

Organolithium Reagents

Hetero-Aggregate Compounds of Aryl and Alkyl Lithium Reagents: A Structurally Intriguing Aspect of Organolithium Chemistry

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Organolithium compounds are often depicted as mononuclear species. However, such compounds are in fact aggregated species and can form hetero-aggregates containing different organic groups, including heteroatom groups. In reactions involving organolithium reagents, the “pure” homo-aggregate organolithium compound can change into a hetero-aggregate, which has a different structure and reactivity to the homo-aggregate. This fact is often overlooked. When there are chiral centers in the organolithium reagent or the substrate, diastereoselective self-assembly (the preferential formation of a particular diastereoisomeric aggregate) plays a role. The importance of these contributions in understanding the structure and reactivity patterns of organolithium reagents is the focus of this Minireview.

1. Introduction

The use of organolithium compounds has evolved from what was an academic curiosity sixty years ago^[1a,b] to what is today an essential component of organic synthesis.^[1c-g] These organometallic reagents are used in a vast variety of chemical reactions from the undergraduate academic level to the large-scale applications in industry.^[2] Organolithium reagents are often depicted schematically as mononuclear species (that is, containing a single Li atom and a single “R” group: for example, *n*-butyllithium as “*n*BuLi”), however, the chemistry and structure of these compounds is much more complex.

Understanding this complexity is important for describing new reactivity patterns and for the interpretation of information related to mechanism(s). To clarify, *n*BuLi itself is a hexamer, [*n*Bu₆Li₆], in the solid state with a structure consisting of a core of alternating Li and C atoms.^[3] This homo-aggregate is at least partially retained in solution in apolar media but in solvents such as diethyl ether, the presence of tetramers and dimers becomes predominant. It is not only the structure but also the reactivity of the various aggregated forms of even simple organolithium compounds that can be very complicated.^[1c-g] The reactivity of organolithium compounds is highly dependent on factors such as the nature of the solvent, concentration, temperature, the availability of potential donor ligands, salts (e.g., LiX) and/or other organolithium compounds.^[1c-g,4]

2. Formation of Hetero-Aggregates

The primary importance of the aggregation properties of (RLi)_x species resides in their potential for profound effect(s) on reactivity.^[5] Two primary examples of this phenomenon are the “LiX effect” and the related influence of lithium alkoxides (R'OLi)_y and amides (R'₂NLi)_z, on organolithium reactivity. The “LiX effect”^[6] is a manifestation of the in situ formation of [(RLi)_x(LiX)_y] aggregates which “self-assemble” upon addition and/or formation of a salt LiX (X = Cl, Br, or I) in a solution of the RLi reagent. Hence, the hetero-aggregated form is more stable than the homo-aggregate (RLi)_n and (LiX)_n species. The formation of this type of multinuclear Li complex has indeed been known for some

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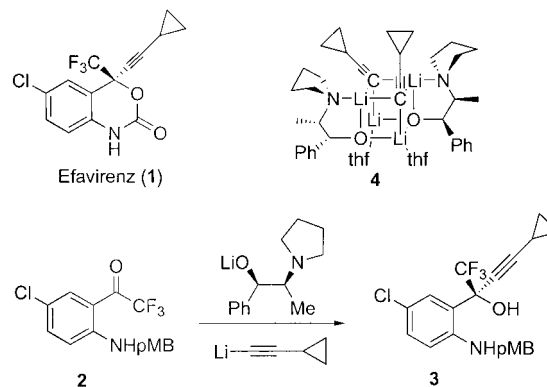
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time.^[7] Its importance lies in the fact that such hetero-aggregation leads to an observable modification (reaction rate, selectivity) of the nucleophilic properties of R relative to those demonstrated by the parent species $(\text{RLi})_x$. The addition of such salts is now common practice in yield-optimization studies in organic and polymer chemistry when organolithium reagents are involved, although the nature of the RLi-LiX interaction and the reasons for the effect on the reactivity of R, are rarely detailed.^[6] An important consequence of this chemistry is described in the following hypothetical situation. In many cases, the “quenching” of a reaction mixture involving an in situ formed organolithium is carried out using electrophilic sources E-X (e.g., $\text{E} = \text{Me}_3\text{Si}(\text{TMS})$; $\text{X} = \text{Cl}$). The product of such an addition is LiX : a potential source of nucleation for a hetero-aggregate with residual RLi . This hetero-aggregate may now begin to modify the reaction profile because “independent” $(\text{RLi})_n$ compounds often react differently with E-X than does the $[(\text{RLi})_x(\text{LiX})_y]$ hetero-aggregate.^[8] Note that such $[(\text{RLi})_x(\text{LiX})_y]$ hetero-aggregate species can be viewed as a “resting state” that forms with E-X and hence is a kinetic intermediate from which product formation occurs. This occurrence may be a further explanation for the often spectacular improvement of yield when TMS-OTf ($\text{OTf} = \text{triflate} = \text{SO}_3\text{CF}_3$) is used to replace TMS-Cl as the electrophile. The OTf group is certainly a better leaving group than the chloride ion but in the situation where LiOTf is also forming a hetero-aggregate, this hetero-aggregate will undoubtedly have different structural features and kinetic reactivity with E-X .

