

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/256091231>

Structure of the Mixed Aggregates between a Chiral Lithium Amide and Phenyllithium or Vinylolithium

ARTICLE *in* ORGANOMETALLICS · JULY 2012

Impact Factor: 4.13 · DOI: 10.1021/om300352p

CITATIONS

13

READS

12

5 AUTHORS, INCLUDING:



[Hassan Oulyadi](#)

Université de Rouen

67 PUBLICATIONS 912 CITATIONS

SEE PROFILE



[Catherine Fressigné](#)

Université de Rouen

28 PUBLICATIONS 435 CITATIONS

SEE PROFILE



[Anne Harrison-Marchand](#)

Université de Rouen

49 PUBLICATIONS 625 CITATIONS

SEE PROFILE

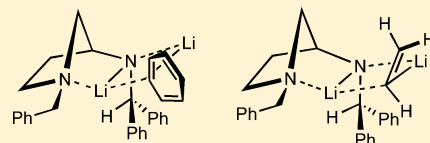
Structure of the Mixed Aggregates between a Chiral Lithium Amide and Phenyllithium or Vinylithium

Hassan Oulyadi, Catherine Fressigné, Yi Yuan, Jacques Maddaluno, and Anne Harrison-Marchand*

Laboratoire COBRA de l'Université de Rouen, INSA de Rouen et CNRS, UMR 6014 & FR 3038, IRCOF, Rue Tesnière, 76821 Mont St Aignan Cédex, France

Supporting Information

ABSTRACT: The structures, in THF, of 1:1 mixed aggregates of phenyllithium or vinylithium with a chiral lithium amide derived from a 3-aminopyrrolidine are proposed on the basis of a multinuclear (^1H , ^6Li , ^{13}C) NMR spectroscopic and DFT theoretical studies. In both cases, the lithium amide adopts an azanorbornyl-like folding and establishes stable coordinations with the C sp^2 reactants, leading to rigid complexes that are expected to be at the origin of the inductions observed for the alcohols resulting from the condensation of these mixed aggregates on *ortho*-tolualdehyde.



INTRODUCTION

Unlike alkylolithium reactants, aryllithium and vinylithium have been little involved in enantioselective nucleophilic additions,^{1,2} and to our knowledge, the structural descriptions of their mixed aggregates with a (chiral) dipolar inductor are seldom. Previous synthetic results obtained in our laboratory refer to the use of phenyllithium,^{1k} then vinylithiums,^{2b} in the enantioselective hydroxyarylations and hydroxyvinylations of *ortho*-tolualdehyde, respectively. ee's in the 56–80% range were obtained in the presence of 3-aminopyrrolidine lithium amides (3APLi) used as chiral inductors. Pursuing our efforts to master the stereochemical outcomes of these transformations,³ we decided to characterize the complexes formed between 3-aminopyrrolidine lithium amide **1** and phenyllithium **2**, and then **1** with vinylithium **3** (Figure 1). This new study addresses two important questions: (i) Can an sp^2 -hybridized organolithium derivative form 1:1 mixed aggregates with a lithium amide? (ii) Is the structure adopted by the resulting complexes similar to that established before for the lithiated sp^3 carbon atoms?⁴ Indeed, with the latter, 1:1 3APLi/ $\text{C}^{\text{sp}^3}\text{Li}$ (C^{sp^3} being a Me or *n*-Bu) mixed aggregates organized around a N–Li– C^{sp^3} –Li quadrilateral were depicted in THF or Et_2O solution.³ They constantly showed an azanorbornyl-like folding of the amide due to an intramolecular coordination of the pyrrolidinic nitrogen with the lithium of the amide.

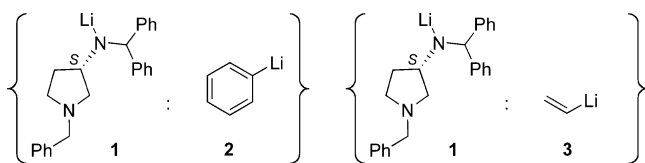


Figure 1. Chiral lithium amide **1** and C sp^2 organolithiums **2** (phenyllithium) and **3** (vinylithium).

RESULTS AND DISCUSSION

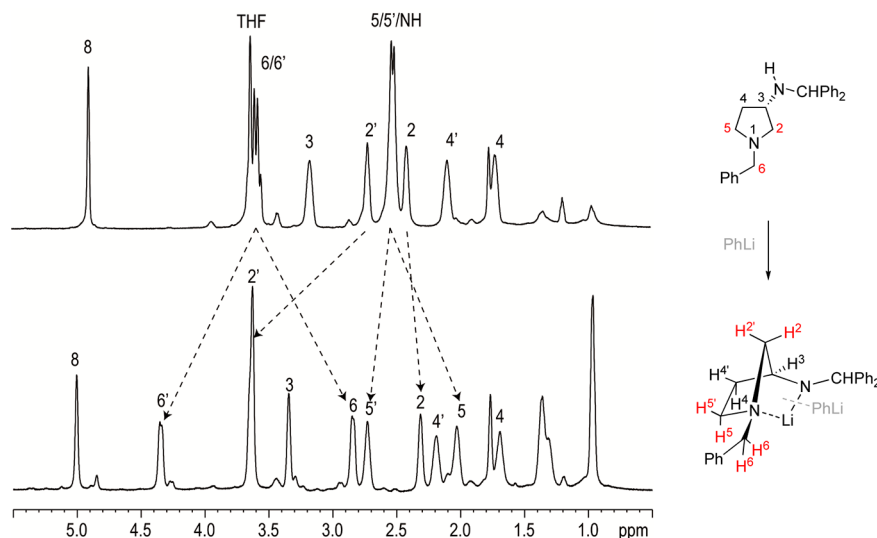
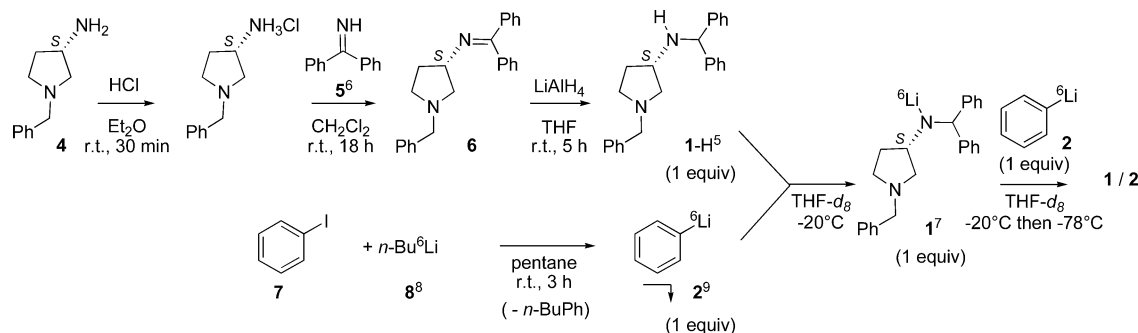
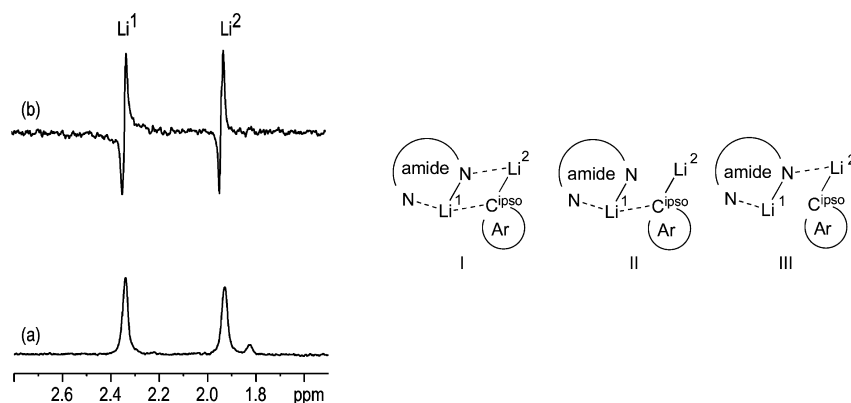
Mixed Aggregate [3-Aminopyrrolidine Lithium Amide **1/Phenyllithium **2**].** The two ^6Li -labeled partners 3-aminopyrrolidine **1** and phenyllithium **2** were first synthesized following well-known protocols (Scheme 1). Thus, the amine precursor of **1** (**1-H**) was obtained in a two-step synthetic scheme⁵ reacting, first, the ammonium chloride of commercial (3*S*)-1-benzyl-3-aminopyrrolidine **4** and freshly prepared diphenylmethanimine **5**.⁶ The resulting imino intermediate **6** was next reduced in the presence of LiAlH_4 to afford amine **1-H**. The latter was then deprotonated, at -20°C in deuteriated THF ($\text{THF-}d_8$), adding 1.2 equiv of a freshly prepared solution of ^6Li -labeled phenyllithium **2** in superdry $\text{THF-}d_8$.⁷ Reactant **2** was prepared beforehand mixing stoichiometric amounts of iodobenzene **7** and ^6Li -labeled *n*-butyllithium **8**⁸ in pentane.⁹ Note that, in hydrocarbon solvents, phenyllithium precipitates, which helps the separation from the reaction mixture, since, at the end of the halogen–metal exchange, there is no more syringing and pumping the pentane solution containing the undesired organic and inorganic species (residual starting material, Wurtz byproduct, lithium iodide) out of the flask. The resulting crystalline phenyllithium was washed with freshly distilled pentane, and then dissolved in freshly distilled $\text{THF-}d_8$. The resulting solution was titrated following the procedure of Duhamel and Plaquevent ($c = 1.2 \text{ mol/L}$).¹⁰ Complex **1/2** was thus prepared by adding, still at -20°C , 1 equiv of **2** on the $\text{THF-}d_8$ solution of **1**. The final solution containing the 1:1 **1/2** mixed aggregate was cooled to -78°C for the NMR analyses.

