17, respectively, in Sup. Info. Section) support the structure of the intramolecularly coordinated monomer-**4a**. Among various evidences, the splitting of the signals attributed to the CH₂^a benzylic group and the MeO-Li interaction are worth reminding. Complementarily, the ¹H-DOSY measurement (see Figures S18-S19 and Table S2 in Sup. Info. Section) run at 195K, with the same internal reference as earlier, led to MW = 500. Knowing that this entity is a monomer, this value can be assigned to monomer-**4a**+3THF (calc. MW = 484). Thus, the sole lithium cation of this monomer would lie in a penta-coordinated location (N + MeO + 3 THF). The same DOSY study run on the minor entity indicates MW = 525. This value strengthens the hypothesis that this second species could correspond to a dimer (calc. MW = 494). The latter would be little solvated by THF (less than 0.5 molecule) at 195K which suggests that Li¹ would be, as in diethylether, tetracoordinated while Li² would essentially be di-coordinated.

In conclusion, the NMR characterization of CLA **4a** in Et₂O and THF shows that this lithium amide behave quite differently in these two solvents. A single dimer (C₂-dimer **4a**) is detected in Et₂O, while a monomer and a dimer (identical to the one observed in diethyl ether but for the solvation, which is slightly better in THF) would coexist in a 8:1 ratio in THF. Worthy of note is the similarity between our results and those reported by Davidsson, Hilmersson and co-authors.^{4c,g} In their major papers on chiral lithium amide **6** (Fig. 7), these authors pointed out that going from Et₂O to THF transforms a monosolvated C₂-dimer into a more solvated monomer.

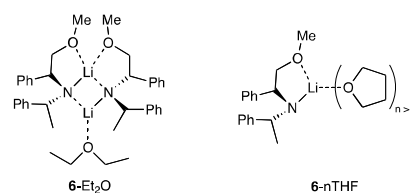


Fig. 7 Dimeric and monomeric structures of CLA **6** studied by Himersson

Characterization of 4a/n-BuLi mixed aggregates in Et₂O and THF. The next step consisted in adding one equivalent of *n*-BuLi onto the amide solution, and look for **4a**/*n*-BuLi mixed aggregates. This addition was conducted at -20°C, and after 10 min, the NMR samples were cooled to -78°C before analysis. In Et₂O, the ¹H and ⁶Li NMR spectra showed, beside the starting amide and *n*-BuLi, the presence of a little amount of a new species (Fig. 8, left and see Figure S20 in Sup. Info. Section). On the ⁶Li spectrum (Fig. 8, right), the two new peaks at 2.61 and 1.89 ppm suggests this entity bears two

distinct lithium atoms in a 1:1 ratio. We could not pursue further the characterization because of the tiny amount of this compound in this solvent.

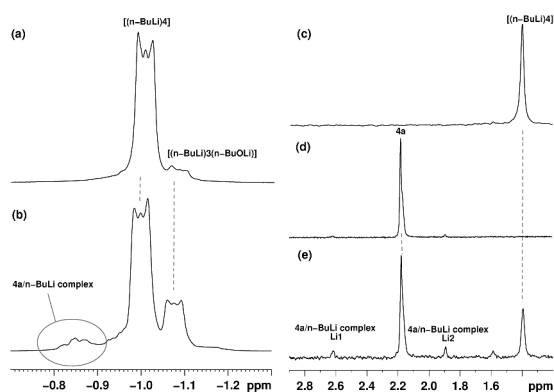


Fig. 8 ^1H NMR spectra (left) of (a) $n\text{-BuLi}$, (b) $4\mathbf{a} + n\text{-BuLi}$ and ^6Li NMR spectra (right) of (c) $n\text{-BuLi}$, (d) $4\mathbf{a}$ and (e) $4\mathbf{a} + n\text{-BuLi}$ in $\text{Et}_2\text{O}_{d10}$ at 195K.

In THF, the ^1H and ^6Li NMR spectra at 195 K showed a comparable evolution. Thus, beside the free $n\text{-BuLi}$ and the two amide arrangements (C_2 -dimer $4\mathbf{a}$ + monomer- $4\mathbf{a}$), a new entity, somewhat similar to that above, was observed, but in higher quantity. The ^1H spectrum (Fig. 9, left, and see Figure S21, bottom, in Sup. Info. Section) shows that this complex incorporates an $n\text{-BuLi}$ unit (new signal at -0.77 ppm, next to the free $n\text{-BuLi}$ at -1.04 ppm and -0.91 ppm, with a pattern suggesting that the two α -protons are enantiotopic) and an amido one (for instance, new H^b at 3.15 ppm and H^a at 4.13 ppm, or MeO at 3.99 ppm). The ^6Li spectrum (Fig. 9, right), still at 195 K, exhibits two new signals at 2.07 ppm and 1.57 ppm, next to the well-known peaks for $n\text{-BuLi}$ (1.99 and 1.59 ppm, for the dimer and tetramer, respectively), C_2 -dimer $4\mathbf{a}$ (2.34 ppm and 1.25 ppm), and monomer- $4\mathbf{a}$ (1.94 ppm).