Such hetero-aggregate formation is also closely mimicked by the presence of $(\text{R}'\text{OLi})_n$ or $(\text{R}'_2\text{NLi})_n$ species in solutions of RLi reagents.^[9,10] This situation occurs frequently in synthesis reactions since reagents such as lithiumdiisopropylamide (LDA ; used for RLi generation), or lithium alkoxide impurities (formed by RLi hydrolysis) are present in solution at the same time as the desired RLi compound. The hetero-aggregate $[(\text{RLi})_x(\text{R}'_2\text{NLi})_y(\text{solvent})_z]$ ($\text{solvent} = \text{solvent}$) can likewise have a great influence on the overall nature and reactivity of the organolithium components that are present in a reaction mixture. The effects and solution structural features of these amido adducts of organolithium reagents have been studied in some detail.^[1c-g,10] The above lithium alkoxide situation is closely related to the recent

investigations by Collum and co-workers^[11] which have demonstrated the important influence of $[(\text{RLi})_x(\text{R}^*\text{OLi})_y(\text{solvent})_z]$ ($\text{R}^*\text{O} = \text{ephedrenato}$) hetero-aggregates on the enantioselective addition of lithium acetylides to quinazolinones.^[1c-g,4,11] A specific example of this enantioselective addition is involved in the formation of the anti-HIV drug, Efavirenz (**1**; Scheme 1) formed by a multi-step process.^[9a] A



Scheme 1. Key enantioselective step in the synthesis of Efavirenz. pMB = *p*-methoxybenzyl.

key step is the formation of intermediate **3** by the low-temperature enantioselective addition of lithium cyclopropylacetylide to quinazolinone **2**. One hetero-aggregate **4** has been specifically identified as an essential intermediate which induces the enantioselective addition of **2** to **3**; aggregate **4** is only formed after the addition of $[\text{R}^*\text{OLi}]$ to lithium cyclopropylacetylide and a suitable induction period.^[4,8,10]

Much less studied (or discussed) are the structures of mixed aryl or alkyl lithium hetero-aggregates, that is, $[(\text{RLi})_x(\text{R}'\text{Li})_y(\text{solvent})_z]$.^[1c-g,10f,10k,11-14] This situation is somewhat surprising since the formation of an ArLi typically either involves Li-X or Li-H exchange reactions. In Li-H exchange, the amount of ArLi formed gradually increases as the lithiating agent, such as $n\text{BuLi}$, is consumed. This is an ideal situation for the formation of hetero-aggregates. These mixed species, consisting of different alkyl and/or aryl carbanion sources, can exert a profound influence on the overall outcome of chemical syntheses that involves RLi reagents.



Gerard van Koten has been Professor of Organic Synthesis and Catalysis at the Debye Institute of Utrecht University since 1986. In 2004 he became Distinguished Professor of Utrecht University. Recently, he was appointed chairman of the committee for the Chemistry Educational Programme at the Secondary School level in the Netherlands. His research interests comprise the study of fundamental processes in organometallic chemistry and the application of organometallic complexes as homogeneous catalysts. His interest in supramolecular systems with (organometallic) catalytically active functionalities include the preparation and use of the first examples of homogeneous metallo-dendrimer catalysts.



