

# Enediolate–Dilithium Amide Mixed Aggregates in the Enantioselective Alkylation of Arylacetic Acids: Structural Studies and a Stereochemical Model

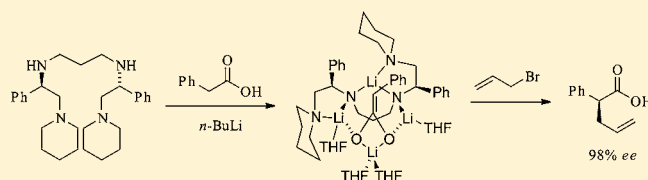
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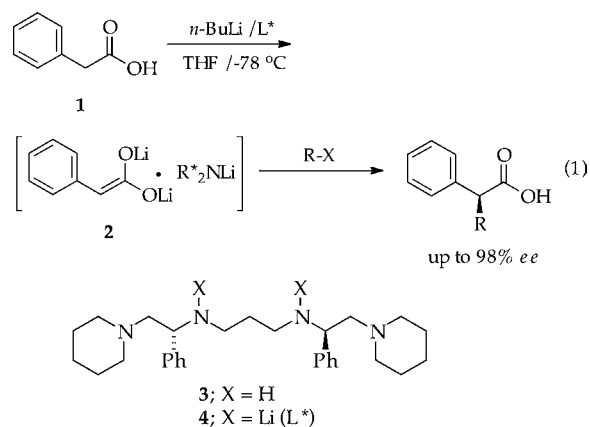
## Supporting Information

**ABSTRACT:** A combination of X-ray crystallography, <sup>6</sup>Li, <sup>15</sup>N, and <sup>13</sup>C NMR spectroscopies, and density functional theory computations affords insight into the structures and reactivities of intervening aggregates underlying highly selective asymmetric alkylations of carboxylic acid dianions (enediolates) mediated by the dilithium salt of a C<sub>2</sub>-symmetric chiral tetraamine. Crystallography shows a trilitiated *n*-butyllithium–dilithiated amide that has dimerized to a hexalithiated form. Spectroscopic studies implicate the non-dimerized trilitiated mixed aggregate. Reaction of the dilithiated amide with the dilithium enediolate derived from phenylacetic acid affords a tetralithio aggregate comprised of the two dianions in solution and the dimerized octalithio form in the solid state. Computational studies shed light on the details of the solution structures and afford a highly predictive stereochemical model.



## INTRODUCTION

Despite remarkable progress in the field of catalytic asymmetric synthesis,<sup>1</sup> asymmetric alkylations of lithium enolates are predominantly based on covalent chiral auxiliaries even in the simplest functionalizations.<sup>2–5</sup> Recently, we developed an alkylation of the dianions of aryl and heteroaryl acetic acids<sup>6</sup> (enediolates)<sup>7</sup> in which a dilithium amide derived from a C<sub>2</sub>-symmetric chiral diamine<sup>8,9</sup> imparts high enantioselectivity (eq 1).<sup>10,11</sup> The enediolate–dilithiated amide complex is generated in situ, circumventing discrete steps to add and remove when covalently bound chiral auxiliaries are used. The reaction shows considerable generality for activated, unactivated, and functionalized electrophiles.



Evidence from a few enantioselective organolithium reactions scrutinized through structural and mechanistic studies<sup>12</sup> has

demonstrated that high stereocontrol can correlate with high structural control of the aggregates.<sup>13</sup> Thus, we presumed that the enantioselectivity in eq 1 derives from a well-defined chiral aggregate, **2**, composed of the dilithium enediolate and the chiral dilithium amide.<sup>11,14</sup> The optimized conditions suggested a 1:1 stoichiometry, although that assertion lacked direct support. Nevertheless, a detailed understanding of the enantioselectivity clearly requires knowledge of the underlying coordination chemistry.