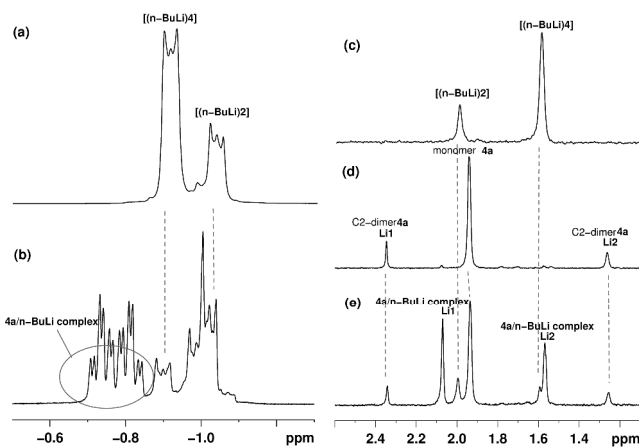


Fig. 9 ^1H NMR spectra (left) of (a) $n\text{-BuLi}$, (b) $4\mathbf{a} + n\text{-BuLi}$ and ^6Li NMR spectra (right) of (c) $n\text{-BuLi}$, (d) $4\mathbf{a}$ and (e) $4\mathbf{a} + n\text{-BuLi}$ in THF_{d8} at 195K.

Providing an exact structure for the new species is difficult because all the NMR spectra in THF are recorded on a mixture of these four compounds. However, the monodimensional $^{13}\text{C}\{^1\text{H}\}$ and bidimensional $^1\text{H},^{13}\text{C}$ -HMQC, $^1\text{H},^{13}\text{C}$ -HMBC, $^1\text{H},^1\text{H}$ -COSY, $^6\text{Li},^1\text{H}$ HOESY, as well as $^1\text{H},^1\text{H}$ -NOESY experiments (see Figures S22-S27 in Sup. Info. Section) hint that a $4\mathbf{a}/n\text{-BuLi}$ 1:1 mixed aggregate such as the

one featured on Fig. 10 is formed. In particular, the ^{13}C signal of the $n\text{-BuLi}$ α -carbon appears as a quintet ($^1J_{\text{C-Li}} = 8.8$ Hz), generally observed for dimers of this type.¹²

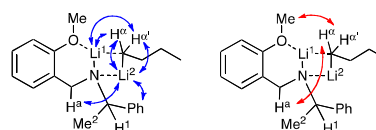


Fig. 10 $^6\text{Li},^1\text{H}$ -HOESY (left) and $^1\text{H},^1\text{H}$ -NOESY (right) NMR correlations observed on the putative $4\mathbf{a}/n\text{-BuLi}$ 1:1 mixed aggregate in THF_{d8} at 195K.

A ^1H -DOSY NMR study on this entity (see Figures S28-S29 and Table S3 in Sup. Info. Section) led to MW = 447. This value is in good agreement with a THF-disolvated $4\mathbf{a}/n\text{-BuLi}$ mixed aggregate [calc. MW($4\mathbf{a}/n\text{-BuLi} + 2\text{THF}$) = 469].

A preliminary conclusion is that the mixtures of $4\mathbf{a}$ and $n\text{-BuLi}$ behave relatively differently in diethyl ether and THF. In the first of these solvents, the two lithiated species remain essentially side by side, and afford marginally a supramolecular compound, that could not be identified precisely but most probably associates the two partners in a 1:1 complex. In THF, the two reactants linked to a larger extent and it became possible to depict a 1:1 mixed aggregate. Satisfyingly, the structure of $4\mathbf{a}/n\text{-BuLi}$ compares well to that obtained by Hilmersson and co-workers on somewhat similar mixed dimers between $n\text{-BuLi}$ and amides $6^{4e,f,j}$ or 7^{4m} (Fig. 11 right) in ethereal solvents, also in equilibrium with their constituents. Note that in toluene or in the solid state, Williard^{6a,c} and Hilmersson^{4m} have identified a trimeric complex associating two amides 7 and one $n\text{-BuLi}$ (Fig. 11 left) that we did not see with $4\mathbf{a}$ in ether or THF.