Johann Jastrzebski was born in Maartensdijk, the Netherlands in 1954. He started his career in organometallic chemistry as a technician in 1974 at the “Organisch Chemisch Instituut TNO, Utrecht, The Netherlands (Prof. G. J. M. van der Kerk). In 1979 he moved to the Inorganic Chemistry Department of the University of Amsterdam (Prof. K. Vrieze and Prof. G. van Koten). In 1986 he joined the group of Prof. G. van Koten at the Organic Chemistry Department of Utrecht University, where he received his Ph.D. in 1991. He is interested in metal-mediated organic synthesis, main-group organometallic chemistry, and homogeneous catalysis.

For example, it has been known for some time that *t*BuLi is at least an order of magnitude more reactive in solutions containing equimolar *i*PrLi.^[5] Detailed study of this class of organolithium hetero-aggregates are quite sparse, but their formation and hence effects on chemical synthesis are probably much more common than currently realized.

The first such hetero-organolithium aggregate characterized in the solid state was not reported until 1993.^[13] The complex [(*n*BuLi)₂(2,4,6-*t*Bu₃C₆H₂Li)₂] (**5**) results from the reaction of 2,4,6-*t*Bu₃C₆H₂Br with *n*BuLi in hexane solution. The solid-state structure is indeed unusual (Figure 1) and

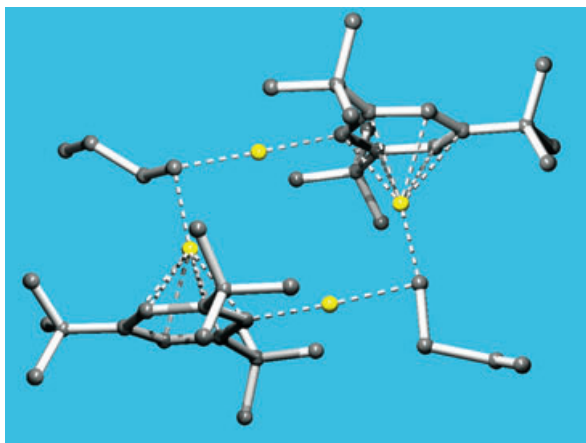


Figure 1. Structure of [(*n*BuLi)₂(2,4,6-*t*Bu₃C₆H₂Li)₂] (**5**) in the solid state determined by X-ray diffraction. Yellow Li.^[13]

contains hydrocarbon fragments which bridge two chemically distinct lithium atoms: one lithium atom is η⁶ bonding with the aromatic ring and the other is η¹ bonding with the butyl group. Apparently, this hetero-aggregate is the end product of the 1:1 molar aggregation of 2,4,6-*t*Bu₃C₆H₂Li and *n*BuLi; note that this situation leaves an equivalent of 2,4,6-*t*Bu₃C₆H₂Br in the reaction solution. The discovery of such a hetero-aggregate was a relatively new phenomenon during the course of an Li–Br exchange reaction and clearly indicates that during Li–Br exchange, stable hetero-aggregates can be formed that are kinetically inert to further reaction with aryl bromides. Hence, the formation of this hetero-organolithium



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aggregate influences not only the yields of desired organolithium homo-aggregate but also leads to an unwanted product that contains residual alkyl lithium. Consequently, such species now become a topic of consideration when attempting to understand and control a reaction profile that is intended to either maximize the in situ formation of the desired RLi species^[15] and/or influence the regio- or stereochemical outcome of a synthetic procedure.^[1c-g,5,6,8-11]

The importance of this concept was first presented by us in 1989 during the course of our studies on the metalation of tertiary nitrogen donor ligands for use in organocopper chemistry.^[15] The reaction of *n*BuLi with (*R*)-[(1-dimethylamino)ethylbenzene] (**6**; dmaebH) in Et₂O solution was envisioned to yield the desired lithiated product **7** (see Scheme 1) by the well-known directed *ortho*-metalation (DoM) reaction.^[16] Analogous chemistry involving the DoM of achiral *N,N*-dimethylbenzylamine (dmbaH) was already known^[17] to yield cleanly (> 95 %) the *ortho*-lithiated product (dmbaLi).^[18] As expected, when *n*BuLi is added to **6**, selective metalation does indeed occur. Quenching of the reaction mixture after an appropriate time period with an electrophile, such as D₂O however, gives direct evidence for a disappointing 50 % yield of the *ortho*-metalated product.