A set of monodimensional NMR experiments was first registered. Comparing with the one of amine **1-H**, the proton spectrum of **1/2** displays a strong splitting of the H^2 , H^5 , and H^6 proton pairs (Figure 2, left). This has been shown before to be characteristic of an azanorbornyl-like folding of the pyrrolidinic ring triggered by the intramolecular coordination

Received: April 27, 2012

Published: June 20, 2012

Scheme 1. Synthetic Scheme for the Preparation of Complex 1/2

Figure 2. 1D proton NMR spectra (500 MHz) of 1 and 1/2 in THF-*d*₈ at -78 °C.Figure 3. 1D ⁶Li NMR spectra of 1/2 mixture in THF-*d*₈ at -78 °C: (a) 1D ⁶Li and (b) 1D ⁶Li-INADEQUATE.

between the lithium of the amide and the pyrrolidinic nitrogen (Figure 2, right).^{3a}

The ⁶Li spectrum evidences two peaks of similar intensities with integration at δ 1.93 ppm and δ 2.35 ppm (Figure 3, bottom left). The measurement of a scalar coupling on the ⁶Li-INADEQUATE recording between these two nuclei (Figure 3, top left) is in accordance with the formation of a single species incorporating the two lithium atoms and resulting from the mixed aggregation between 1 and 2. By analogy with our previous work,³ we first assumed that the two lithium atoms belonged to a N–Li–C–Li quadrilateral core, such as I (Figure 3, right). Unfortunately, we were unable to buttress this

hypothesis using the ¹³C NMR data since the *ipso*-carbon corresponds to a poorly resolved multiplet (see page S3 in the Supporting Information). Thus, at this stage of the study, open mixed aggregates, such as II or III, cannot be excluded.

The NOESY experiment (Figure 4, left) suggests that H⁸ and H⁴, on one hand, and H⁸ and H⁵, on the other, are close to each other, in agreement with a puckered pyrrolidine core. The same experiment also exhibits strong correlations between protons H⁵ and H⁶. In addition, the correlations observed between the two diastereotopic H² protons of 1 and one H^{ortho} of 2 suggest that these two sorts of protons are also close and, therefore, that the phenyl ring lies along the methylenic bridge (CH²H^{2'})