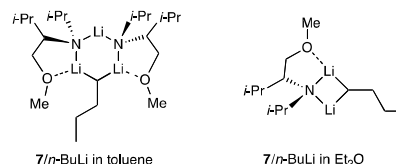


Fig. 11 Mixed complexes formed between 7 and $n\text{-BuLi}$ in toluene (left) and an ethereal solvent (right)

Assuming that the two new species formed in each solvent are the same, *i.e.* an 1:1 $4\mathbf{a}/n\text{-BuLi}$ aggregate, it seems that the concentrations of this aggregate correlate directly to the level of induction measured during the nucleophilic alkylation of *o*-toluylaldehyde in these two solvents. Indeed, the putative $4\mathbf{a}/n\text{-BuLi}$ concentration (calculated on the lithium basis) is about 10% in Et_2O and 30% in THF while the ees in these same solvents are 11% and 30%, respectively (Table 1, entries 1 and 2).

We checked if a similar reasoning applied to $4\mathbf{b}$. Thus, samples of $4\mathbf{b}/n\text{-BuLi}$ in Et_2O and THF were prepared from $3\mathbf{b}$ in the above conditions.¹³ Recording the ^6Li NMR spectrum in Et_2O (Fig. 12, top) showed two peaks at 2.76 ppm and 1.72 ppm of similar integrations that we assign to the 1:1 $4\mathbf{b}/n\text{-BuLi}$ complex.¹³ In this solvent, the mixed aggregate concentration amounts approximately 30% (based on the ^6Li integration) for a 27% ee (entry 3 of Table 1). In THF (Fig. 13, bottom), 67% complex, identified by the two ^6Li peaks at 1.96 ppm and 1.59 ppm, is formed, a figure to relate to the 75% ee measured for the same reaction in this solvent (Table 1, entry 4).

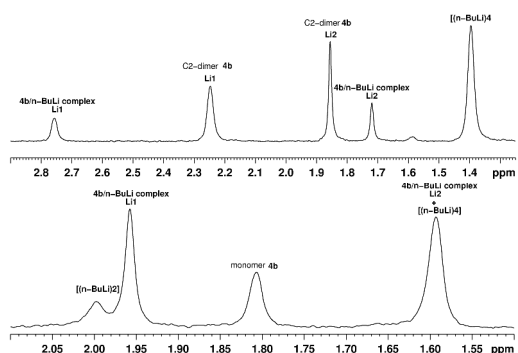


Fig. 12 ^6Li NMR spectra of **4b** + $n\text{-BuLi}$ in $\text{Et}_2\text{O}_{d10}$ (top) and in THF_{d8} (bottom)

Plotting the ees vs. the $[\text{4}/n\text{-BuLi}]$ confirms the good correlation ($R^2 \approx 0.99$, Fig. 12).

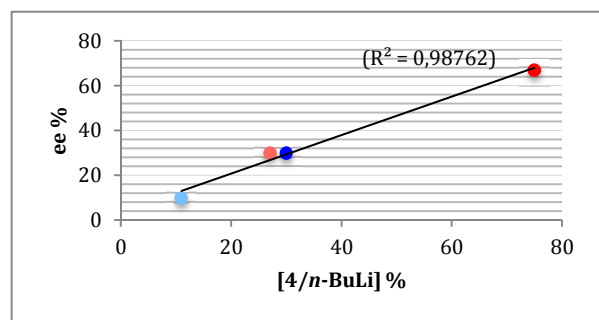


Fig. 12 Correlation between the ees and $[\text{4}/n\text{-BuLi}]$ (blue dots: **4a**, red dots **4b**) in Et_2O (light dots) and THF (dark dots)

These figures suggest that : i) the reaction rate of the $4/n\text{-BuLi}$ mixed aggregate is significantly higher than that of the $[(n\text{-BuLi})_2] + (n\text{-BuLi})_4$ mixture with which it is in equilibrium;¹⁴ ii) this aggregate is directly involved in the kinetically-determining step of the enantioselective alkylation of *o*-tolualdehyde (Scheme in Table 1). It is however difficult to go further in the conclusions since the Curtin-Hammett principle forbids to correlate the aggregate and the enantioselectivity. Complementary NMR investigations will soon be launched to identify a fully-loaded complex incorporating the reactive aggregate and the aldehyde (or another less reactive electrophile). The possible involvement of still unknown trimeric entities we have postulated to rationalize a set of results obtained with a different class of lithium amide suggests could also be considered.¹⁵

Finally, the differences between amides **4** and those studied before by Hogeveen,^{4a} Hilmersson^{4c-v} and Williard⁶ (among which amides **6** and **7**, Fig. 13) are worth pointing out.