We describe herein a combination of X-ray crystallography, <sup>6</sup>Li, <sup>13</sup>C, and <sup>15</sup>N NMR spectroscopies, and density functional theory (DFT) computations that afford insight into the structures and reactivities of intervening aggregates **5–8**.<sup>15–17</sup> These studies suggest a mechanistic model affording remarkable agreement between observed and computed enantioselectivities.

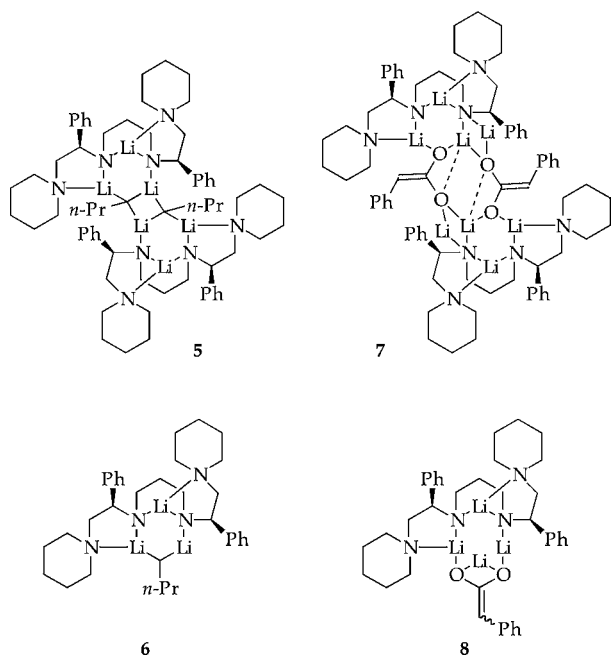
To help guide the reader, we note that the detailed organolithium chemistry delineated in the Results section is summarized for the generalists at the start of the Discussion section. This summary is followed by a discussion of the possible implications and predictive capabilities of the seemingly robust stereochemical model.

## RESULTS

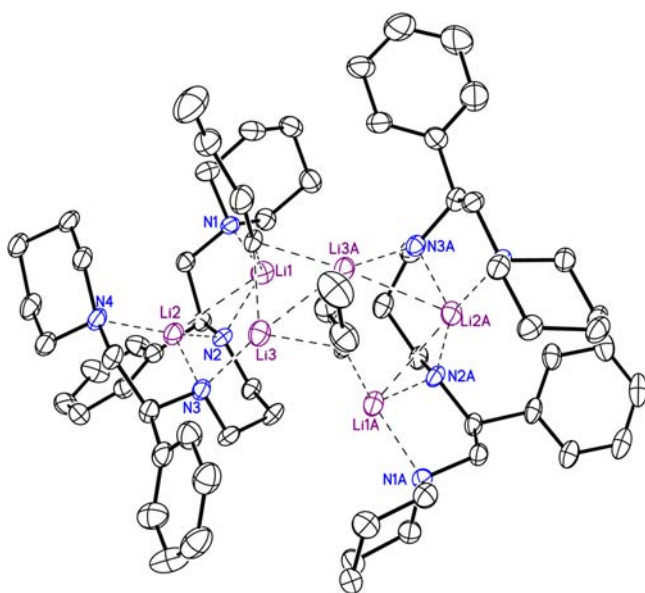
The structures of mixed aggregates **5–8** were determined using a combination of X-ray crystallography, multinuclear NMR spectroscopies, and DFT computations as described below. In addition, COSY, TOCSY, HSQC, HMBC, and ROESY spectroscopies provided support to both the aggregate assignments and spatial orientations. These are archived in the Supporting Information.