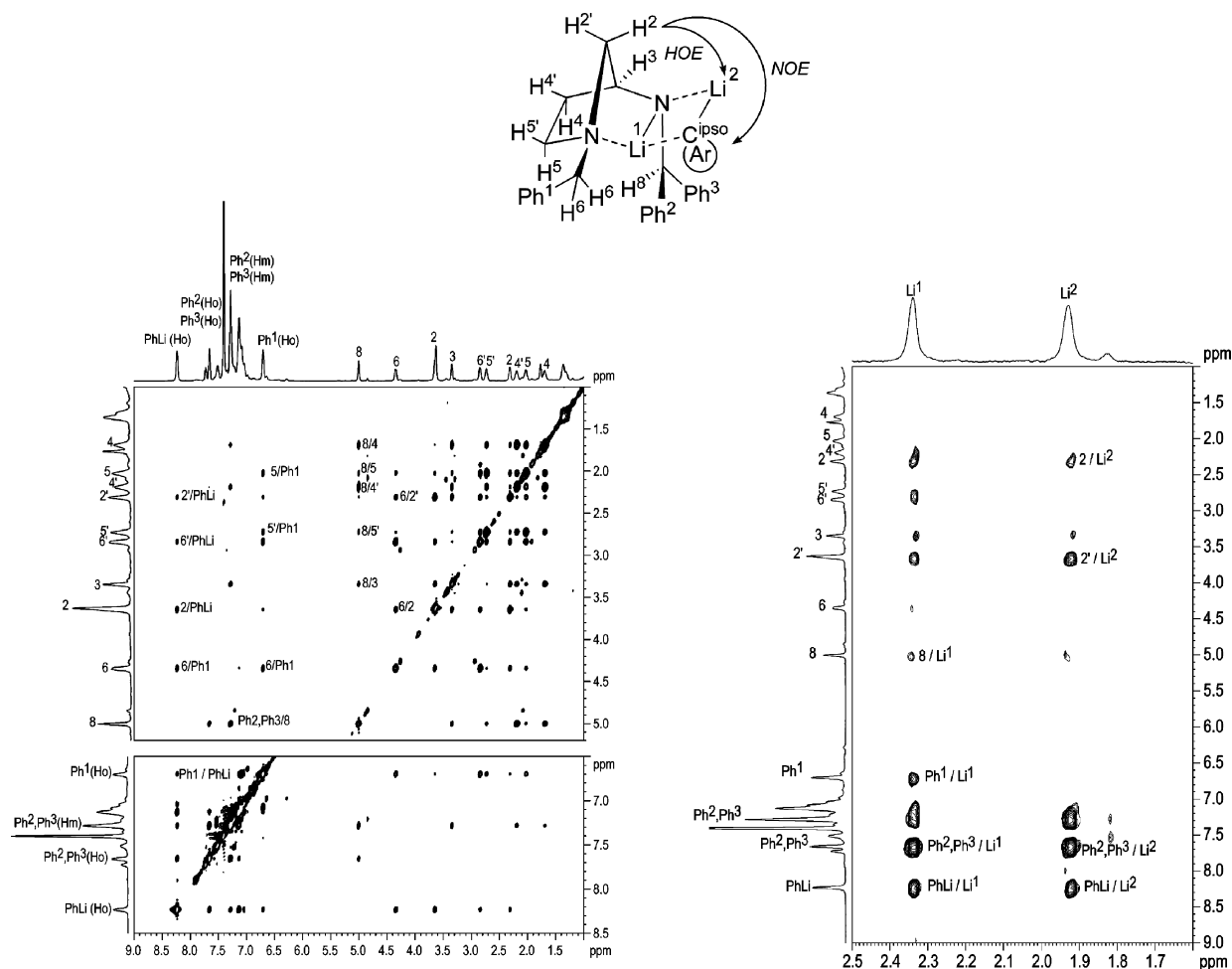


Figure 4. 2D NMR spectra of 1/2 in THF- d_8 at $-78\text{ }^{\circ}\text{C}$: $^1\text{H},^1\text{H}$ -NOESY (left) and $^6\text{Li},^1\text{H}$ -HOESY (right).

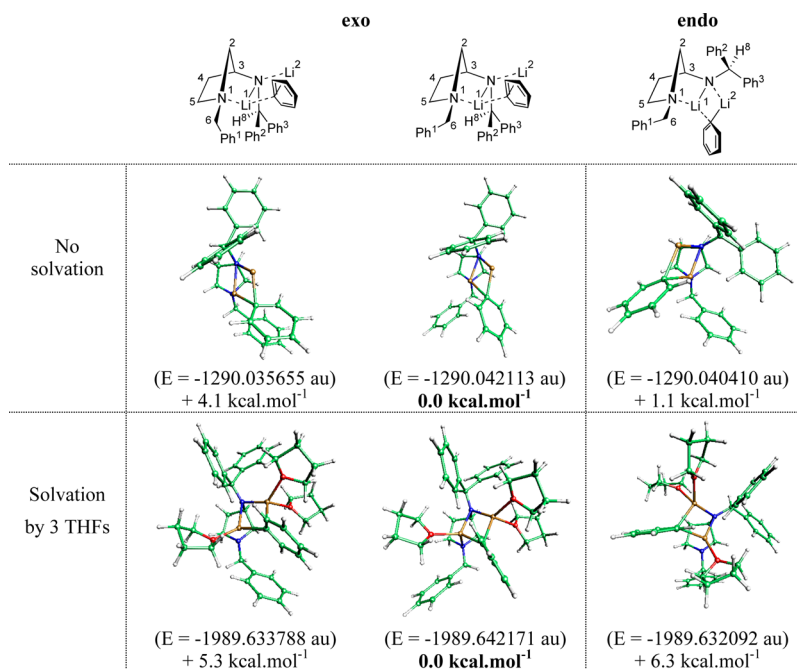


Figure 5. DFT optimized geometrical arrangements of the *exo* (left) and *endo* (right) topologies of the mixed aggregates 1/2: (top line) unsolvated structures and (bottom line) solvated structures.

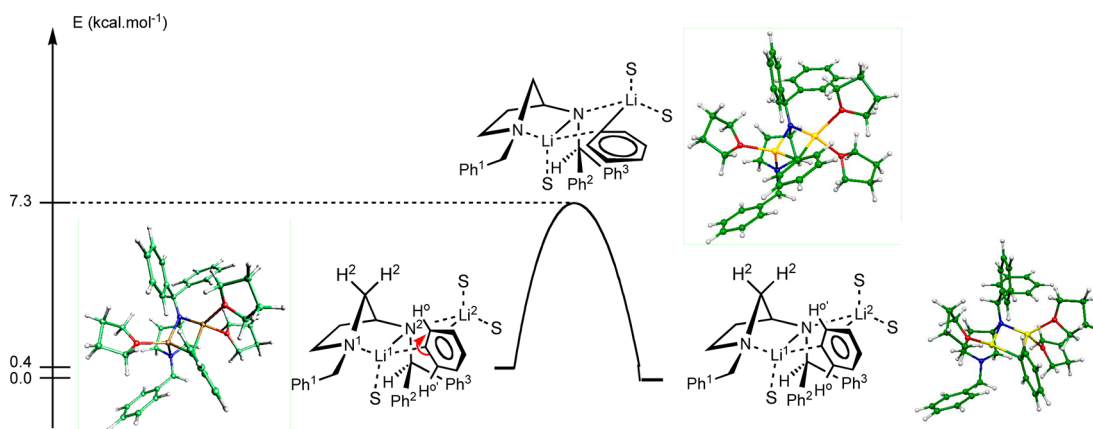
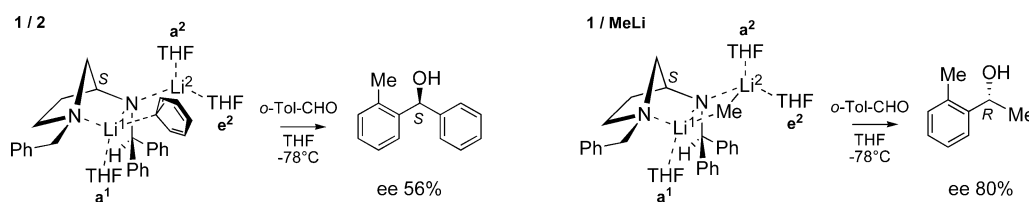


Figure 6. Rotation of the phenyl ring around the *para*–*ipso* carbon axis in the aggregate 1/2.

Scheme 2. Nucleophilic Addition of 1/2 (Left) and 1/MeLi (Right) onto *o*-Tolualdehyde at -78°C in THF



of **1** (Figure 4).³ Such an arrangement could be confirmed thanks to a $^6\text{Li}/^1\text{H}$ HOESY experiment (Figure 4, right), 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^2 (confirming **2** is tightly “bound” along the methylenic bridge of the amide). The fact that both H^{ortho} and Li^2 are in the immediate vicinity of the H^2 protons is in favor of a type-I mixed aggregate.