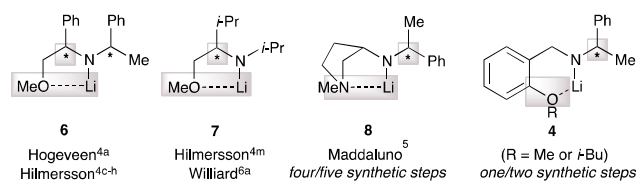


Fig. 13 Structural comparison of CLAs **6** (Hogeveen and Hilmersson), **7** (Hilmersson and Williard), **8** (3APLi) and **4**.

The CLA employed by these authors all bear an heteroatom coordinating the lithium cation (such as the OMe group) and

this intramolecular interaction elicits a rigid folding of the amide which seems to favor high ees. All these CLAs also bear a stereogenic carbon close by the heteroatom, the amide **6** bearing even two stereogenic centers. In contrast, the structure of amide **4** places the heteroatom responsible of the coordination on one appendage of the amide and the stereogenic carbon on the second one, following previous observations on 3-aminopyrrolidine lithium amides (3APLi **8**, Fig. 13).⁵⁰

Experimental section

General aspects

All synthetic and spectroscopic manipulations were carried out under an atmosphere of anhydrous and deoxygenated argon in flame- or oven-dried glassware. Argon was dried and deoxygenated by bubbling through a commercial solution of $n\text{-BuLi}$ in hexanes. All solvents and reagents were purchased from commercial sources at the highest commercial quality and used without further purification, unless otherwise stated. Tetrahydrofuran (THF), diethyl ether (Et_2O), tetrahydrofuran- d_8 (THF_{d8}) and diethyl ether- d_{10} ($\text{Et}_2\text{O}_{d10}$) were distilled over sodium and benzophenone. Pentane and cyclohexane were distilled over calcium hydride. Methanol and N,N' -dimethylformamide (DMF) were purchased in anhydrous form and used without further purifications. ^6Li (95%) was washed in freshly distilled pentane prior the use. 2-Methoxybenzaldehyde and salicylaldehyde were distilled over powdered K_2CO_3 at reduced pressure. 2-Methylbromopropane was distilled over P_2O_5 . *o*-Tolualdehyde was diluted in CH_2Cl_2 , washed with saturated aq NaHCO_3 , then H_2O , dried (MgSO_4), concentrated (rotavapor[®]) and distilled under vacuum in the presence of powdered K_2CO_3 . Then, it was stored in glass ampoules under argon in the dark. Cyclooctene (COE) and hexamethyldisilane (HMDS) were distilled over CaH_2 , while squalene (SQA) was used without purifications. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck 0.25 mm silica gel coated aluminium plates using UV light at 254 nm as visualizing agent and aqueous KMnO_4 solution followed by heating as developing agent. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. Routine ^1H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance DMX-300 spectrometer at 300 MHz and 75 MHz, respectively, and calibrated using residual undeuterated solvent as an internal reference. The solvent was deuteriochloroform (CDCl_3) with a calibration at 7.26 for ^1H spectra and 77.16 for ^{13}C spectra. Chemical shifts (δ) are given in parts per million (ppm) and the coupling constants (J) in hertz (Hz). The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept = septuplet, m = multiplet, br = broad, ps = pseudo. IR spectra were recorded by transmission on a PerkinElmer 16PC IRTF spectrometer. ESI-MS spectra were obtained by direct injection of the sample solution using a Thermo LCQ Advantage Max with acetonitrile as solvent. Every signal is expressed in mass/charge (m/z) and the peak abundance is reported as a percentage in relationship with the basic peak. Optical rotations were recorded on a PerkinElmer Model 341 polarimeter at 20 °C using the sodium D line (589 nm) and $[\alpha]_D$ are given in units of $10^{-1} \text{ deg cm}^{-2} \text{ g}^{-1}$. Elemental analyses were carried out on a Thermo Scientific FLASH 2000 Series CHNS-O Analyzer. Chiral HPLC separations

were performed on a Thermo Scientific SpectraSYSTEM™ UV100 (for 1-*ortho*-tolylpenta-1-ol 5: Chiracel® OD-H 250 x 4.6 mm 5 μ L column, flow: 1 mL min⁻¹, mobile phase: *n*-heptane / 2-isopropanol 99:1, retention times: 5.50 min (*S* enantiomer), 6.20 min (*R* enantiomer)). The commercially available *n*-BuLi solution (1.6 M in hexanes) and the synthesized lithium-6 *n*-BuLi solutions (in pentane, in THF₆₈ and in Et₂O₁₀) were titrated using a procedure reported by Duhamel.¹⁶

