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Lithiation

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NMR and DFT Studies with a Doubly Labelled $^{15}N/^{6}Li$ *S*-Trifluoromethyl Sulfoximine Reveal Why a Directed *ortho*-Lithiation Requires an Excess of *n*-BuLi

Matthieu Hédouin, Anne-Laure Barthelemy, Nicolas Vanthuyne, Hend Besrour, Jacques Maddaluno, Emmanuel Magnier,* and Hassan Oulyadi**

Abstract: This work shows why it is imperious to use an excess of butyllithium for a directed *ortho*-lithiation of a trifluoromethyl sulfoximine. The analysis of mixtures of *n*-BuLi and sulfoximine **1** in THF-d_8 using {^{1}H, ^{6}Li, ^{13}C, ^{15}N, ^{19}F} NMR experiments at low temperatures reveal that a first deprotonation occurs that leads to dimeric and tetrameric N-lithiated sulfoximine (93:7). Using an excess *n*-BuLi (5 equivalents), the second deprotonation on the *ortho*-position of the aromatic occurs. Six species were observed and characterized on the way. It includes three aggregates involving a sulfoximine: i) a [dilithiated sulfoximine/(*n*-BuLi)] dimer solvated by four molecules of THF (**Agg2**, 39 %); ii) a [dilithiated sulfoximine/(*n*-BuLi)$_3$] tetramer solvated by six molecules of THF (**Agg3**, 39 %); iii) a [dilithiated sulfoximine/(*n*-BuOLi)$_3$] tetramer solvated by four molecules of THF (**Agg1**, 22 %). A DFT study afforded optimized solvated structures for all these aggregates, fully consistent with the NMR data.

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Introduction

Discovered independently by Gilman and Wittig, the *ortho*-lithiation of substituted arenes is among the most important reactions in organolithium chemistry because of its practical applications in organic synthesis.[1] Its simple and useful character explains it is largely employed to functionalize aromatic substrates using routine and cheap organolithium reagents such as *n*-butyllithium.[2] Practically, this reaction requires, in most cases, a significant excess of base (generally 2–4 equivalents),[3] an observation suggesting that reality is more complex than the formation of a simple anion, as often written for convenience or simplification. The need for this extra reagent is generally overlooked in literature, and, to our knowledge, no mechanistic study hints on the origin of this practically crucial problem. The *ortho*-lithiation of anisole has been the object of a pioneer study by Bauer and Schleyer,[4] who resorted to a ^{6}Li NMR and semi-empirical theoretical study. The results suggest that the tetrameric aggregate of *n*-BuLi in toluene-d_8 is unable to trigger the reaction and that tetramethyl ethylenediamine (TMEDA) is required to dissociate the tetramer into active dimers. Collum and others have confirmed this point later on, showing that the lithium coordination by the methoxy group of anisole is of no or little importance in the transition state.[5]

In this article, we present a case study in which intermediates of a known *ortho*-lithiation reaction were expected to be sufficiently stable to become the objects of a detailed multinuclear NMR investigation. We have indeed retained a class of substrate, the sulfoximines, of which backbone is particularly suited to a multi-nuclei NMR study and is also an original and rapidly emerging group in chemistry. Noticed in the late 1940s by serendipity, sulfoximines[6] can be regarded as the mono-aza analogues of sulfones. They are considered as bioisosteres of this function but display a much greater structural diversity:[7] switching an oxygen by a nitrogen atom makes the sulfur stereogenic and enlarges the structure of this family through the many possible functionalizations of the nitrogen atom. These two properties account for the extensive applications of sulfoximines, especially in asymmetric synthesis,[8] in crop sciences,[9] or in medicinal chemistry.[10,11]

The S-perfluoroalkyl sulfoximines are unique members of this family. They differ both in their preparation and in their use.[12] During their ongoing research program dedi-

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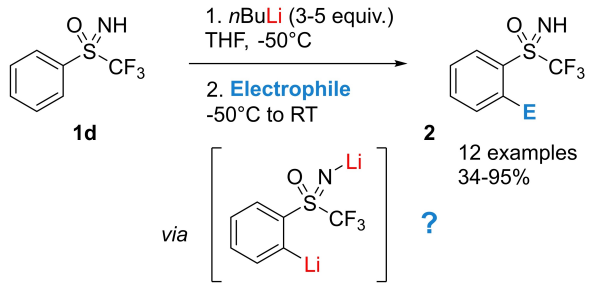
cated to the increase of the structural complexity of these halogenated sulfur(VI) compounds, Magnier and co-workers disclosed that a free NH-S-trifluoromethyl sulfoximine can be used as a directing group for deprotonation (Scheme 1).[13] By this simple methodology,[14] various electrophiles (halogen, oxygen, sulfur, boron, stannyl) could be attached to the aromatic ring through an *ortho*-lithiation reaction.

The optimization of the reaction revealed that S-perfluoroalkyl sulfoximines behave quite differently from their S-alkyl analogs (Table 1). In their 1999 seminal study, Levacher and co-workers showed that the *ortho*-lithiation of N–H S-*t*Bu sulfoximine **1a** was limited to 50 % yield, even with an excess of base (Table 1, entry 1),[15] whereas the N–Me sulfoximine analog **1b** led to a quantitative yield with a single equivalent *n*-butyllithium (entry 2). In contrast, Magnier and co-workers noticed that replacing the S*t*-Bu motive with a S-trifluoromethyl one (**1c**) revealed deleterious (entries 3–5). When **1c** was treated with one or two equivalents of base, no conversion was observed (entries 3 and 4), while using three equivalents of butyllithium led to degradation (entry 5). Working with a free N–H sulfoximine was then considered. Adding one equivalent of *n*-BuLi to the free N–H sulfoximine **1d** did not afford any *ortho*-functionalization (entry 6). A gradual increase of the proportion of butyllithium resulted in a complete conversion and a yield of 95 % was reached upon addition of three equivalents *n*-BuLi (entry 7–8). This has proven to be the minimum necessary, but five equivalents achieve the maximum yield and an excellent reproducibility (entry 9).