This puzzling result precludes the use of such synthetic methods for further reactions with species such as CuX, owing to contamination by residual **6** and the potential presence of remaining *n*BuLi. The yields cannot be increased by the addition of excess *n*BuLi. Such a result is often attributed to ill-defined “steric effects” or the “weak” nucleophilicity of the butyl anion derived from *n*BuLi. Justification for this “weak” nucleophilicity conclusion is provided by the fact that complete *ortho*-lithiation of **6** to yield pure **7** (Figure 2) can be realized using *t*BuLi.^[19] This supports the hypothesis that the *t*Bu anion is simply a stronger or “harder” nucleophile than *n*Bu anion. However, NMR spectroscopic investigations of a 1:1 mixture of *n*BuLi and **6** revealed that in contrast to the reaction with dmbaH, the product of DoM, compound **7**, readily self-assembles with further equivalents of the reagent *n*BuLi and residual **6** to form a presumably thermodynamically stable mixed species [(dmaebLi)₂(*n*BuLi)₂(dmaebH)₂]

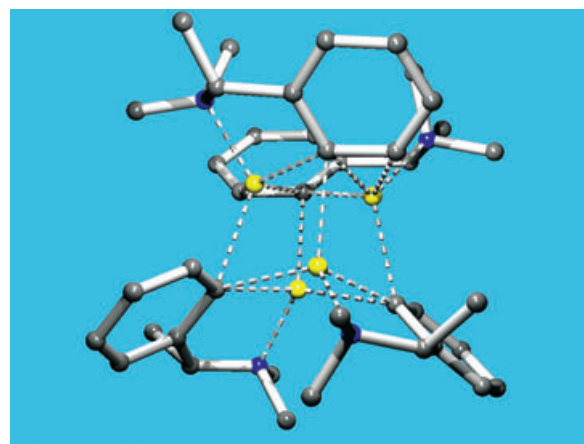
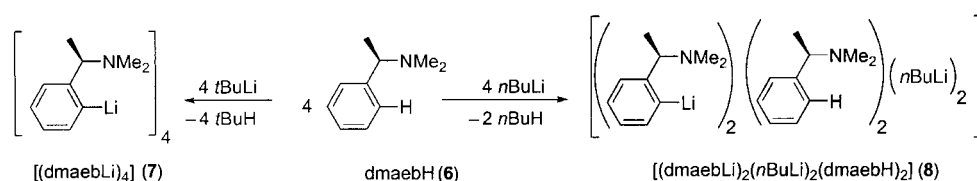


Figure 2. Structure of (dmaebLi)₂(*n*BuLi)₂(dmaebH)₂ (**7**) in the solid state determined by X-ray diffraction. Blue N, yellow Li.^[19]



Scheme 2.

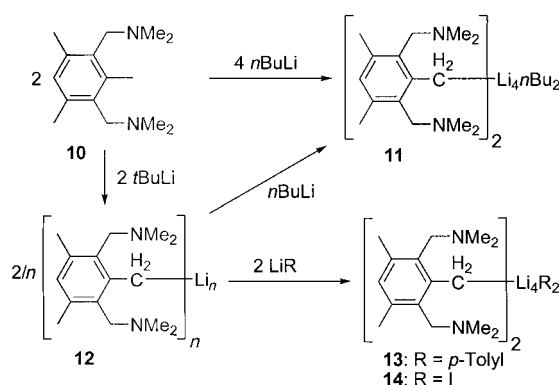
(8, Scheme 2). Hetero-aggregate **8** is so stable that in essence an equivalent of *n*BuLi and an equivalent of arene **6** have been “trapped” by each equivalent of **7** formed (compare with **5**, Figure 1).