10 Procedures

(*R*)-*N*-(2-Methoxybenzyl)-1-phenylethanamine 3a. In an apparatus equipped with a Dean-Stark trap arranged for azeotropic removal of water, a mixture of (*R*)-(α -methylbenzylamine (1.90 mL, 14.9 mmol) and 2-methoxybenzaldehyde **1a** (2.0 mL, 16.5 mmol) was refluxed in anhydrous cyclohexane (40 mL) for 2 hours under argon atmosphere. After cooling down to room temperature (rt), the solution was concentrated to give crude imine **2a** in quantitative yield. This crude product was dissolved in anhydrous methanol (30 mL) and NaBH₄ (0.8 g, 21.2 mmol) was slowly added at 0°C. After 10 minutes, the temperature was raised up to room temperature, and the resulting reaction mixture was stirred at rt for 2 hours. The reaction mixture was then concentrated under vacuum and 30% aqueous NH₄OH (50 mL) was introduced. The product was extracted with Et₂O (3 x 30 mL) and the combined organic layers were washed with brine (2 x 50 mL), dried over MgSO₄, filtered and concentrated at reduced pressure to give crude **3a** as a yellow oil. The latter was then diluted in Et₂O (100 mL) and treated with 1N aqueous HCl (10 mL). The white solid formed was filtered, washed with Et₂O and dissolved with 4N aqueous NaOH (40 mL). The basic solution was extracted with Et₂O (3 x 30 mL), and the combined organic layers were washed with brine (1 x 100 mL), dried over MgSO₄, filtered and concentrated to give pure **3a** as a colorless oil (3.6 g, 14.8 mmol, 99%). ¹H NMR (300 MHz, CDCl₃, 298K) δ : 7.29-7.06 (m, 7H), 6.83-6.75 (m, 2H), 3.72 (s, 3H), 3.68 (q, *J* = 6.6 Hz, 1H), 3.56 (m [qAB], 2H), 1.84 (br. s, 1H), 1.26 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (75MHz, CDCl₃, 298K) δ : 157.8, 145.9, 130.0, 128.7, 128.5 (2C), 128.2, 127.0 (2C), 126.9, 120.5, 110.4, 57.3, 55.3, 47.3, 24.7. IR (neat): 2960, 1600, 1238, 1028, 750, 699 cm⁻¹. ESI-MS: *m/z* 519.07 (100, 2MH⁺ + 2H₂O), 242.20 (93, MH⁺). [α]_D²⁰ = +56.4 (c = 1.13, CHCl₃). Elemental analysis: Anal. Calcd for C₁₆H₁₉NO: C 79.63, H 7.94, N 5.80; found C 80.54, H 8.17, N 5.92.

2-Isobutoxybenzaldehyde 1b. In a three-necked round flask equipped with a bubble condenser, and placed under argon, 2-methylbromopropane (14.0 mL, 128.7 mmol) and K₂CO₃ (12.5 g, 9.7 mmol) were slowly added at room temperature to a solution of salicylaldehyde (5.40 mL, 50.7 mmol) in anhydrous DMF (200.0 mL). After 10 minutes at rt the yellowish solution was heated at 40°C for 16h. Aqueous saturated NH₄Cl (20 mL) was introduced after cooling to room temperature, followed by 1N aqueous HCl (20 mL). The mixture was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with aqueous saturated NaHCO₃ solution (2 x 100 mL) then brine (2 x 100 mL), dried over MgSO₄, filtered and concentrated at reduced pressure. Aldehyde **1b** was recovered as a yellow oil (9.90 g, 50.7 mmol, >99%) and used for the next step without further purifications. ¹H NMR (300 MHz, CDCl₃, 298K) δ : 10.55 (s, 1H), 7.82 (dd, *J* = 8.0 and 2.0 Hz, 1H), 7.52 (ps. td, *J* = 8.0 and 2.0 Hz, 1H), 7.03-6.95 (m, 2H), 3.84 (d, *J* = 6.4 Hz, 2H), 2.24-2.08 (m, 1H), 1.06 (d, *J* = 6.6 Hz, 6H). ¹³C NMR

(75MHz, CDCl₃, 298K) δ : 189.8, 161.6, 136.0, 128.1, 124.8, 120.4, 112.5, 74.7, 28.3, 19.2 (2C). IR (neat): 2958, 2873, 1685, 1597, 1239 cm⁻¹. ESI-MS: *m/z* 179.05 (100, MH⁺).