Such a difference between the S-perfluoroalkyl and S-alkyl series can be explained by the electronic deficiency induced by the CF_3 group on the sulfur atom. This latter thus becomes sensitive to a nucleophilic attack by the base, leading to a degradation of the sulfoximine moiety. Conversely, the *t*Bu group protects the sulfur atom by both electronic enrichment and steric hindrance.

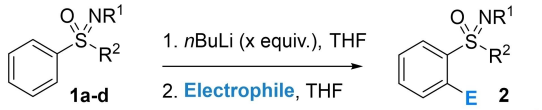
We assumed that the first equivalent deprotonated the nitrogen atom, this preliminary step being essential to the *ortho*-lithiation itself. However, the need for at least 3 equivalents *n*-BuLi remained enigmatic, as highlighted by Gais in his recent review.[14b]

Understanding why an excess of lithium base is required for this reaction to be efficient and characterizing the intermediate reactive species appeared as challenging projects. The priceless lights that multinuclear NMR using doubly-labelled {^{6}Li, ^{15}N} compounds shined previously on fairly comparable problems[16] led us to embark into this project, and we have been nicely rewarded.



Scheme 1. *ortho*-Functionalization of sulfoximines by deprotonation.

Table 1: Comparison of deprotonation conditions between S-alkyl and S-trifluoromethyl sulfoximines.

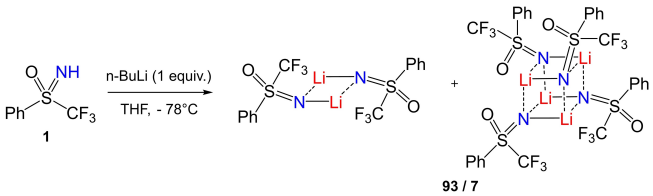


Entry	R^1	R^2	Cpd	x	Conv. (%)	Yield (%)
1	H	*t*-Bu	1a	2 or 3	n.d.	50
2	Me	*t*-Bu	1b	1	n.d.	95
3	Me	CF_3	1c	1	0	0
4	Me	CF_3	1c	2	0	0
5	Me	CF_3	1c	3	100	0
6	H	CF_3	1d	1	0	0
7	H	CF_3	1d	2	21	14
8	H	CF_3	1d	3	100	95
9	H	CF_3	1d	5	100	98

Results and Discussion

We began examining the action of a first equivalent of *n*-BuLi on *S*-aryl-*S*-trifluoromethyl sulfoximine **1d**. The sample was prepared directly in the NMR tube by adding one equivalent of homemade *n*-Bu^{6}Li to a 0.15 M solution of ^{15}N-labelled sulfoximine in THF-d_8 at 200 K. The ^{1}H and ^{6}Li one-dimensional NMR spectra (recorded at 185 K) shown a progressive fading of the ^{15}NH group signal at 6.4 ppm (Figure 1). To avoid adding an excess of *n*-BuLi, we continuously monitored the absence of CH_2Li signals at −1 ppm.

The ^{6}Li spectrum revealed that, after addition of exactly one equivalent *n*-BuLi, two aggregates arise: a major one (93 %) linked to a triplet signal with a coupling constant $^1J_{6Li\text{-}15N}$ = 3.5 Hz, and a minor one characterized by a quadruplet (7 %, $^1J_{6Li\text{-}15N}$ = 2.4 Hz). The values of the $^1J_{6Li\text{-}15N}$, as well as the multiplicity of the signals,[17] indicate that the lithium atom is coupled to, respectively, two and three nitrogen nuclei. Therefore, the major amide complex seems to correspond to a dimer[18] while the minor one adopts probably a tetrameric structure (Scheme 2). These hypoth-



Scheme 2. Deprotonation of **1** by 1 equiv *n*-BuLi at −78 °C. Solvent is omitted for clarity reasons.

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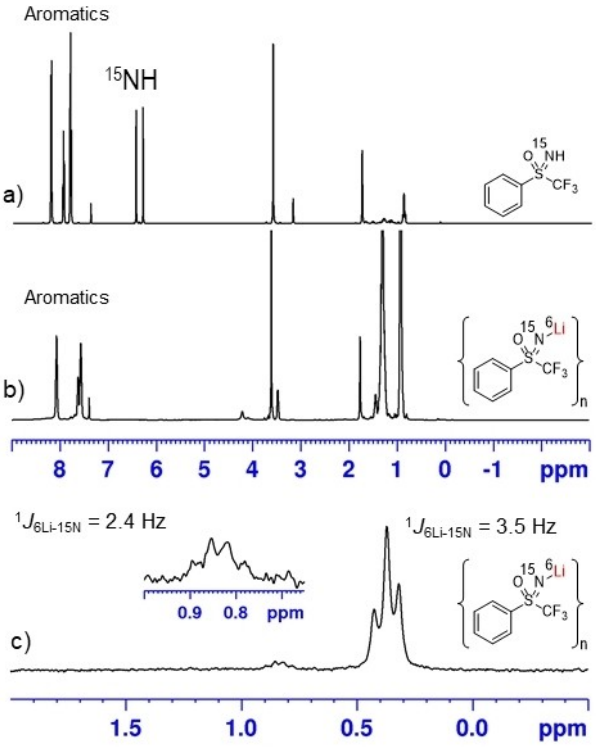

Figure 1. 1D ^{1}H spectra (500 MHz, THF-d_8, 185 K) of: a) ^{15}N sulfoximine, b) mixture of ^{15}N sulfoximine (0.15 M) and 1 equiv of *n*-Bu^{6}Li and c) 1D ^{6}Li spectrum (73 MHz, THF-d_8, 185 K) of a mixture of ^{15}N sulfoximine (0.15 M) and 1 equiv of *n*-Bu^{6}Li.