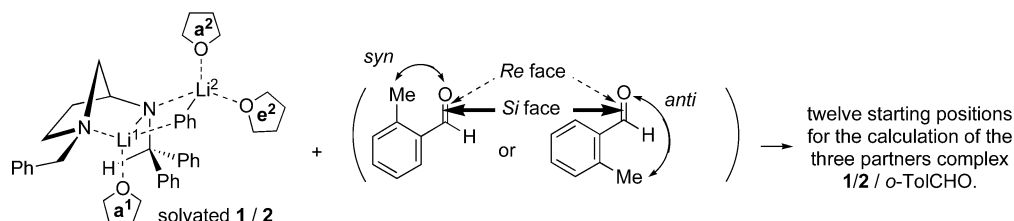
DFT calculations (run like in our previous papers with the B3P86 functional, using the 6-31G** basis set and the Jaguar 5.0 software; see computational details on page S4 in the Supporting Information) were complementarily undertaken to examine the structures built out of the NMR data. A full optimization of the unsolvated mixed aggregate 1/2 was first performed (Figure 5, top). Aggregates organized around a N–Li–C–Li quadrilateral core following an *exo* (PhLi facing the C^2 bridge, Figure 5, top left) or *endo* (PhLi facing the C^4 – C^5 bridge, Figure 5, top right) topology were studied. Calculations based on the *exo* arrangement led to two local minima, which correspond to different orientations of the *N*-benzyl group. They are separated by about 4 kcal·mol^{−1} in favor of the conformer in which the phenyl and benzyl appendages are *anti* one to the other. On the other hand, the *endo* conformer afforded a single optimum that is less stable than the *exo* isomer of lowest energy, but by only ≈ 1 kcal·mol^{−1}.

The importance of solvation on the DFT modeling of the aggregation of organolithiated species being well-established,¹¹ a discrete solvation model incorporating three molecules of THF putting each lithium cation in a “standard” tetrahedral coordination sphere (two on Li^1 and one on Li^2) was next considered (Figure 5, bottom). In this case, two *exo* conformers were found to correspond to local minima (Figure 5, bottom left) separated by ≈ 5 kcal·mol^{−1}, in favor of the same conformer found with the unsolvated model. The *endo* solvated complex corresponded to a single optimum, once again less stable than the best *exo* arrangement, by 6 kcal·mol^{−1}. Thus, this preliminary series of calculations shows that the first

solvation shell has little influence on the aggregation pattern of the systems. Note that, in all of these minima, the phenyl ring stands “on the edge” between the two lithium cations.

The NMR data related to the two *ortho* positions of the aromatic ring of **2** helped to determine its orientation. One can note indeed that both H^{ortho} –PhLi (designated as PhLi(*Ho*) in Figure 4) and C^{ortho} –PhLi (designated as “PhLi *o*” on page S3 in the Supporting Information) are characterized by a single signal on their respective spectra. In addition, these two “equivalent” H^{ortho} protons exhibit dipolar correlations with all $\text{H}^{2/2'}$, $\text{H}^{6/6'}$, Ph^2 , and Ph^3 (Figure 4), suggesting that they both interact with protons from the *exo* and the *endo* face of the amide. Therefore, at the time scale of the NMR, the benzenic appendage seems to freely rotate, even at -78°C , around its *ipso*-carbon between two threshold positions in which the ring stands “on the edge” between the two lithium cations, as already pointed out by the DFT study (Figure 6). The rotation around an axis close to the *para*–*ipso* carbon axis was, therefore, studied by DFT, at the same computational level as above. A 7.3 kcal·mol^{−1} energy barrier is associated with this motion, which can be easily overcome at -78°C . It is worth noting that the 180° rotation leads to a TS at which the phenyl ring and the N–Li– C^{ipso} –Li quadrilateral are almost coplanar. This rotation could be observed only in one direction (rotation of the C^{ortho} – C^{ipso} – Li^1 – N^2 angle, taken to materialize the *para*–*ipso* axis), suggesting that this movement takes place only clockwise and is thus oriented by the asymmetric structure that acts as a ratchet wheel. Such results are to be used with care since they are obtained on a static model that does not take into account a possible dynamic behavior of the THF molecules. This rotation brings to a local minimum almost similar to the starting point ($\delta E = 0.4$ kcal·mol^{−1}).

We next tried to relate the topology of the complex to the 56% ee in favor of the *S* enantiomer measured when reacting **1/2** onto the *ortho*-tolualdehyde (Scheme 2, left).¹² Note that an

Scheme 3. Parameters to Consider before Theoretically Computing the 1/2/*o*-TolCHO Complex

R configuration (80%) was obtained for the alcohol when working with alkyl lithium nucleophiles (Scheme 2, right).^{3b,5b}

Since both 1/PhLi and 1/MeLi adopt a similar topology, the origin of the inversion of the sense of the induction was to be found elsewhere. We thus considered the early stages of the reaction and thought that the differentiation could be due to the docking of the oxygen of the aldehyde along one or the other of its lone pairs. Another possibility could be an inversion in the sense of the rotation of the aldehyde (along the C=O) axis after its docking, or when facing the nucleophile before the docking. Unfortunately, these hypotheses could not be verified spectroscopically, for the reaction was running too fast on the NMR time scale.¹³ We thus decided to carry out a DFT theoretical analysis of the docking and condensation.

Undertaking a “complete” investigation of the 1/2/*o*-TolCHO ternary complex represents a major endeavor because of the large number of degrees of freedom at stake. However, we have previously shown that the problem can be brought down to the extensive study of four crucial parameters that are (Scheme 3) (i) the lithium (Li¹ or Li²) approached by the substrate, (ii) the location (a¹, a², or e²) of the solvent molecule expelled upon docking of the aldehyde, (iii) the conformation (*syn* or *anti*) of the aldehyde during its docking, and (iv) the face (*Re* or *Si*) exposed to the nucleophile during the docking step. All of these matters led to 12 starting positions (see the 12 starting positions on page S5 in the Supporting Information).

To compare the total and partial solvation energies of aggregate 1/2 in THF, we followed a procedure that proved successful previously.¹² It consists of taking the trisolvated system as the reference, then removing each THF molecule alternatively and recomputing the energy of the system while keeping its geometry frozen. The difference between the energy of the fully optimized trisolvated complex and that of the “frozen” disolvated one gives an estimate of the missing THF contribution (Table 1). It appears that Li¹ is more difficult to desolvate, as already observed with the 1/MeLi mixed aggregate.¹²

Consequently, among the 12 starting points mentioned above, only the fully loaded complexes in which the docking of the aldehyde takes place on Li² were considered further. Note

that, on this lithium, the δE between the a² and the e² sites is too low to favor a substitution over the other, thus eight starting arrangements remained relevant. Sorting among the eight ones on the basis of their thermodynamic stability led to four ternary arrangements of lower energy by about 2 kcal·mol^{−1} (e²-*anti Re*, a²-*syn Si*, e²-*syn Re*, and e²-*syn*). Finally, the evolution of these four aggregates was fully optimized (Table 2).¹⁴

The activation energy values suggest that going through an a²-*syn Si* complex is significantly disfavored. In contrast, the e²-*anti Re* and e²-*syn Re* arrangements, which are almost isoenergetic at the starting point, are governed by comparable activation barriers, and both lead to the (*S*) final product. In contrast, e²-*syn Si*, for which the starting point is slightly less stable than the two latter (by about 1 kcal·mol^{−1}), but with a similar activation barrier, leads to the (*R*) enantiomer. Therefore, this enantiomer should be slightly less favored on both thermodynamic and kinetic points of view. The feeble differences between the three routes in term of energies suggest that the three possibilities are all possible and thus let us expect a 1:2 *R/S* ratio, a result in rough agreement with the 22:78 enantiomeric ratio (ee 56%) obtained experimentally.