(*R*)-*N*-(2-Isobutoxybenzyl)-1-phenylethanamine 3b. In an apparatus equipped with a Dean-Stark trap arranged for azeotropic removal of water, a mixture of (*R*)-(α -methylbenzylamine (2.00 mL, 15.7 mmol) and 2-isobutoxybenzaldehyde **1b** (3.0 g, 16.7 mmol) in anhydrous cyclohexane (40 mL) was refluxed for 2 hours. After cooling down to room temperature, the solution was concentrated to give crude imine **2b** in quantitative yield. This crude product was diluted in anhydrous methanol (40 mL), and NaBH₄ (0.86 g, 22.7 mmol) was slowly added at 0°C. After 10 minutes, the temperature was raised up to rt and the resulting reaction mixture was stirred at this temperature for two hours. The reaction mixture was then concentrated under vacuum and 30% aqueous NH₄OH (50 mL) was introduced. The product was extracted with Et₂O (3 x 30 mL) and the combined organic layers were washed with brine (2 x 50 mL), dried over MgSO₄, filtered and concentrated at reduced pressure to give crude **3b** as a yellow oil. The latter was then diluted in Et₂O (100 mL) and treated with 1N aqueous HCl (10 mL). The white solid formed was filtered, washed with Et₂O and dissolved with 4N aqueous NaOH (40 mL). The basic solution was then extracted with Et₂O (3 x 30 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried over MgSO₄, filtered and concentrated to give pure **3b** as a pale yellowish oil (3.0 g, 10.5 mmol, 67%). ¹H NMR (300 MHz, CDCl₃, 298K) δ : 7.38-7.13 (m, 7H), 6.92-6.84 (m, 2H), 3.82-3.73 (m, 5H), 3.61-3.57 (m [B part of qAB], 1H), 2.12 (sept, *J* = 6.6 Hz, 1H), 1.90 (br. s, 1H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.04 (dd, *J* = 6.6 and 2 Hz, 6H). ¹³C NMR (75MHz, CDCl₃, 298K) δ : 157.5, 145.8, 130.3, 128.6, 128.5 (2C), 128.3, 127.0 (2C), 126.9, 120.3, 111.1, 74.3, 57.3, 47.8, 28.5, 24.7, 19.6, 19.5. IR (neat): 2959, 1601, 1451, 1367, 1237, 1116, 1029, 749, 699 cm⁻¹. ESI-MS: *m/z* 284.13 (100, MH⁺). [α]_D²⁰ = +51.0 (c = 1.30, CHCl₃). Elemental analysis: Anal. Calcd for C₁₉H₂₅NO: C 80.52, H 8.89, N 4.94; found C 80.62, H 8.90, N 5.01.

General procedure for the alkylation of ortho-tolualdehyde in the presence of 4a-b/n-butyllithium mixed aggregates. A solution of *n*-BuLi (1.6 M in hexanes; 0.5 mL, 0.75 mmol) was added at -20°C to a solution of amine **3** (0.75 mmol) in anhydrous ethereal solvent (THF or Et₂O, 15 mL). After stirring at -20°C for 20 minutes, a second aliquot of *n*-BuLi (1.6M in hexanes; 0.5 mL, 0.75 mmol) was added dropwise and the reaction was let stirring at this temperature for 30 additional minutes. Then the mixture was cooled down to -78°C and aged for 30 minutes. A solution of *o*-tolualdehyde (0.5 mmol) in the same solvent (THF or Et₂O, respectively, 2 mL) was added for a 5 minutes period and, after 2 hours, the reaction was quenched with 3N aqueous HCl (10 mL). The medium was let reaching room temperature and the resulting aqueous layer was extracted with Et₂O (3 x 15 mL). The organic layers were combined, washed with aqueous saturated NaHCO₃ (2 x 10 mL) then brine (1 x 10 mL), dried (MgSO₄), filtered and concentrated. The resulting alcohol (**5**) was purified by flash column chromatography.

1-ortho-Tolylpenta-1-ol 5. Purification of crude **5** by column chromatography (Pentane / Et₂O 10:1) gave the pure **5** as a colorless oil. Yields and ees are gathered Table 1. ¹H NMR (300 MHz, CDCl₃, 298K) δ : 7.39 (d, *J* = 7.2 Hz, 1H), 7.20-6.95 (m, 3H), 4.85 (dd, *J* = 7.2 and 5.3 Hz, 1H), 2.25 (s, 3H); 1.74 (br. s, 1H), 1.70-1.50 (m, 2H), 1.50-1.10 (m, 4H), 0.83 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (75MHz, CDCl₃, 298K) δ : 143.2,

134.6, 130.5, 127.2, 126.4, 125.3, 70.8, 38.0, 28.3, 22.8, 19.2, 14.2. IR (neat): 3344 (OH), 2957, 2856, 1465 cm^{-1} . ESI-MS: m/z 178 (11, M^+), 121 (100, $\text{M}^+ - n\text{-Bu}$). The data are in agreement with those reported in the literature⁵⁰