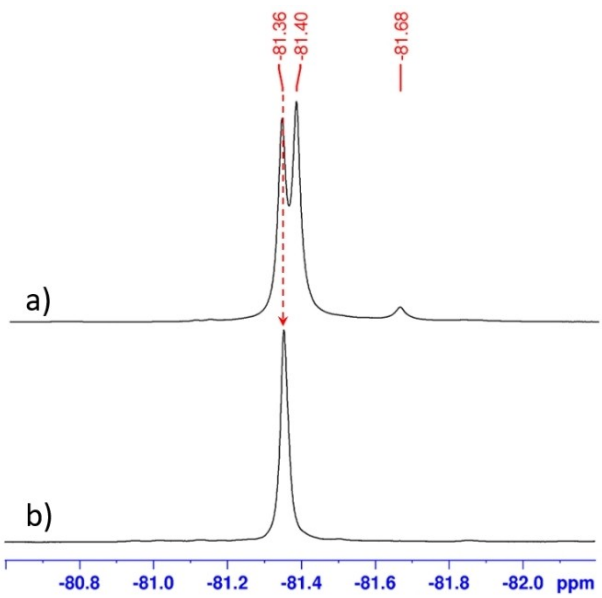

Figure 2. 1D ^{19}F spectra (476 MHz, THF-d$_8$, 185 K) of: a) racemic sulfoximine with 1 equiv of *n*-Bu^{6}Li. b) 100 % (+) sulfoximine after addition of 1 equiv *n*-Bu^{6}Li.

eses, in line with previous observations for polar amides in THF,[19] could be confirmed, for the dimer, by a ^{1}H-DOSY experiment (Figure 1S, Table 1S), using Stalke's external calibration method.[20] A calculated mass of 553 g mol^{-1} was found, a value in good accord with a disolvated dimer (M = 574 g mol^{-1}, error = 3.8 %).

Unexpectedly, the 1D ^{19}F spectrum exhibited not two but three signals: two juxtaposed 1:1 peaks at −81.36 and −81.40 ppm, integrating together for 93 %, plus one singlet at −81.68 ppm (7 %). The identity of the twin-peaks could be revealed by working with the separated[21] pure enantiomers: the 1D ^{19}F spectrum of each deprotonated enantiomer was characterized by the sole peak at −81.36 ppm (Figure 2b), while the racemic sulfoximine mixture displayed an extra singlet at −81.40 ppm (Figure 2a).

We deduce that homo- and hetero-chiral dimers are formed, that have slightly different chemical shifts: −81.36 ppm for the homo-dimer, −81.40 ppm for its hetero counterpart. The 1:1 ratio between these peaks indicates that the formation of the dimers is not diastereoselective, the two being more or less isoenergetic. In addition, we noticed that the solution derived from the enantiomerically pure substrates is devoid of the minor tetramer (at −81.68 ppm, Figure 2a), suggesting that this latter is "racemic" and assembles the (+) and (−) enantiomers selectively in 2:2 proportions.[22]

On the basis of the chemical results, transferring a second equivalent of *n*-Bu^{6}Li expected to the solution of monolithiated sulfoximine was to trigger an extra deprotonation, of the aromatic ring this time, *ortho* to the sulfoximine group. The resulting ^{6}Li one-dimensional NMR spectrum (Figure 3c) turned out to be difficult to decipher. We thought, that working with 3 equivalents butyllithium would lead to simpler NMR spectra. Instead, we noticed that, in these conditions, the ^{6}Li spectrum is less cluttered but still shows signal superpositions that make the analysis confusing (Figure S2-a). The direct addition to the NMR tube of an excess of *n*-Bu^{6}Li (more than 4 equiv) over sulfoximine led to much better ^{6}Li NMR spectra (Figure S2-b and S2-c). We thus decided to follow the protocol adopted by Magnier et al.[13] that consists in the direct addition of an excess (5 equivalents) of *n*-Bu^{6}Li relative to sulfoximine (0.15 M). The experiments were run straight in the NMR tube in THF-d_8 at 185 K and led to spectra much more prone to analysis (Figure 3d).

Again, the observation of the signals of the 1D ^{1}H NMR turned out to be a good way to monitor the reaction progress: as above, the deprotonation of ^{15}NH is first observed, followed by the appearance and continuous rise of signals at ≈−1 ppm corresponding to the CH_2Li of the *n*-Bu^{6}Li in excess (Figure S3). Simultaneously, the proton spectrum showed the gradual fading of signals between 7.4 and 8.2 ppm associated to the aromatic protons of the monolithiated sulfoximine aggregates and the upsurge of wide signals between 6.8 and 8.0 ppm, corresponding to aromatic protons of new dilithiated species (Figure S4).

These observations were confirmed on the 1D ^{6}Li spectrum by the disappearance of the ^{6}Li signal of monolithiated sulfoximine at 0.38 ppm and the rise of peaks corresponding to *n*-Bu^{6}Li in excess (Figure 3d). Two peaks at 1.55 and 0.78 ppm (1:3) are observed, beside the signals at 1.48 ppm ((*n*-BuLi)$_4$) and 1.90 ppm ((*n*-BuLi)$_2$), to be