Mixed Aggregate [3-Aminopyrrolidine Lithium Amide 1/Vinyl lithium 3]. The study was repeated on the aggregate between the same chiral amide and vinyl lithium, requiring the synthesis of ⁶Li-labeled vinyl lithium 3. The procedure that has been retained consisted of reacting commercial tetravinyl tin 9 with ⁶Li-labeled *n*-butyllithium 8 in pentane (Scheme 4).¹⁵ Once again, the expected organolithium product precipitated, and after washing twice with dry pentane, it was dissolved in THF-*d*₈ and titrated (*c* = 1.2 mol/L) by both pH-metry¹⁶ and NMR spectroscopy¹⁷ in the presence of an internal standard (cyclohexane).

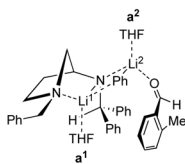
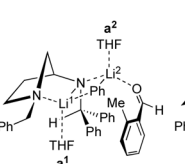
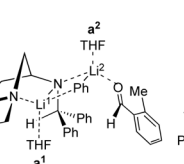
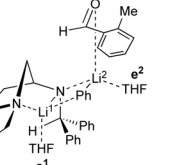
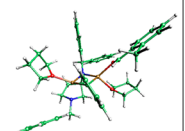
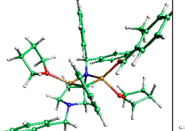
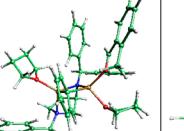
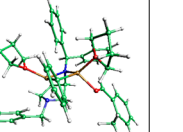
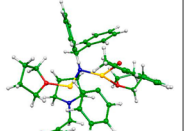
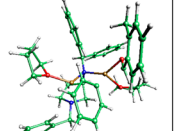
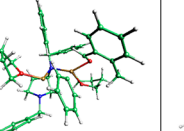
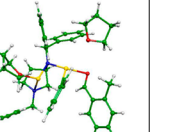
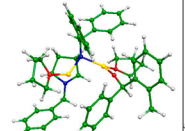
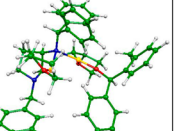
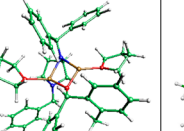
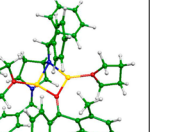
The amide 1 was formed by adding, at −20 °C, 1.2 equiv of the ⁶Li-vinyl lithium solution onto 1-H in THF-*d*₈. The quality of the amide was rapidly checked before a second equivalent of vinyl lithium was introduced at the same temperature. After cooling the sample at −78 °C, the ¹H, ⁶Li, and ¹³C one-dimensional NMR experiments were registered. The persistency of the azanorbornyl-like conformation of the amide in the complex formed was checked by comparing the chemical shifts of the 1-H and 1/3 proton spectra that evidence the splitting of the H^{2,2'}, H^{5,5'}, and H^{6,6'} protons (Figure 7c). More precise information was extracted from the lithium and the carbon spectra. Hence, the ⁶Li spectrum exhibits two main singlets at 1.47 and 2.00 ppm of equal intensities (Figure 7a), which present a scalar coupling highlighted by an INADEQUATE ⁶Li experiment (Figure 7b). The two Li signals thus belong to a same 1:1 complex. The signal at 192.3 ppm on the ¹³C spectrum corresponds to the =C^αHLi carbon and presents a quintet (*J*_{13C-6Li} = 7.6 Hz, Figure 7d). According to the Winshester–Bauer–Schleyer rule, such multiplicity and coupling constant are in favor of a species in which the =C^αH^αLi

Table 1. Total and Partial Solvation Energies of Aggregate 1/2 in THF

entries	solvation ^a (<i>q</i> _{Li¹} / <i>q</i> _{Li²}) ^b	δE^c (kcal·mol ^{−1})
1	a ¹ + a ² + e ² (0.85/0.86)	
2	a ² + e ² (0.88/0.86)	$\delta E = -13.4$
3	a ¹ + e ² (0.85/0.88)	$\delta E = -10.5$
4	a ¹ + a ² (0.85/0.88)	$\delta E = -11.8$

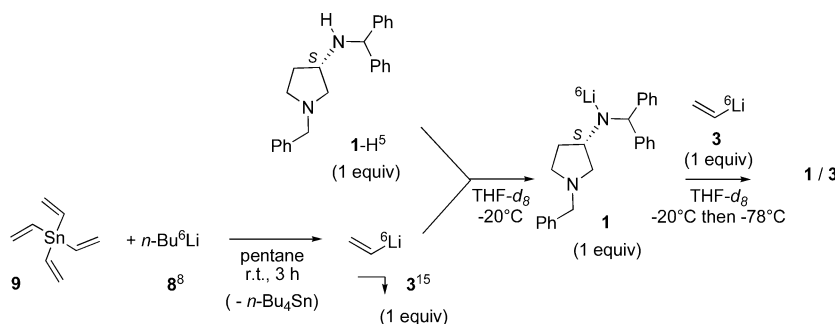
^aLabeling of the solvents as in Scheme 3. ^bNBO charges calculated on Li¹ and Li². ^cValues in kcal·mol^{−1}. $\delta E = E(\text{trisolv}) - [E(\text{disolv}) + E(\text{solvent})]$.

Table 2. Reaction Pathways for the Various Conformers of the Fully Loaded Starting Complex^{a,b,c}

				
	e²-anti <i>Re</i>	e²-syn <i>Re</i>	e²-syn <i>Si</i>	a²-syn <i>Si</i>
SC	 (<i>E</i> = -2142.5062 a.u.) + 0.4 kcal.mol ⁻¹	 (<i>E</i> = -2142.5068 a.u.) 0.0 kcal.mol ⁻¹	 (<i>E</i> = -2142.5052 a.u.) + 1.1 kcal.mol ⁻¹	 (<i>E</i> = -2142.5051 a.u.) + 1.1 kcal.mol ⁻¹
TS ^a	 <i>E</i> [‡] = +8.9 kcal.mol ⁻¹	 <i>E</i> [‡] = +9.5 kcal.mol ⁻¹	 <i>E</i> [‡] = +9.8 kcal.mol ⁻¹	 <i>E</i> [‡] = +16.1 kcal.mol ⁻¹
FP ^c				

^a*E*[‡] = *E*(TS) – *E*(SM). ^bThe reaction pathway was not computed for this starting point of higher energy. ^c*E* = *E*(FP) – *E*(TS).

Scheme 4. Synthetic Scheme for the Preparation of Complex 1/3



carbon is surrounded by two lithiums. Thus, one can already suggest that the two lithiated species are interacting around a N–Li–C^α–Li quadrilateral (Figure 7, left).

The NOESY (Figure 8, left) and HOESY (Figure 8, right) experiments then give access to the tridimensional structure of the aggregate.

From these measurements, the azanorbornyl-like folding is confirmed thanks to the NOE correlations between H⁸ and H⁴, H⁵, as well as the HOE correlation between Li¹ and H⁶. The HOESY dimension complementarily evidences the proximity between the lithium brought by the vinyl moiety (Li²) and protons H², which is in accordance with a topology placing the vinyl lithium in front of the C² bridge of the azanorbornyl-like conformation of the amide. Such a position for the vinyl appendage is further confirmed by the two NOE correlations involving H^α (H^α/H⁶ and H^α/H^{6'}), and two NOE correlations involving H^β (H^β/H², H^β/H⁶) of much smaller intensity. Those

observations suggest that the vinyl group is on the edge of the N–Li–C–Li quadrilateral, facing the methylenic bridge.