⁵ **[⁶Li] *n*-Butyllithium “salt-free solution” in pentane.**^{5p,v,17} Finely cut 6-lithium metal ribbon (0.6 g, 100 mmol), 0.5% (weight) of sodium (ca. 3.0 mg, 0.12 mmol), and three small pieces of broken glass were introduced into a two-necked pear-shaped flask (100 mL) equipped with a glass stopper and a condenser fitted with a balloon of dry argon. The metallic cuttings were covered with octadecane (10 g), and the solution was heated (reflux of octadecane: 317°C) with a hot air gun with vigorous stirring. When a maximum amount of the lithium was melted, the flask was placed in a cold bath (–40°C) allowing the lithium to precipitate as a fine shiny shot. The octadecane was pumped off with a syringe and the residue was washed with freshly distilled pentane (15 mL). After intensive stirring, the pentane was removed and the metal was washed twice with this same solvent. The condenser was quickly replaced by a septum and a new amount of 10 mL of pentane was introduced. Then, a solution of freshly distilled *n*-bromobutane (4.3 mL, 40 mmol) in pentane (12 mL) was syringed at room temperature over a 30 minutes period. The resulting reaction mixture was stirred for 20 hours at room temperature under dry argon. The hydrocarbon solution was then pumped off the flask with a syringe and directly inserted into centrifugation tubes placed under dry argon. The LiBr salt was centrifuged, and the clear final solution was collected in a dry flask flushed under dry argon, then titrated (1.0 to 1.5 M) and kept until further use.

[⁶Li] *n*-Butyllithium “salt-free solution” in THF_{d8}.^{5p,v,17} A solution of [⁶Li] *n*-butyllithium in pentane prepared above (2.5 mL) was syringed into a tube fitted with a septum and flushed under dry argon. The tube was then placed under vacuum (20 mmHg) for 1 hour to evaporate the pentane. The resulting white solid was then dissolved in freshly distilled THF_{d8} and concentrated under vacuum for 1 hour to evaporate the last traces of pentane. A new volume of THF_{d8} (3.0 to 3.5 mL) was finally added at –78°C, and the resulting solution was titrated (0.5 to 0.7 M).

[⁶Li] *n*-Butyllithium “salt-free solution” in Et₂O_{d10}. A solution of [⁶Li] *n*-butyllithium in pentane prepared above (2.5 mL) was syringed into a tube fitted with a septum and flushed under dry argon. The tube was then placed under vacuum (20 mmHg) for 1 hour to evaporate the pentane. The resulting white solid was then dissolved in freshly distilled Et₂O_{d10} and concentrated under vacuum for 1 hour to evaporate the last traces of pentane. A new volume of Et₂O_{d10} (3 to 3.5 mL) was finally added at –78°C and the resulting solution was titrated (0.5 to 0.7 M).

[⁶Li]-Lithium amide 4a in Et₂O_{d10} solution. A solution of amine **3a** (24.1 mg, 0.1 mmol) in freshly distilled Et₂O_{d10} (0.6 mL) was prepared into a dry 5-mm NMR tube fitted with a septum and flushed under argon. A 0.5 to 0.7 M [⁶Li] *n*-BuLi Et₂O_{d10} solution (1 equiv) was added dropwise at –20°C with a syringe to the above solution. The tube was vigorously shaken and, after 10 minutes, it was dropped in the pre-cooled (–78°C) NMR probe.

[⁶Li]-Lithium amide 4a in THF_{d8} solution. A solution of amine **3a** (24.1 mg, 0.1 mmol) in freshly distilled THF_{d8} (0.6 mL) was prepared into a dry 5-mm NMR tube fitted with a septum and flushed under argon. A 0.5 to 0.7 M [⁶Li] *n*-BuLi THF_{d8} solution (1 equiv) was added dropwise at –20°C with a syringe to the above solution. The tube was vigorously shaken and, after 10 minutes, it was dropped in the pre-cooled (–

78°C) NMR probe.

[⁶Li]-4a/*n*-BuLi mixed aggregate in Et₂O_{d10} solution. A second equivalent of [⁶Li] *n*-butyllithium (0.5 to 0.7 M Et₂O_{d10} solution) was added at –20 °C into a dry 5-mm NMR tube containing a solution of [⁶Li]-lithium amide **4a** in Et₂O_{d10}. The tube was vigorously shaken and, after 10 minutes, it was dropped in the pre-cooled (–78°C) NMR probe.