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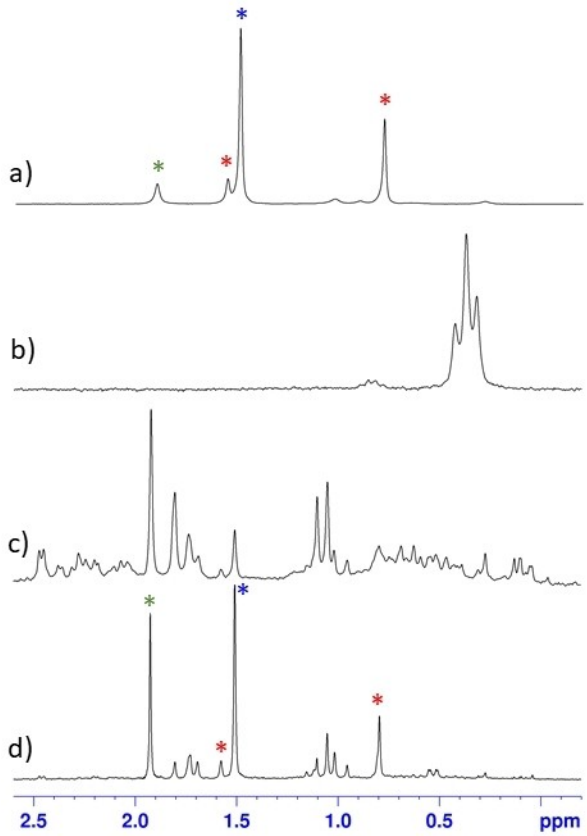

Figure 3. 1D ^{6}Li spectra (73 MHz, THF-d_8, 185 K) of: a) *n*-Bu^{6}Li (blue star (*n*-BuLi)$_4$, green star (*n*-BuLi)$_2$, red stars (*n*-BuLi)$_3$(*n*-BuOLi)$_1$). Bottom spectra correspond to ^{15}N sulfoximine after addition of b) 1 equiv of *n*-Bu^{6}Li; c) 2 equiv of *n*-Bu^{6}Li; d) 5 equiv of *n*-Bu^{6}Li.

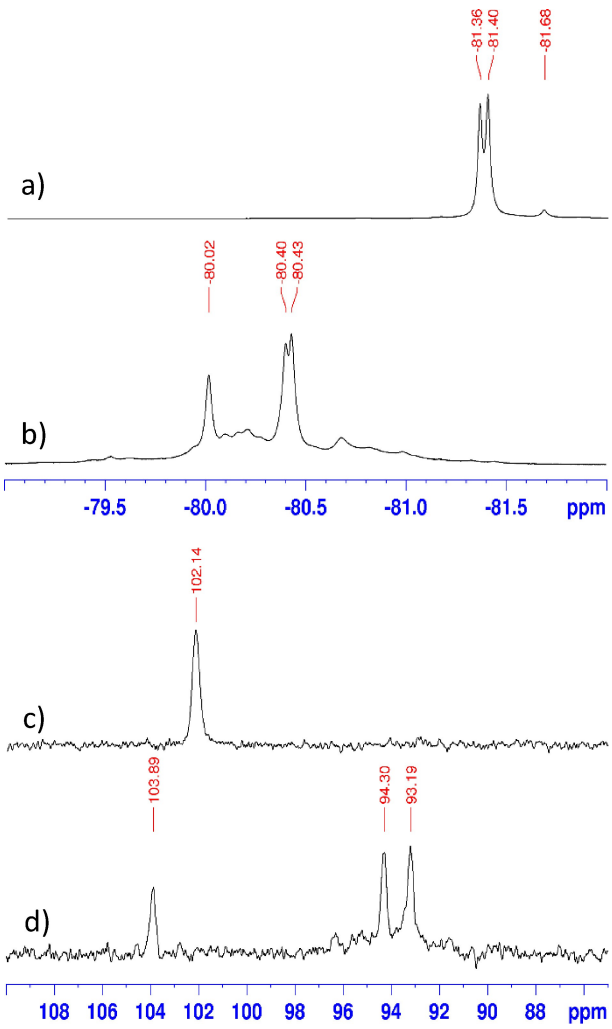

Figure 4. 1D ^{19}F (476 MHz, a, b) and ^{15}N (51 MHz, c, d) spectra of ^{15}N sulfoximine, in THF-d_8 at 185 K, after addition of: a, c) 1 equiv of *n*-Bu^{6}Li and b, d) 5 equiv of *n*-Bu^{6}Li.

assigned to the known mixed tetramer (*n*-BuLi)$_3$(*n*-BuOLi). Note that lithium butoxide is a well-known side-product usually accompanying homemade or commercial *n*-BuLi.[23]

Going further in the analysis of the spectrum requires to identify the signals of the lithium amide aggregates. This was carried out comparing the 1D ^{6}Li spectra of ^{15}N labelled to that of unlabeled sulfoximine, both being reacted with 5 equivalents *n*-Bu^{6}Li. The ^{15}N labelled sample (Figure S4) showed the doubling of the four signals, at 1.14, 1.04 and 0.53 ppm (with $^{1}J_{\text{Li-N}}=2.6$ Hz characteristic of a tetramer aggregate), and at 1.08 ppm (with $^{1}J_{\text{Li-N}}=3.7$ Hz, characteristic of a dimeric or trimeric aggregate).[17]

Complementarily, 1D ^{19}F and ^{15}N spectra were run that confirmed the vanishing of the signals of the monolithiated dimer and the arising of three signals for these two nuclei (Figure 4), suggesting the formation of three new sulfoximine aggregates, labelled in the following **Agg1**, **Agg2** and **Agg3**. Thus, the signals at −80.02 ppm on the ^{19}F spectrum and +103.89 ppm on the ^{15}N spectrum were assigned to **Agg1**, while **Agg2** and **Agg3** exhibited adjacent ^{19}F peaks at −80.40 and −80.43 ppm, and at +94.30 ppm and +93.19 ppm on the ^{15}N spectrum, suggesting closely related structures. Unfortunately, the large half width of the ^{15}N signals ($\Delta\nu_{1/2}\approx 13$ Hz) did not give access to the coupling constant (and therefore the aggregation state) between the ^{15}N and ^{6}Li nuclei in none of these three species.