The above observation in DoM chemistry is very likely a direct result of the stability of the in situ formed hetero-aggregate **8** and neither a consequence of steric effects nor the weak nucleophilicity of the butyl anion derived from *n*BuLi. The effectiveness of *t*BuLi can therefore be explained by invoking the idea that hetero-aggregates analogous to **8** containing sterically more demanding alkyl lithium species are significantly less stable or kinetically more disposed to initiate further DoM reactions. In other words, such hetero-aggregates are intermediates or kinetically short-lived ordered transition states (Scheme 2). Hence, *t*BuLi mediates complete DoM. The overall stability of aggregates such as **8** is highlighted by the fact that pure homo-aggregate **7** reacts cleanly in apolar solvents (yield > 90 %) with *n*BuLi to form a hetero-aggregate (free of **6**) that we have been able to isolate in pure form $[(\text{dmaebLi})_2(\text{nBuLi})_2]$ (**9**) and thereafter fully characterize by solution NMR spectroscopy, cryoscopy, and single-crystal X-ray diffraction (Figure 3).^[20]

As yield optimization is a vital aspect of synthesis involving in situ formed RLi reagents, the two above examples should serve as a caveat to those using RLi. This situation is especially true in cases where yields are “suspiciously” measured as being 50% or 75%; such values suggest the formation of “whole number” hetero-aggregates. For example, a 75% yield suggests a 3:1 hetero-aggregate of the desired R’Li (3 equiv) product and the initial RLi molecule (1 equiv),

in other words, $[(\text{RLi})(\text{R}'\text{Li})_3]$ is formed. Such aggregation phenomena and their consequences, which are unexpected because we typically envision RLi reagents as mononuclear species, is of importance to synthetic organic (and organometallic) chemistry.

Other such hetero-aggregates can be formed with modified tertiary amine containing NCN “pincer” ligands,^[21] such as during the metalation of 1,3-bis[(dimethylamino)methyl]-2,4,6-trimethylbenzene (**10**).^[22] Reaction of **10** with 2 equivalents of *n*BuLi (in truth a 1/3 equivalent of $[\text{nBu}_6\text{Li}_6]$, see above) in hexane solution yields the hetero-aggregate **11** (Scheme 3). The solid-state structure of **11** (Figure 4) is more



Scheme 3.

typical of organolithium compounds in general than that observed earlier by Power et al. with complex **5**.^[13] The structure of **11** was at the time only the second such hetero-aggregate to be characterized by single-crystal X-ray diffraction. In relation to **6** discussed earlier, *t*BuLi will fully monodeprotonate **10** at the 2-methyl position to yield **12** (the bis-*ortho*-substituted benzyl lithium) and in a similar way, homo-aggregate **12** reacts with *n*BuLi to give back hetero-aggregate **11**. Hence, the formation of thermodynamically stable hetero-aggregates are suggested since **11** is definitely a minimum on the potential energy surface, regardless of whether its formation is approached directly from **10** or via **12**. This chemistry is not limited to the *n*BuLi aggregate, as structurally analogous and stable hetero-aggregates of **10**, each having the $[(\text{NCN})_2\text{Li}_4]^{2+}$ core structure in common, are formed from **12** with the *p*-tolyl anion (\rightarrow **13**) or an iodide anion (\rightarrow **14**; Scheme 3; LiX effect, see above).^[23] In a similar way, 1,3-bis[(dimethylamino)methyl]-2-[(trimethylsilyl)methyl]-4,6-dimethylbenzene (**15**) can be selectively deprotonated at the silylmethylene position with *n*BuLi, *t*BuLi, or *p*-tolyl lithium to form lithium clusters **16a–c** and in all three

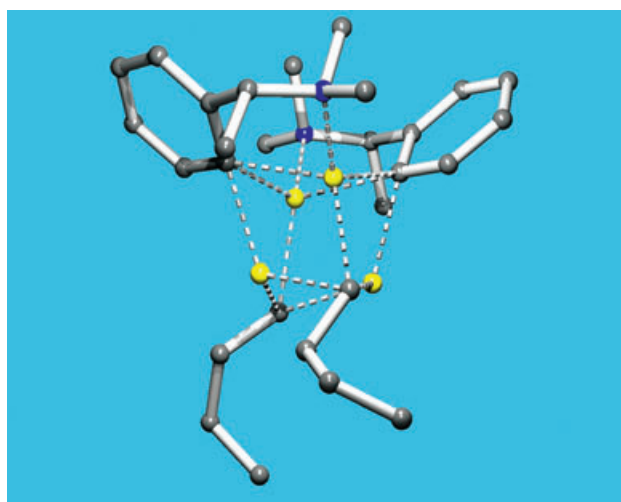


Figure 3. Structure of $[(\text{dmaebLi})_2(\text{nBuLi})_2]$ (**9**) in the solid state determined by X-ray diffraction. Blue N, yellow Li.^[20]