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***n*-BuLi–Dilithiated Amide Mixed Aggregate.** *X-ray Crystal Structure.*<sup>14,18</sup> Addition of 4.0 equiv of *n*-BuLi (2.5 M) to a hexane solution of amine 3 at  $-25\text{ }^{\circ}\text{C}$  affords a pale yellow solution. Subsequent crystallization from a hexane/pentane mixture yields  $[\text{Li}_3(\mathbf{1})(n\text{-Bu})_2]$  (**5**) as a colorless microcrystalline solid in 46% yield. The composition of **5** was confirmed with an X-ray diffraction study, and its solid-state structure is shown in Figure 1. Complex **5** crystallizes in the orthorhombic space group



**Figure 1.** ORTEP of hexalithio *n*-BuLi–dilithiated amide mixed aggregate **5**.

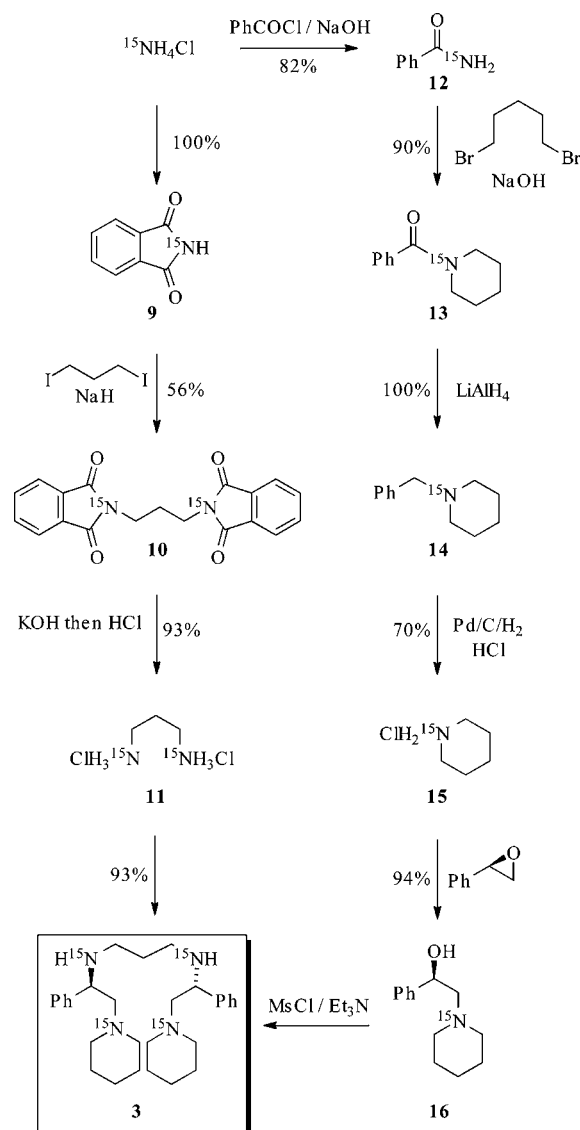
$P2_12_1$  as the pentane solvate **5**. Complex **5** displays overall  $C_2$  symmetry and is assembled from two trilithio components each constituted from an *n*-BuLi and a doubly deprotonated diamine subunit.

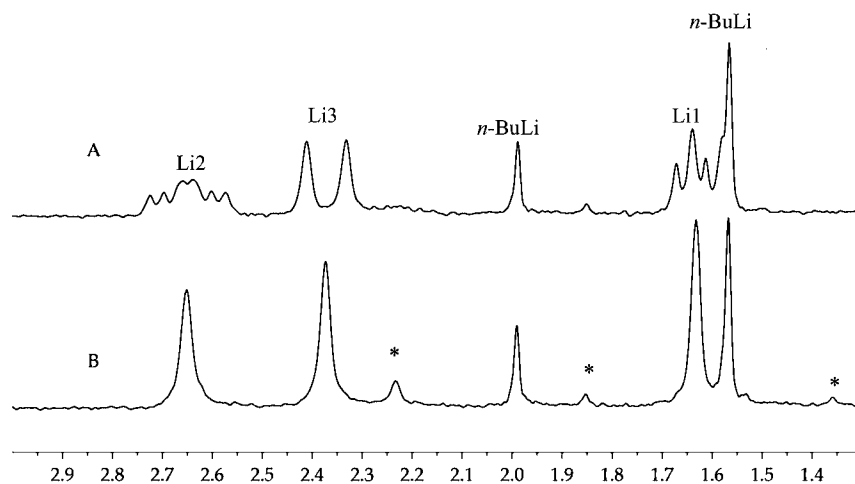
The metrical parameters of each trilithiated fragment are similar to those found in other alkyllithium aggregates.<sup>7</sup> Incorporation of *n*-BuLi into the structure of an organo- or