The structure of these aggregates was further investigated resorting to 2D ^{6}Li-^{6}Li COSYLr, ^{6}Li-^{6}Li EXSY, ^{6}Li-^{1}H HOESY, ^{6}Li and ^{1}H DOSY experiments in THF-d_8 at 185 K with ^{15}N labelled or unlabelled sulfoximine, using directly 5 equivalents of *n*-Bu^{6}Li. For the sake of clarity, we describe below the characterization of the three aggregates **Agg1-3** independently.

The 2D ^{6}Li-^{6}Li EXSY spectrum (Figure S5) showed exchange correlations between the doublet at 1.14 ppm, the singlet at 0.95 ppm and the doublet at 0.53 ppm. The intramolecular character of this exchange was established running a 2D ^{6}Li-^{6}Li COSYLr spectrum (Figure S6) that exhibited a scalar coupling correlation between the same doublet at 1.14 ppm and singlet at 0.95 ppm. These observations imply that the three lithium nuclei belonged to the same aggregate. In addition, the absence of correlation of these three lithium signals with the CH_2Li protons of *n*-Bu^{6}Li on the 2D ^{6}Li-^{1}H HOESY map (Figure S7), suggests

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Table 2: Analysis of the 2D ^{6}Li and ^{1}H DOSY results for sulfoximine/*n*-BuLi (1:5).

	−Log D (^{6}Li)	−Log D (^{1}H)	**Exp. Mw [g mol^{-1}]**	**Theo. Mw [g mol^{-1}]**	(%) error
Extern THF	–	8.644	72	72	–
Intern THF	–	5.199	72	72	–
(*n*-BuLi)$_4$*THF$_4$	6.653	5.702	544	544	–
Agg1	6.735	5.736	638	669	4.9
Agg2	6.656	5.704	560	573	2.3
Agg3	6.772	5.804	832	845	1.6

D: apparent diffusion coefficient. Mw: molecular weight of solvated species.

the absence of *n*-Bu^{6}Li in this dilithiated sulfoximine aggregate.

Being aware that our homemade *n*-Bu^{6}Li THF solution contained *n*-BuOLi, we considered the possibility that a mixed aggregate incorporating this highly polar species could form in the parallel.[23] To substantiate this hypothesis, we prepared two mixtures of *n*-BuLi containing respectively 3 % and 11 % butoxide (Figure S8). The 1D ^{6}Li spectrum of the mixture showed indeed that the intensity of the three signals at 1.14, 0.95 and 0.53 ppm undergo a sharp increase with the concentration of butoxide, confirming that these signals are associated to a mixed tetrameric aggregate **Agg1** composed of dilithiated sulfoximine and *n*-BuOLi.

The structure and the solvation of **Agg1** was further investigated resorting to 2D ^{1}H (not shown) and ^{6}Li DOSY experiments (Figure S9-a) using the external calibration method.[20] The tetramer (*n*-BuLi)$_4$, of which ^{6}Li and ^{1}H signals can be easily identified, was used as an internal reference. The resulting diffusion coefficients are reported in Table 2. Use of the external calibration corresponding to the dissipated and ellipsoidal spheres, led to an experimental molar weight of 638 g mol^{-1}. This figure deviates by 4.9 % with respect to the theoretical value for a tetrasolvated mixed tetramer[24] consisting of one molecule of dilithiated sulfoximine and two molecules of *n*-BuOLi. This set of data is consistent with the scalar coupling $^{1}J_{6Li\text{-}15N}$ = 2.6 Hz and the spatial proximities extracted from the 2D ^{6}Li-^{1}H HOESY experiment.

Deconvolution of the signals of the 1D ^{6}Li spectrum at 1.14, 0.95 and 0.53 ppm was carried out, using Dmfit software,[25] and led, to, respectively, a doublet ($^{1}J_{6Li\text{-}15N}$ = 2.6 Hz), a singlet and another doublet ($^{1}J_{6Li\text{-}15N}$ = 2.7 Hz) with relative integrations of 8, 6 and 15 (Figure S10-d, Table S2). This analysis allowed the assignment of these three signals to, respectively Li^{3}, Li^{2} and to the two Li^{1} of the tetrameric structure displayed on Figure 5 that is [dilithiated sulfoximine/(*n*-BuOLi)$_2$]·4 THF.

Note that the Li^{3} signal at 0.53 ppm is a doublet of doublet (Figure S11-a). A 0.6 Hz splitting, too small to be due to a $^{1}J_{15N\text{-}6Li}$ scalar coupling and also observed on the spectrum of the unlabelled sulfoximine (Figure S11-b), uncovers the chemical inequivalence of Li^{3}/Li$^{3'}$ induced by the sulfur stereogenic center.

To buttress the DOSY measurements (Table 2), which suggest that there is one THF molecule per lithium atom, we undertook a computational study at the M06-2X/6-31++G** level of theory, followed by a frequency calculation, using the Gaussian software. At each stage, the bulk solvent effect has been considered using the PCM methods. The results showed that a tetrasolvated **Agg1** indeed corresponds to a local minimum, onto which no extra THF can be appended. The DFT optimized structure of the [sulfoximine/(*n*-BuOLi)$_2$] aggregate exhibits a distorted cubic core in which the C and N summits are bridged by two 5-membered metala-rings (Figure 5). This strong distortion can explain the absence of a scalar coupling between atoms Li^{1}, Li^{2} and Li^{3}.[26]

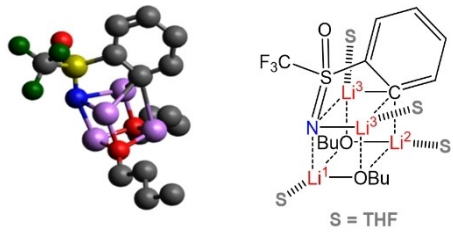

Figure 5. PCM(THF)-M06-2X/6-31++G** optimized structures of mixed aggregate **Agg1** [dilithiated sulfoximine/(n-BuOLi)2]*4THF. THF and hydrogens are omitted for clarity. For a full representation of solvated mixed tetramer, see Supporting Information.