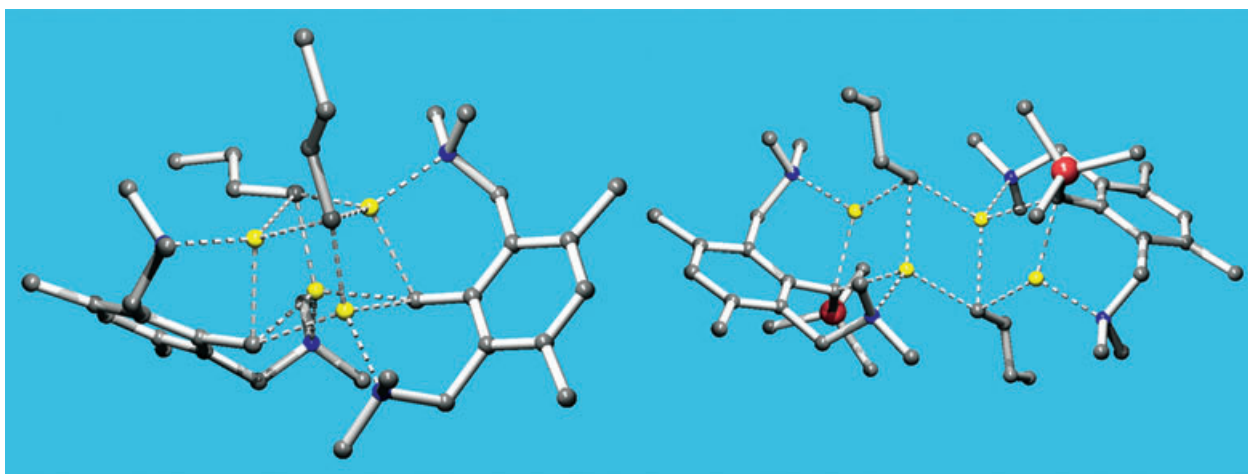
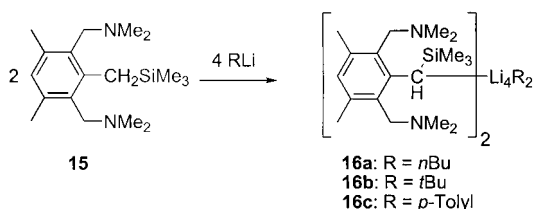


Figure 4. Structures of **11** (left) and **16a** (right) in the solid state determined by X-ray diffraction. Blue N, yellow Li, red Si.

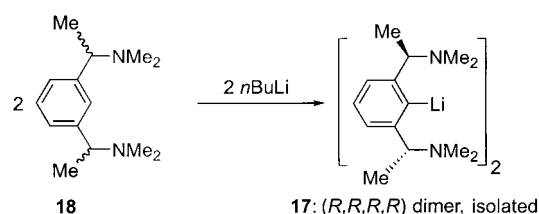
cases, 2:2 hetero-aggregates result (Scheme 4).^[24] These particular lithiated “pincer” hetero-aggregates are, in terms of the $[\text{R}_2\text{Li}_4]^{2+}$ core structure, distinct from that of **11** in the solid-state (Figure 4).^[25]



Scheme 4.