CONCLUSIONS

In this paper, two new three-dimensional structures of mixed aggregates between a chiral lithium amide (CLA) and phenyllithium, or vinyl lithium, are described in THF solution. The CLA is derived from 3-aminopyrrolidine, and in the two arrangements, an azanorbornyl-like folding is observed for the pyrrolidinic core. Dipolar interactions between this partner and each of the lithio reactants afford an arrangement with an *exo* topology, like that defined in previous work: the phenyllithium or the vinyl lithium faces the methylenic group of the pyrrolidine. In the case of the aggregate with phenyllithium, a rational interpretation of the inductions measured experimentally was undertaken and the theoretical results fit almost perfectly with the experience.

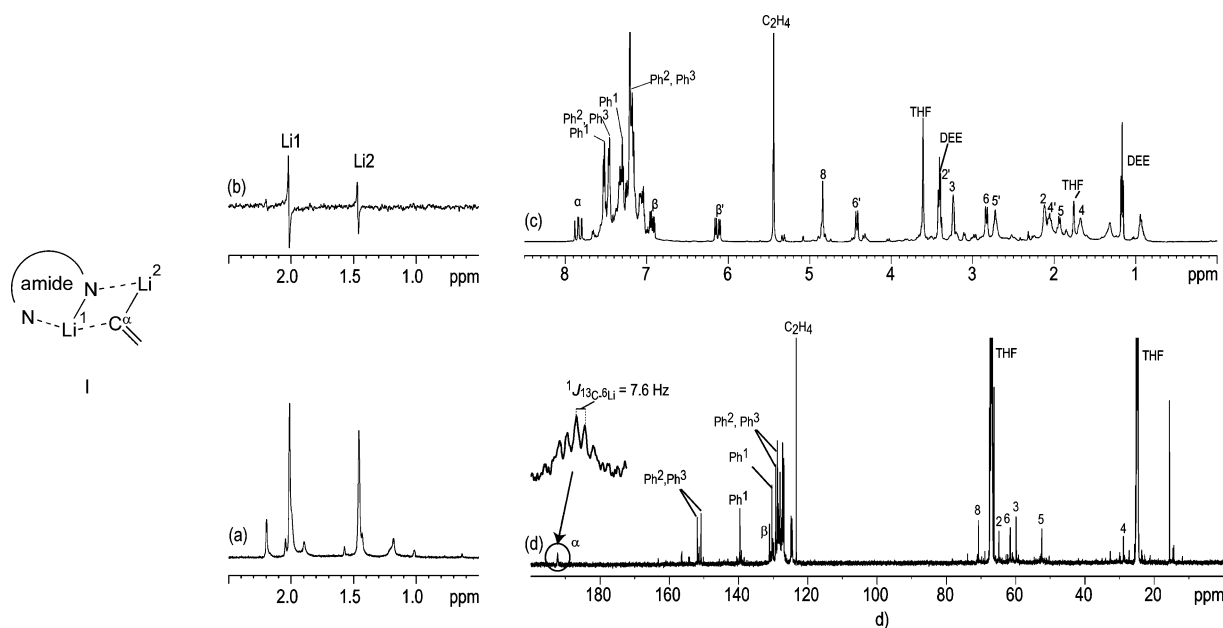


Figure 7. 1D NMR spectra of 1/3 mixture in THF-*d*₈ at -78 °C: (a) 1D ⁶Li, (b) 1D ⁶Li-INADEQUATE, (c) 1D ¹H, and (d) 1D ¹³C spectrum.

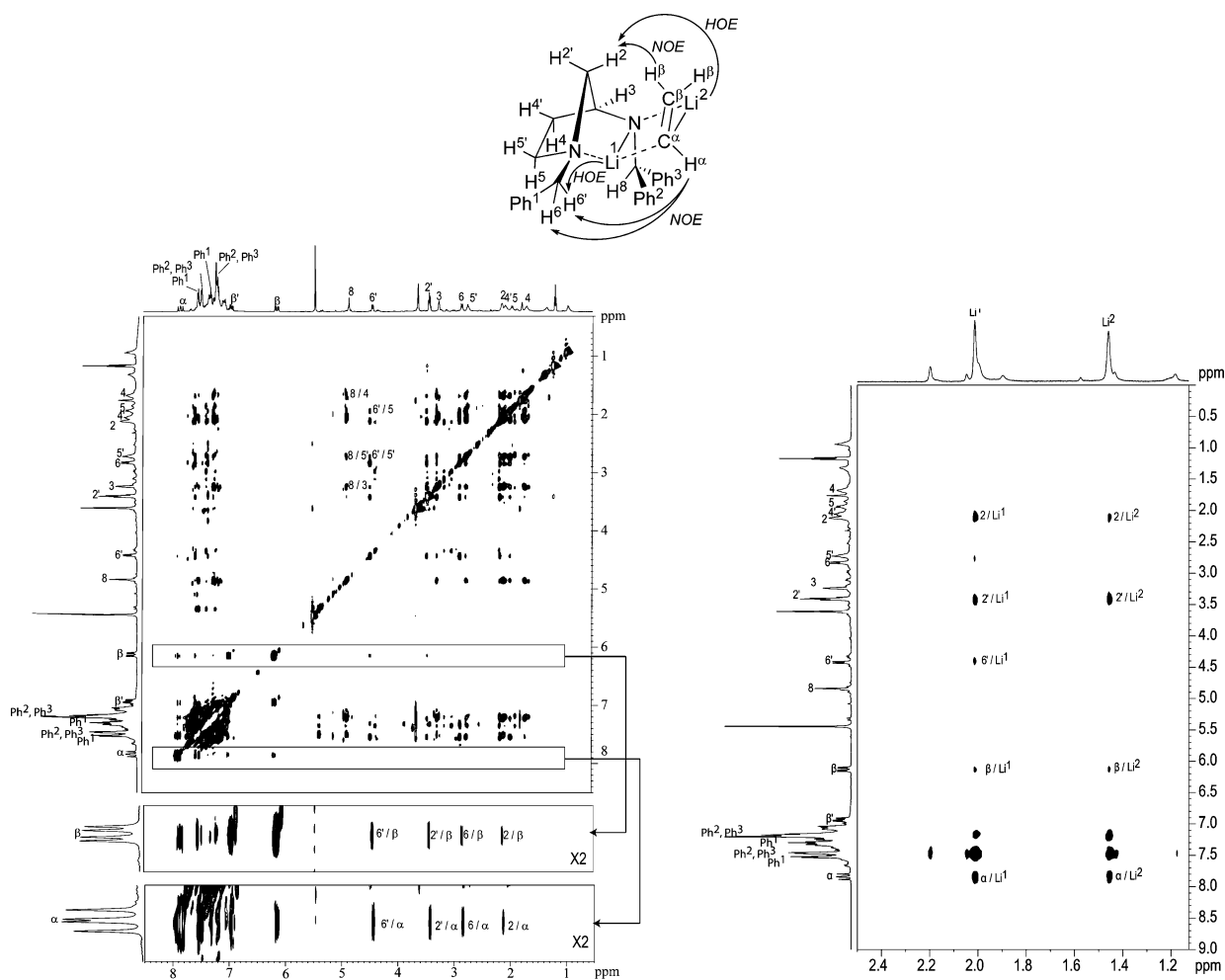


Figure 8. 2D NMR spectra of 1/3 mixture in THF-*d*₈ at -78 °C: ¹H, ¹H-NOESY (left) and ⁶Li, ¹H-HOESY (right).