amidolithium reagent was reported previously.<sup>19</sup> The most interesting feature of the solid-state structure of **5** is the binding mode of the amine ligand. Each piperidine-derived nitrogen atom is coordinated to a single lithium cation, whereas each amide nitrogen atom is coordinated to two lithium cations. More specifically, Li2 is chelated by three nitrogen atoms, N2, N3, and N4, thereby generating a five-membered ring and a six-membered ring. Additionally, Li2, N2, N3, and N4 are all roughly coplanar. This orientation places both phenyl groups in the amine backbones pseudoequatorially. Li1 is coordinated by two nitrogen atoms (N1 and N2), thereby generating a five-membered ring. Finally, Li3 is only coordinated by one nitrogen atom (N3) in addition to the carbon atom (C1 and C1A) of the *n*-Bu fragment. The Li–N(amide) bond lengths are 1.979(5) Å (Li2–N2), 1.923(4) Å (Li2–N3), 1.936(4) Å (Li1–N2), and 1.953(4) Å (Li3–N3), whereas the Li–N(amine) bond lengths are 2.089(4) Å (Li1–N1) and 2.167(4) Å (Li2–N4). Similar bond lengths are seen in the lithium salt of a related bidentate Koga base, *N*-neopentyl-1-phenyl-2-(1-piperidino)ethylamine.<sup>20</sup>

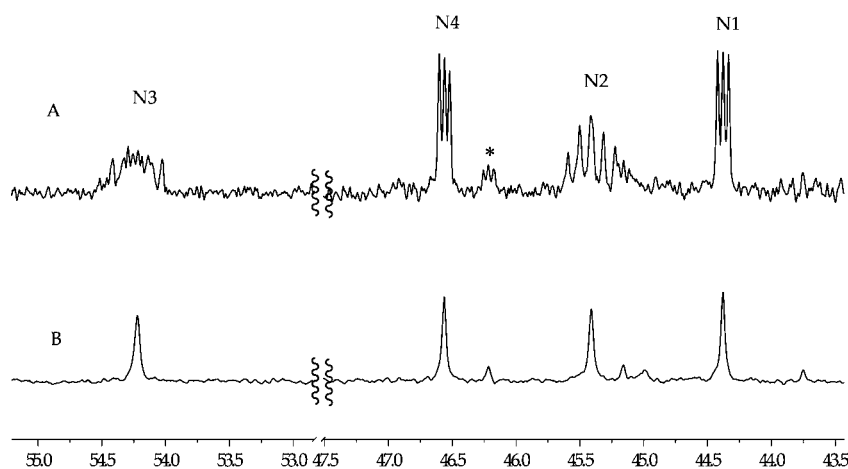
**Solution Structure.** The structural assignments used a tetra- $^{15}\text{N}$ -labeled analogue,  $[\text{Li}_3\text{N}_4]\mathbf{3}$ , prepared using a modification of the original synthesis, as illustrated in Scheme 1.

**Scheme 1**





**Figure 2.**  $^6\text{Li}$  NMR spectra of 0.10 M  $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\mathbf{6}$  prepared from  $[\text{}^{15}\text{N}_4]\mathbf{3}$  with 4.0 equiv of *n*-BuLi in 6.10 M THF/pentane recorded at  $-90\text{ }^\circ\text{C}$  after aging at  $-78\text{ }^\circ\text{C}$  for 2.0 h: (A) fully coupled and (B) broadband  $^{15}\text{N}$  decoupled. \* indicates unknown impurities that appear sporadically.