3. Diastereoselective Self-Aggregation

We have put forward the idea that alkyl/aryl lithium hetero-aggregates can have important reactivity consequences. We have yet to consider one other important feature of this concept; this is the idea of induced chiral selection during aggregate formation. The lithium atom in these (and most lithium containing) organic materials is typically tetrahedrally coordinated and hence the presence of four chemically distinct groups attached to the lithium atom infers the formation of a stereogenic lithium center. As the precursor molecules to these aggregates are typically achiral, enantioselective aggregate formation seems intuitively unlikely. This possibility has, however, been previously demonstrated. An early example of this idea was the specific formation and isolation of both complex **16a** (see Scheme 4)^[24,26] and our independent isolation of (*R,R,R,R*)- $[(\text{NCNLi})_2]$ (NCN = 2,6- $[\text{Me}_2\text{NCH}(\text{Me})_2\text{C}_6\text{H}_3]$) from mixtures of 1:1 *rac/meso* 2,6-bis[1-(dimethylamino)ethyl]-1-lithiobenzene (**17**; (Scheme 5).^[27] Lithiation of arene **18**, known to exist as a 1:1 *rac/meso* mixture, lead to the isolation of dimeric **17** (Scheme 5; Figure 5).^[27] Following lithiation, the *R,R* form of $[(\text{NCNLi})]$ aggregates only with a second moiety of identical chirality to form selectively isolable (*R,R,R,R*)- $[(\text{NCNLi})_2]$.^[27] In this



Scheme 5.

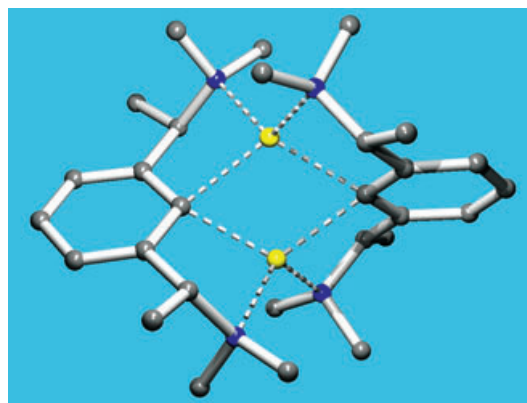
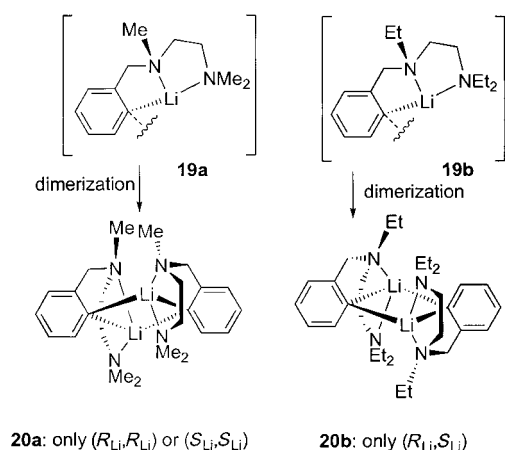


Figure 5. Structure of (*R,R,R,R*)- $[(\text{NCNLi})_2]$ (**17**) in the solid state determined by X-ray diffraction. Blue N, yellow Li.

case, pure chiral centers (per molecule) were present at the benzylic positions before aggregate formation, although a *rac/meso* isomeric mixture of individual molecules was present. This result suggested to us that chirality resulting only after lithiation might induce the same kind of selectivity.

The formation of fragments **19a** (R = Me) and **19b** (R = Et; Scheme 6) from Li–Br exchange of *o*- $\text{BrC}_6\text{H}_4\text{CH}_2\text{N}(\text{R})\text{CH}_2\text{CH}_2\text{NR}_2$ results in each case in the formation of two possible stereogenic centers: one with a stable configuration at the benzylic N atom, the second stereogenic center is created at the lithium centers when two such $[(\text{CNN})\text{Li}]$ moieties combine to form the dimeric aggregates **20a** or **20b** (Scheme 6).^[28] In the case of **19a**, the



Scheme 6.

stable species is always formed between two $[(CNN)Li]$ fragments with the same chirality at the lithium atom. Hence, selective formation of 1:1 (R_{Li}, R_{Li})- $[(CNN)_2Li_2]$ (Figure 6) and (S_{Li}, S_{Li})- $[(CNN)_2Li_2]$ is accomplished (chirality in this case being defined only at the lithium centers). The “meso” form dimer of **19a** (that is, (R_{Li}, S_{Li})- $[(CNN)_2Li_2]$) is not a thermodynamically stable aggregate and hence only enantioselective dimerization occurs. This situation is reversed, perhaps for steric reasons, when two **19b** $[(CNN)Li]$ moieties combine. This combination gives only the meso form: (R_{Li}, S_{Li})- $[(CNN)_2Li_2]$ (Figure 6). Hence, aggregate formation