Therefore, these results answer the two questions mentioned in the Introduction: (i) yes, *sp*²-hybridized organolithium derivatives can form 1:1 mixed aggregates with a lithium amide,

at least with an amide derived from a 3-aminopyrrolidine, and (ii) yes, the resulting complexes adopt a structure extremely similar to that established before for the lithiated *sp*³ carbon

atoms. Note that these data are in fine agreement with the structural propositions we made before on the basis of DFT computational results.¹² It would next be interesting to check if sp-hybridized lithium derivatives (lithium acetylides) undergo mixed aggregations. We are currently exploring this possibility, and the results will be reported in due time.

■ EXPERIMENTAL SECTION

General Considerations. Argon was dried and deoxygenated by bubbling through a commercial solution of butyllithium in hexane. Commercial tetrahydrofuran-*d*₈ was distilled over sodium and benzophenone. ⁶Li (95%) was purchased from Aldrich and washed in freshly distilled pentane. Pentane and heptane were distilled over lithium aluminum hydride.

[⁶Li] *n*-Butyllithium Salt-Free Solution in Pentane.^{8,18} Finely cut ⁶Li metal ribbon (0.3 g, 50 mmol) was introduced in a two-neck pear-shaped flask (50 mL) equipped with a balloon of dry argon. The metallic cuttings were covered with freshly distilled pentane (10 mL). After intensive stirring, the pentane was removed and the metal washed twice with this same solvent. A new amount of 10 mL of pentane was introduced, and a solution of freshly distilled *n*-bromobutane (2.14 mL, 20 mmol) in pentane (6 mL) was syringed at room temperature over a period of 30 min. The resulting reaction mixture was stirred for 20 h 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 titrated¹⁰ and kept until further use.

[⁶Li] Phenyllithium 2 Salt-Free Solution in Tetrahydrofuran-*d*₈.⁹ A solution of salt-free [⁶Li]-*n*-butyllithium in pentane (1 equiv) was added, at room temperature and under a dry argon atmosphere, to a solution of iodobenzene (1 equiv), also in pentane (*c* ≈ 1.3 mol/L). The suspension was stirred for 15 min at room temperature. The hydrocarbon solution was then pumped off the flask with a syringe, and the residual solid that stayed in the reaction flask was washed three times with freshly distilled pentane. The mass of PhLi was noted, and after cooling at −78 °C, a known volume of freshly distilled THF (to attain ≈1.5 mol/L) was slowly introduced. The clear final solution was titrated¹⁰ and quickly used for further experiments.

[⁶Li] Vinylithium 3 Salt-Free Solution in Tetrahydrofuran-*d*₈.¹⁵ A solution of salt-free [⁶Li]-*n*-butyllithium in hexane (2.5 equiv) was added, at room temperature and under a dry argon atmosphere, to a solution of tetravinyltin (1 equiv) in pentane (*c* = 0.2 mol/L). A white solid precipitated immediately. The suspension was stirred for 30 min at room temperature. The hydrocarbon solution was then pumped off the flask with a syringe, and the residual solid that stayed in the reaction flask was washed three times with freshly distilled pentane. The mass of vinylLi was noted, and after cooling at −78 °C, a known volume of freshly distilled THF (to attain ≈1.5 mol/L) was slowly introduced. The clear final solution was titrated¹⁰ and quickly used for further experiments.

[⁶Li]-Lithium Amides 1 Solution in Tetrahydrofuran-*d*₈. A solution of amine 1 (0.137 mmol) in freshly distilled tetrahydrofuran-*d*₈ (0.2 mL) was transferred into a dry 5 mm NMR tube fitted with a septum and flushed under argon. A solution of freshly prepared [⁶Li]-phenyllithium or vinylithium (1 equiv) in tetrahydrofuran-*d*₈ was added dropwise with a syringe to the above solution kept at −20 °C. The tube was vigorously shaken while keeping cooled, then quickly dropped in the precooled (−78 °C) NMR probe.

[⁶Li] 1:1 Lithium Amides/Phenyllithium 1/2 Mixed Aggregate Solution in Tetrahydrofuran-*d*₈. A solution of freshly prepared [⁶Li]-phenyllithium (1 equiv) in tetrahydrofuran-*d*₈ was added, at −20 °C and under a dry argon atmosphere, to the above THF-*d*₈ solution of amide 1 (prepared itself with the same organolithium reactant, *viz* phenyllithium) placed in a dry 5 mm NMR tube. The tube was vigorously shaken while keeping cooled, then quickly dropped in the precooled (−78 °C) NMR probe.

[⁶Li] 1:1 Lithium Amides/Vinylithium 1/3 Mixed Aggregate Solution in Tetrahydrofuran-*d*₈. A solution of freshly prepared [⁶Li]-vinylithium (1 equiv) in tetrahydrofuran-*d*₈ was added, at −20 °C and under a dry argon atmosphere, to the above THF-*d*₈ solution of amide 1 (prepared itself with the same organolithium reactant, *viz* vinylithium) placed in a dry 5 mm NMR tube. The tube was vigorously shaken while keeping cooled, then quickly dropped in the precooled (−78 °C) NMR probe.

Instrumental Considerations. All NMR experiments were performed on a Bruker Avance DMX 500 spectrometer, equipped with a z-gradient unit and a 5 mm {¹H, ⁶Li, ¹³C, and ¹⁵N} quadruple-resonance probe. Measuring frequencies were 500 MHz (¹H), 125 MHz (¹³C), and 73 MHz (⁶Li). ¹H and ¹³C 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 ⁶LiCl in MeOH-*d*₄ (δ 0.0).

1D NMR Measurements. The proton and lithium one-dimensional experiments were recorded with standard parameters. To remove the ¹³C–¹H coupling, the one-dimensional ¹³C spectra were recorded with broad-band proton decoupling.

⁶Li-INADEQUATE.¹⁹ The one-dimensional ⁶Li-INADEQUATE was used to detect scalar coupling between nonequivalent lithium in the complex. A standard pulse sequence was used with Δ = 1/2J_{6Li–6Li} of 500 ms.

2D NMR Measurements. ¹H/¹H NOESY.²⁰ 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 was obtained by using time proportional phase incrementation (TPPI) phase cycling; variable mixing times, depending on the sample, were used; one time zero filling in *f*₁; π/2 shifted sine square window functions were applied to *f*₂ and *f*₁ dimensions before Fourier transformation.

⁶Li/¹H HOESY.¹⁸ The following parameters were used for acquiring and processing the spectra in phase-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 (TPPI) phase cycling; variable mixing times, depending on the sample, were used; one time zero filling in *f*₁; π/2 and π/3 shifted sine square window functions were applied to *f*₂ and *f*₁ dimensions, respectively, before Fourier transformation.

Processing of NMR data was performed on an SGI O2 computer, using the manufacturer's program Xwinmr2.1 (Bruker).