A similar analytical approach was adopted for the second aggregate **Agg2**. Let us first consider the ^{6}Li doublet signal at 1.08 ppm (Figure 3d): it exhibits a $^{1}J_{Li\text{-}N}$ = 3.7 Hz that corresponds to a lithium bound to two nitrogen atoms in a dimeric (or trimeric) aggregate. In addition: i) no homonuclear scalar coupling correlation can be observed for this signal on the 2D ^{6}Li-^{6}Li COSYLr map (Figure S6); ii) an exchange correlation with a singlet signal at 1.73 ppm is evidenced on the 2D ^{6}Li-^{6}Li EXSY map (Figure S5). These two observations suggest that the lithium atoms at the origin of the signals at 1.08 and 1.73 ppm belong to the same aggregate **Agg2**.[26]

A relative integration between the two lithium signals could be performed after deconvolution of the 1D ^{6}Li signal at 1.08 ppm into a Li^{4} doublet signal with a scalar coupling $^{1}J_{6Li\text{-}15N}$ = 3.7 Hz plus a Li^{5} singlet signal at 1.73 ppm. A good fit between the experimental and the rebuilt spectra was obtained for a 2:1 integration ratio between the two signals, indicating that this aggregate comprised 3 lithium atoms, two of which were equivalent (Figure S10-b, Table S2).

An enlargement of the ^{6}Li-^{1}H HOESY spectrum over the ^{1}H chemical shift between −0.7 and −1.4 ppm (CH_2Li proton signals of *n*-BuLi) showed a correlation characteristic of a proximity between the lithium at 1.08 ppm and the

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CH_2Li protons of *n*-BuLi (Figure S7). This suggests that **Agg2** is a mixed dimer (or trimer) involving a dilithiated sulfoximine and *n*-BuLi. The diffusion coefficients, extracted as above from the 2D ^{6}Li DOSY map for the two lithium signals at 1.08 and 1.73 ppm, pointed to a molar weight of 539 g mol^{-1} (Figure S9-b, Table S2). This data, together with the above spectroscopical evidences listed above, indicates that **Agg2** is a mixed dimer between a dilithiated sulfoximine and one *n*-BuLi, solvated, on average, by four molecules of THF [dilithiated sulfoximine/*n*-BuLi]*4 THF.

We next ran a DFT optimization of this complex following the same computational protocol. The results show that no more than two THF molecules can be coordinated to Li^4 and Li^5, leading to a hexa-solvated complex (Figure 6a). This discrepancy between the DOSY and DFT solvation schemes can be assigned to the dynamic vs. static characters of the two approaches.[27]

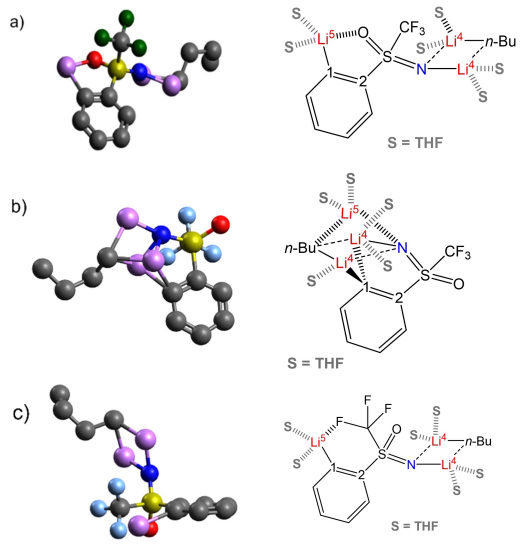

Figure 6. PCM(THF)-M06-2X/6-31++G** optimized structures of mixed aggregate **Agg2** [dilithiated sulfoximine/*n*-BuLi]*6THF. THF and hydrogens are omitted for clarity. a) Li^5-O coordination. b) Li^5-N coordination. c) Li^5-F coordination. For a full representation of the solvated mixed dimer, see Supporting Information.

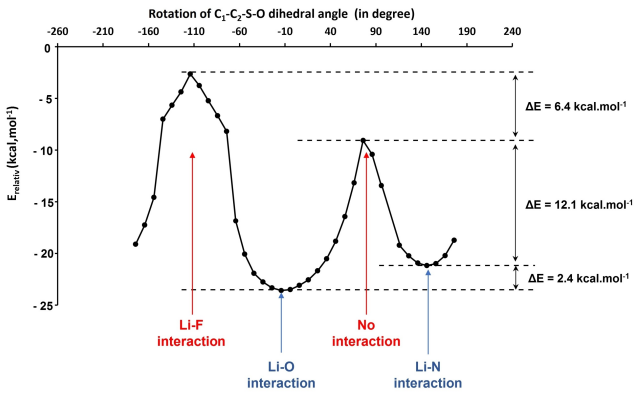

Figure 7. Energy of [sulfoximine/*n*-BuLi] aggregate as a function of the C_1–C_2–S–O dihedral angle.

The unexpected O-Li interaction resulting from the coordination of the Li^5 lithium atom by the oxygen of sulfoximine is worth underlining ($d_{O\text{-}Li5} \approx 1.9$ Å),[28] and the strength of this O-Li^5 interaction was worth probing. The sulfur atom carrying two other groups also able to coordinate the lithium cation, we thus exerted an incremental rotation (10 degree steps) around the bond between the sulfur and the aromatic carbon with a constrained re-optimization at each step.