[⁶Li]-4a/*n*-BuLi mixed aggregate in THF_{d8} solution. A second equivalent of [⁶Li] *n*-butyllithium (0.5 to 0.7 M THF_{d8} solution) was added at –20 °C into a dry 5-mm NMR tube containing a solution of [⁶Li]-lithium amide **4a** in THF_{d8}. The tube was vigorously shaken and, after 10 minutes, it was dropped in the pre-cooled (–78°C) NMR probe.

NMR Instrumentation

NMR spectra were recorded at 195K and 250K on a Bruker AVIII 500 spectrometer operating at 500.13 MHz for ¹H, 125.13 MHz for ¹³C and 73.60 MHz for ⁶Li. Experiments were run under TopSpin (version 2.1, Bruker Biospin, Karlsruhe) with a BBFO{¹H,X} probe and a z gradient coil giving a maximum gradient of 50 G cm^{-1} . ¹H and ¹³C chemical shifts were referenced to the solvent residual signals (for Et₂O_{d10} at δ 3.34 ppm (¹H) and 14.5 ppm (¹³C)), for THF_{d8} at δ 1.73 (¹H) and 25.31 ppm (¹³C)). Lithium spectra were referenced to external 0.3 M ⁶LiCl solution in THF_{d8} (δ 0.0).

1D NMR Measurements. The proton and lithium one dimensional experiments were recorded with standard parameters. ⁶Li NMR experiments with selective proton decoupling were carried out with a 1D sequence using continuous wave decoupling. In order to remove ¹³C - ¹H coupling, the one-dimensional ¹³C spectra were recorded with broadband proton decoupling.

⁶Li/¹H HOESY¹⁸ The following parameters were used for acquiring and processing the spectrum in phase-sensitive mode: 128 experiments with 1024 data points and 16 scans each were recorded; pure phase line shapes were obtained by using time proportional phase incrementation (TPPI) phase cycling; variable mixing times, depending on the sample, were used; one time zero filling in f1; $\pi/2$ and $\pi/3$ shifted sine square window functions were applied to f2 and f1 dimensions, respectively, before Fourier transformation.

¹H/¹H COSY¹⁹ The following parameters were used for acquiring and processing the spectra in absolute values: 256 experiments with 2048 data points and 8 scans each were recorded; one time zero filling in f1; pure sine bell window function was applied before Fourier transformation.

¹H/¹³C HMQC²⁰ The following parameters were used for acquiring and processing the spectra in phase-sensitive mode: 512 experiments with 2048 data points and 8 scans each were recorded; pure phase line shapes were obtained by using time proportional phase incrementation (TPPI) phase cycling, one time zero filling in f1; $\pi/2$ shifted sine square window functions were applied to f2 and f1 dimensions before Fourier transformation.

¹H/¹H NOESY²¹ The following parameters were used for acquiring and processing the spectra in phase-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 (TPPI) phase cycling, variable mixing times, depending on the sample, were used; one time zero filling in f1; $\pi/2$ shifted sine square window functions were applied to f2 and f1 dimensions before Fourier Transformation.

¹H DOSY²² The experiments were acquired with the standard Bruker ledbpgp2s program2 using 16 t1 increments of 32

transients. The acquisition time was 1 s and the relaxation delay was 2.5 s (D1). Diffusion time was between 0.5 and 0.05 s (D20) and rectangular gradient pulse duration was between 2.5 and 1.0 ms (P30). Gradient recovery delays of 150 ms followed the application of each gradient pulse. Data was accumulated by linearly varying the diffusion encoding gradients over a range from 2 to 95 % for 16 gradient increment values.

DOSY processing. Processing of NMR data was performed using Topspin, the constructor's program (Bruker), and the diffusion coefficient was measured by T1/T2 relaxation module.

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Notes and references

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† Electronic Supplementary Information (ESI) available: all monodimensional and bidimensional NMR spectra. See DOI: 10.1039/b000000x/

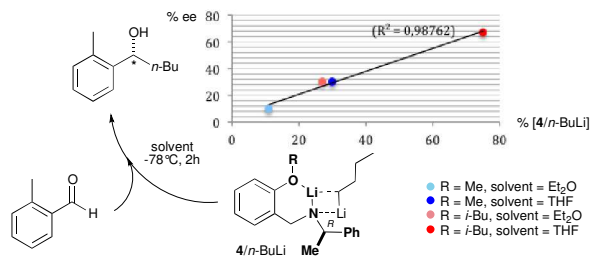
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Table of content :

Probing Solvent Effects on Mixed Aggregates Associating a Chiral Lithium Amide and *n*-BuLi by NMR: From Structure to Reactivity

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NMR shows a direct correlation between the concentration of a chiral lithium amide/*n*-BuLi complex and ee's of a test reaction.