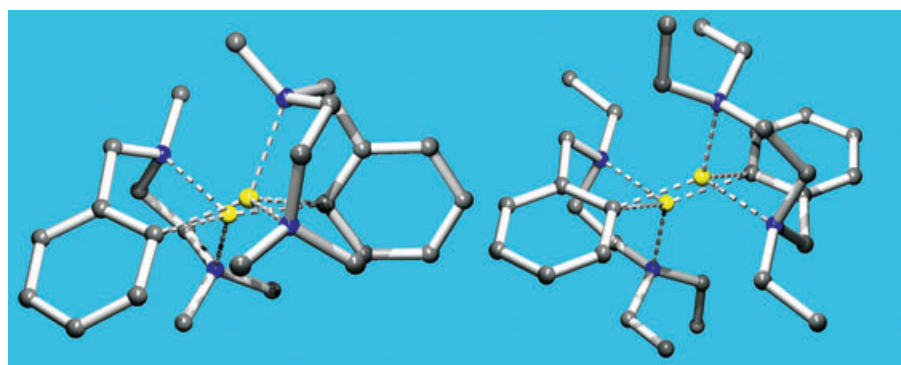


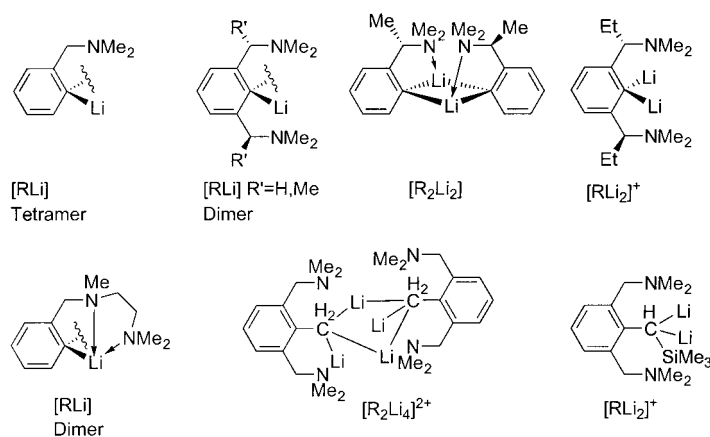
Figure 6. Structures of (R,R)- $[(CNN)_2Li_2]$ (**20a**; left) and (R,S)- $[(CNN)_2Li_2]$ (**20b**, right) in the solid state determined by X-ray diffraction. Blue N, yellow Li.

can induce and control chirality. Complex **20b** is an aryl–aryl organolithium hetero-aggregate where the only difference between two moieties that combine to form the aggregate itself is their chirality.

This concept may become important in cases of hetero organolithium aggregates that contain chiral and/or achiral fragments. Pre-defined chirality may or, more importantly, may not allow the formation of specific organolithium aggregates to be controlled in a predictable way. These species could indeed have unique (enantioselective) reaction pathways. The subtle changes in the ligands in **19a** and **19b** and their influence on the products **20a** and **20b** are a testimony to that idea.

4. Concluding Remarks

A summary of the types of fragments that can self-assemble with themselves, with each other, and with other organolithium species is shown in Scheme 7. Note that the



Scheme 7.

dimeric fragments are structurally similar to the classical “monomer” representation of an organolithium, that is, simply “RLi” and the lithium atoms act as bridges between these units. The aggregates of RLi fragments can be viewed as thermodynamically stable resting states of the reactive formal

R anion. The effect of this state on the chemical role of R in synthesis however, can be directly dictated by the relative stability of this aggregated state (or in other words, the depth of the potential energy well); this is a concept that is frequently encountered in enantioselective catalysis. This aspect of organolithium chemistry and its consequences in synthesis clearly deserve further scrutiny.

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