Plotting the energy of the [sulfoximine/*n*-BuLi] aggregate **Agg2** *vs.* the C^1–C^2–S–O dihedral angle shows two minima (Figure 7). The slightly more stable conformer ($\Delta E = 2.4$ kcal mol^{-1} at the 6-31++G** level and 2.3 kcal mol^{-1} at the 6-311++G** level) is observed when C^1–C^2–S–O = −24.1 degrees (**Agg2-a**), for which the O-Li coordination is optimal. Overall, the coordination of Li^5 by the oxygen of sulfoximine stabilizes the complex by ≈14.5 kcal mol^{-1}, in good accord with literature data.[29]

Interestingly, a second minimum is found, in which the nitrogen coordinates Li^5 ($d_{N\text{-}Li5} \approx 2.0$ Å, Figure 6b) in place of the oxygen (C^1–C^2–S–O = 145.9 and C^1–C^2–S–N = 5.1 degrees, **Agg2-b**). In the resulting structure, the three lithium cations are located in the same portion of space, where they are in interaction with both the nitrogen and the C_α of *n*-BuLi. In addition, two of these Li atoms interact with C^1. Such a compact arrangement is probably favoured in the solid state, as observed on the X-ray data of a deprotonated aromatic sulfoximine.[30] Note that an energy maximum is computed when the CF_3 group faces Li^5, probably because a Li–F interaction arises ($d_{Li\text{-}F} = 1.96$ Å) that destabilizes the complex by splitting the N–Li or O–Li coordination and dragging the lithium cation away from C^1 (Li being pulled off the aromatic plane, Figure 6c). A QTAIM electron density analysis[31] supports this hypothesis (see Table S3).

Since the rotation study was run with the non-solvated **Agg2**, the two local minima were reoptimized after explicit solvation by the highest possible number of 5 THF molecules.[32] This extra-step increased the stability of **Agg2-a-5THF** which becomes favored by 5.8 kcal mol^{-1} with respect to **Agg2-b-5THF**, suggesting that **Agg2-a** is clearly the favored conformation in solution.

We completed our analysis checking that the three remaining ^{6}Li signals, one doublet at 1.04 ppm and two singlets at 1.69 ppm and 1.74 ppm, belonged to a single **Agg3**.

At 185 K, we observe: i) an intra-aggregate exchange correlation between the doublet at 1.04 ppm and the singlet at 1.69 ppm on the 2D ^{6}Li-^{6}Li EXSY (Figure S5); ii) a $^2J_{Li\text{-}Li}$ scalar coupling between the doublet at 1.04 ppm and the singlet at 1.74 ppm on the 2D ^{6}Li-^{6}Li COSYLr (Figure S6) maps. Complementarily, a 2D ^{6}Li-^{1}H HOESY map (Figure S7) showed correlations between the two lithium signals, at 1.04 and 1.69 ppm, and the CH_2Li signal of *n*-BuLi. These observations suggested we delt with a mixed aggregate between a dilithiated sulfoximine and one or more molecules of *n*-BuLi. As discussed above, the coupling constant $^1J_{6Li\text{-}15N} = 2.7$ Hz (measured on the lithium signal at

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1.04 ppm) and the integration ratio 3:1 (obtained by deconvolution of the 1D ^{6}Li spectrum, see Figure S10-c and Table S2) of the two coupled lithium signals establish they belong to a same tetrameric aggregate.

The complementary 2D ^{6}Li DOSY and ^{1}H DOSY experiments led to an experimental molecular weight of 803 g mol^{-1} (Figure S9-c, Table S2). This value, in conjunction to the spectroscopical data presented above, suggests that **Agg3** is a tetrameric aggregate associating one dilithiated sulfoximine and three molecules of *n*-BuLi, solvated by six molecules of THF in average.

On a mechanistic point of view, we assume that **Agg3** ensues from the exchange between **Agg2** and the abundant (*n*-BuLi)$_4$, an equilibrium (Figure 8) that can be summarized as: **Agg2** + (*n*-BuLi)$_4$ = **Agg3** + (*n*-BuLi)$_2$.[33] Note that, provided kinetic parameters permit, this can also explain the uncommon (*n*-BuLi)$_4$/(*n*-BuLi)$_2$ ratio observed in Figure 3d.

A DFT optimization of the geometry suggests a coordination between Li^{8} and the oxygen of sulfoximine, similar to that discussed above, and the solvation by six molecules of THF, in accord with the DOSY spectroscopical observations. Four THF molecules solvate the lithium cations of the cubic appendage (Li^{6}+Li^{7}), while two stick on Li^{8} (Figure 9).

The match between the 1D ^{6}Li experimental signals and the proposed [dilithiated sulfoximine/(*n*-BuLi)$_3$] aggregate was checked reproducing, with the Dmfit software,[25] the spectrum of a spin system made up of three signals: i) a Li^{6} doublet at 1.04 ppm with a scalar coupling $^{1}J_{6Li\text{-}15N}$ = 2.7 Hz and a relative integration of 37; ii) a second Li^{8} singlet at 1.69 ppm with a relative integration of 13; and iii) a third Li^{7} singlet at 1.74 ppm with a relative integration of 14. These data are in good agreement with the 3:1:1 ratio expected for Li^{6}/Li^{7}/Li^{8} (Figure S10-c, Table S2).

Finally, what happens when *n*-butyllithium is added to sulfoximine **1d**? Our results suggest that the first equivalent *n*-BuLi expectedly deprotonates NH, affording a dimer organized around a disolvated N–Li–N–Li quadrilateral core (Scheme 3). Adding an excess of *n*-BuLi leads to a combination of mixed aggregates associating the N–Li sulfoximine and *n*-butyllithium in various proportions. It seems that the *n*-BuLi molecules sequestrated in the inner organometallic core of the aggregates cannot deprotonate the *ortho*-aryl position and that an extra equivalent of *n*-butyllithium is needed to trigger this reaction and afford **Agg2**.