■ ASSOCIATED CONTENT

Supporting Information

¹³C NMR spectrum of complex 1/2, computational details, and representation of the 12 starting positions of the three-partner complex 1/2/*o*-TolCHO. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: anne.harrison@univ-rouen.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was conducted on equipment bought and maintained thanks to the continuous and generous support of the Conseil Régional de Haute-Normandie and CNRS. Part of the funding came through the inter-regional network CRUNCH that is acknowledged for its commitment. Computations have been carried out at the Centre de Ressources Informatiques de Haute-Normandie (CRIHAN, Saint Étienne du Rouvray, France). These results received indirect support by the Agence Nationale pour la Recherche through the grant ANR-07-BLAN-0294-01.

■ REFERENCES

- (1) For aryllithiums used in enantioselective nucleophilic reactions, see: (a) Mazaleyra, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585–4586. (b) Kanoh, S.; Muramoto, H.; Maeda, K.; Kawaguchi, N.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2244–2246. (c) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681–6684. (d) Denmark, S. E.; Nakajima, N.; Nicaise, O. *J.-C. J. Am. Chem. Soc.* **1994**, *116*, 8797–8798. (e) Jones, C. A.; Jones, I. G.; North, M.; Pool, C. R. *Tetrahedron Lett.* **1995**, *36*, 7885–7888. (f) Andersson, P. G.; Johansson, F.; Tanner, D. *Tetrahedron* **1998**, *54*, 11549–11566. (g) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron Lett.* **2000**, *41*, 5533–5536. (h) Hasegawa, M.; Taniyama, D.; Tomioka, K. *Tetrahedron* **2000**, *56*, 10153–10158. (i) Chrzanowska, M.; Sokolowska, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1435–1440. (j) Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron: Asymmetry* **2001**, *12*, 2077–2082. (k) Flinois, K.; Yuan, Y.; Bastide, C.; Harrison-Marchand, A.; Maddaluno, J. *Tetrahedron* **2002**, *58*, 4707–4716. (l) Amiot, F.; Cointeaux, L.; Silve, E. J.; Alexakis, A. *Tetrahedron* **2004**, *60*, 8221–8231. (m) Cabello, N.; Kizirian, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2004**, *45*, 4639–4642. (n) Cabello, N.; Kizirian, J.-C.; Gille, S.; Alexakis, A.; Bernardinelli, G.; Pinchard, L.; Caille, J.-C. *Eur. J. Org. Chem.* **2005**, 4835–4842. (o) Cointeaux, L.; Alexakis, A. *Tetrahedron: Asymmetry* **2005**, *16*, 925–929. (p) Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2021–2027.
- (2) For vinylolithiums used in enantioselective nucleophilic reactions, see: (a) References 1b and 1c. (b) Yuan, Y.; Harrison-Marchand, A.; Maddaluno, J. *Synlett* **2005**, 1555–1558.
- (3) (a) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Prigent, Y.; Davoust, D.; Duhamel, P. *J. Am. Chem. Soc.* **1997**, *119*, 10042–10048. (b) Corruble, A.; Davoust, D.; Desjardins, S.; Fressigné, C.; Giessner-Prettre, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267–15279. (c) Parisel, O.; Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C. *J. Org. Chem.* **2003**, *68*, 1290–1294.
- (4) Fressigné, C.; Lautrette, A.; Maddaluno, J. *J. Org. Chem.* **2005**, *70*, 7816–7828.
- (5) (a) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663–2666. (b) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266–8275.
- (6) Pickard, P. L.; Tolbert, T. L. *Org. Synth.* **1973**, *5*, 520–522.
- (7) The ^1H NMR spectrum of **1** registered at -78°C is identical to those already described for this amide when obtained using alkylolithium to deprotonate amine **1-H**; see ref 3a.
- (8) Paté, F.; Oulyadi, H.; Harrison-Marchand, A.; Maddaluno, J. *Organometallics* **2008**, *27*, 3564–3569.
- (9) (a) Gilman, H.; Zoellner, E. A.; Selby, W. M. *J. Am. Chem. Soc.* **1932**, *54*, 1957–1962. (b) Bauer, W.; Winchester, W. R.; von R. Schleyer, P. *Organometallics* **1987**, *6*, 2371–2379. (c) Wehman, E.; Jastrzebski, J. T. B. H.; Ernsting, J.-M.; Grove, D. M.; van Koten, G. J. *Organomet. Chem.* **1988**, *353*, 133–143.
- (10) Duhamel, L.; Plaquevent, J.-C. *J. Organomet. Chem.* **1993**, *448*, 1–3.
- (11) (a) Khartabil, H. K.; Gros, P. C.; Fort, Y.; Ruiz-López, M. F. *J. Org. Chem.* **2008**, *73*, 9393–9402. (b) Popenova, S.; Mawhinney, R. C.; Schreckenbach, G. *Inorg. Chem.* **2007**, *46*, 3856–3864. (c) Deora, N.; Carlier, P. R. *J. Org. Chem.* **2010**, *75*, 1061–1069. (d) Pratt, L. M.; Jones, D.; Sease, A.; Busch, D.; Faluade, E.; Nguyen, S. C.; Thanh, B. T. *Int. J. Quantum Chem.* **2009**, *109*, 34–42. (e) Pratt, L. M. *J. Mol. Struct.: THEOCHEM* **2007**, *811*, 191–196.
- (12) Yuan, Y.; Desjardins, S.; Harrison-Marchand, A.; Oulyadi, H.; Fressigné, C.; Giessner-Prettre, C.; Maddaluno, J. *Tetrahedron* **2005**, *61*, 3325–3334.
- (13) (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805–1810. (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810–1815.
- (14) The systems we have kept are more stable than those we have skipped by at least $2\text{ kcal}\cdot\text{mol}^{-1}$. We are aware that such a procedure relies on the assumption that all of these aggregates are in rapid equilibrium and that no high kinetic barrier limits the progression of the system. We believe that this hypothesis is reasonable as long as the electrostatic-driven long-distance interaction between the lithium cation and the oxygen of the aldehyde is the driving force for the addition reaction. Anyway, the system we consider here is unfortunately too large to ensure that calculations up to the TS for all the starting points can be reasonably pursued.
- (15) (a) Seyferth, D.; Weiner, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 3583–3586. (b) Gassman, P. G.; Valcho, J. J.; Proehl, G. S.; Cooper, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 6519–6526.
- (16) A known volumic amount of freshly prepared ^6Li -vinylolithium solution in THF was hydrolyzed; then a pH measurement of the solution was carried out using a Mettler Toledo MP 220 equipped with a combined electrode.
- (17) This titration consists of adding a known amount of an inert chemical (here, freshly distilled cyclohexane) to a tube containing a known volume of the vinylolithium solution in a known amount of THF. Comparison of the integrations of the standard and protons of the lithium derivative leads to the concentration of the organolithium reactant.
- (18) Fraenkel, G.; Henrichs, M.; Hewitt, J. M.; Su, B. M.; Geckle, M. *J. Am. Chem. Soc.* **1980**, *102*, 3345–3350.
- (19) (a) Bax, A.; Freeman, R.; Kempell, S. P. *J. Am. Chem. Soc.* **1980**, *102*, 4849–4851. (b) Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542–561. (c) Bax, A.; Freeman, R.; Frenkiel, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 2102–2104. (d) Eppers, O.; Fox, T.; Günther, H. *Helv. Chim. Acta* **1992**, *75*, 883–891.
- (20) Aue, W. P.; Bartholdi, E.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229–2246.