The remaining excess of *n*-BuLi would finally transform progressively **Agg2** into **Agg3**. Note that in those two complexes, the reactive aryl center lies away from the cohesive N–Li–Bu–Li core, and seems therefore fully accessible to the electrophile. A minor **Agg1** contaminates these species; it incorporates the usual side-product of *n*-BuLi, *viz.* lithium butoxide. This alkoxide gives a more

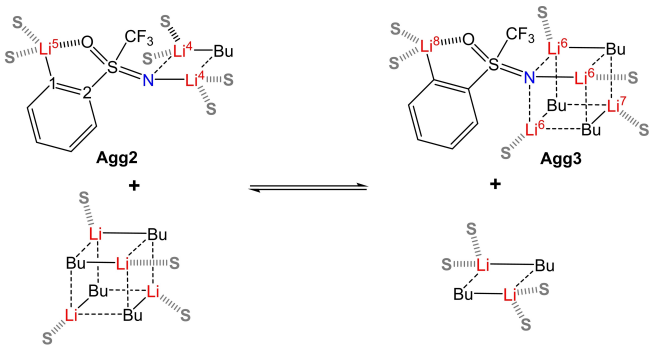


Figure 8. Association of **Agg2** and (*n*-BuLi)$_4$ to form **Agg3**.

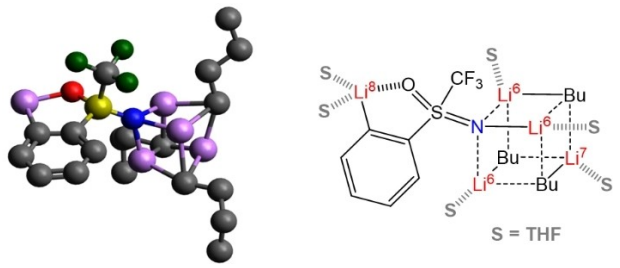
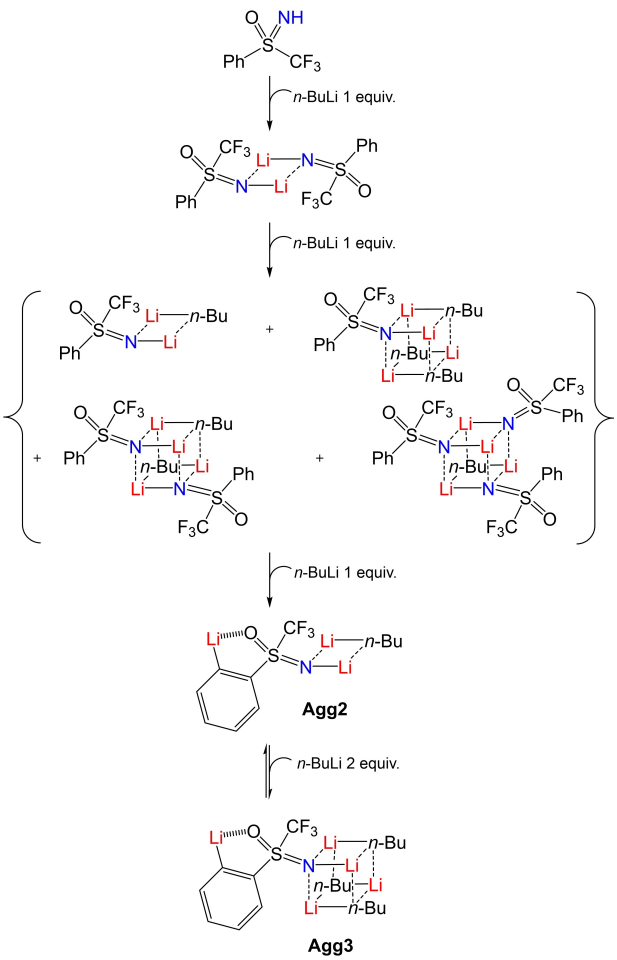


Figure 9. PCM(THF)-M06-2X/6-31++G** optimized structures of **Agg3**. THF and hydrogens are omitted for clarity. For a full representation of solvated mixed tetramer, see Supporting Information.



Scheme 3. Assumed evolution of sulfoximine aggregation as a function of added *n*-BuLi.

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compact tetrameric aggregate to which the aryllithium participates and is therefore probably less reactive.

Conclusion

In conclusion, this study explains why an excess of *n*-butyllithium is needed to efficiently deprotonate the aromatic ring bound to the sulfoximine unit. An early NH deprotonation is observed when the first equivalent *n*-BuLi is added. The next *n*-BuLi equivalents trigger the formation of three aggregates, of which structure could be unambiguously established. The two major ones **Agg2** and **Agg3** (78 % total), which may be the reactive species within the Curtin–Hammett frame, have similar structures, and their DFT modelling shows that oxygen plays the role of the stabilizing ligand. This feature was difficult to predict since the N and F atoms could also play the role of the coordinating group.[34] The structure of the three aggregates also precises the ubiquitous role played by *n*-butyllithium: if this trapped *n*-BuLi cannot behave as an "intramolecular" base, the steric and electronic shielding it exerts around the sulfur atom probably protects this sensitive center from nucleophilic attacks. Such an aggregation cannot occur with the N-methyl sulfoximine, possibly accounting for its degradation in similar conditions. Last, not least, the aromatic C–H deprotonation irreversibly occurs when enough extra (free) *n*-BuLi is finally available as a base.

We believe this work participates to the effort by the chemists' community to better understand the structure of reactive intermediates. Such approaches, made possible by the recent and spectacular progresses of analytical sciences, are expected to clarify problems of reactivity left unexplained and calling, in general, for empiric solutions. Getting access to the inside information of processes becoming increasingly important in a world of data-management, high-precision mechanisms are likely to bring soon a high added-value.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Density-Functional Calculations · Intermediates · Lithiation · NMR Spectroscopy · Sulfoximines

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