**Figure 3.**  $^{15}\text{N}$  NMR spectra of 0.10 M  $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\mathbf{6}$  prepared from  $[\text{}^{15}\text{N}_4]\mathbf{3}$  with 4.0 equiv of *n*-BuLi in 6.10 M THF/pentane recorded at  $-90\text{ }^\circ\text{C}$  after aging at  $-78\text{ }^\circ\text{C}$  overnight: (A) fully coupled and (B) broadband  $^{15}\text{N}$  decoupled. \* indicates unknown impurities that appear sporadically.

Metalation of  $[\text{}^{15}\text{N}_4]\mathbf{3}$  with 2 equiv of recrystallized  $[\text{}^6\text{Li}]\textit{n}\text{-BuLi}^{21}$  in THF at  $-78\text{ }^\circ\text{C}$  was incomplete, affording lithium amide–*n*-BuLi mixed aggregate  $\mathbf{6}$  along with unreacted *n*-BuLi and diamine  $\mathbf{3}$ .<sup>22–24</sup> Subsequent warming to  $-20\text{ }^\circ\text{C}$  for 10 min caused complete consumption of  $\mathbf{3}$ , affording dilithiated amide homoaggregate  $\mathbf{4}$  as a complex mixture that was not investigated further.<sup>25,26</sup>

Lithiation of  $[\text{}^{15}\text{N}_4]\mathbf{3}$  with  $\geq 3.0$  equiv of  $[\text{}^6\text{Li}]\textit{n}\text{-BuLi}^{21}$  in 6.1 M THF/hexane affords a dilithium amide–*n*-BuLi mixed aggregate displaying three  $^6\text{Li}$  resonances (1:1:1) along with resonances of residual *n*-BuLi dimer and tetramer<sup>26</sup> at elevated *n*-BuLi concentrations (Figures 2 and 3). The resonance count and intensities, most easily observed in the  $^{15}\text{N}$  broadband decoupled spectrum (Figure 2B), are consistent with those of trilitiated mixed aggregate  $\mathbf{6}$  or the corresponding dimerized hexalithiated  $\mathbf{5}$  observed crystallographically. (The trace impurities noted by asterisks were initially believed to be *n*-BuOLi-derived mixed aggregates, but addition of *n*-BuOH incrementally reveals a distinctly different mixed aggregate.) The connectivities in the trilitio subunit (indicated in red in Table 1) were assigned from the splitting patterns in the coupled spectra (Figures 2A and 3A) with the aid of single-frequency decoupling<sup>27</sup> and  $[\text{}^6\text{Li}, \text{}^{15}\text{N}]$ -HMQC spectroscopy<sup>28,29</sup> (Supporting Information). Spectroscopic data are compiled in Table 1. The primary Li–N linkages of the lithium amide

moieties showed characteristically large (3.6–5.8 Hz) coupling constants,<sup>30</sup> whereas the dative Li–N linkages deriving from chelation by the piperidino moieties displayed much smaller (1.9–2.2 Hz) coupling constants.<sup>31</sup> The assignment as trilitiated  $\mathbf{6}$  rather than hexalithio  $\mathbf{5}$  stems from a  $^{13}\text{C}$  NMR spectrum showing a multiplet that was tentatively assigned as a quintet corresponding to the Li–C–Li' and the heptet of the *n*-BuLi tetramer (Figure 4).<sup>26,32</sup>

**DFT Computed Structure.** DFT calculations were performed with the Gaussian 09 package using Gaussview 5.0 and WebMO as a graphical user interface.<sup>33</sup> Geometry optimizations and frequency calculations were performed at the B3LYP level of theory using the 6-31G(d) and 6-31+G(d) Pople basis sets. Free energies were calculated from an MP2-derived single-point energy [6-31G(d) basis set] and a B3LYP-derived thermal correction [6-31G(d)] at 195 K ( $-78\text{ }^\circ\text{C}$ ) and 1 atm. (MP2 corrections seem to provide superior correlations of theory and experiment, especially for highly congested structures.)

We followed a pedagogically interesting protocol by providing only the atomic connectivities—no detailed NMR or crystallographic data—to the co-worker (J.L.) doing computations. Comparing the computed structures to the crystal structure revealed remarkable similarities, but we had computationally

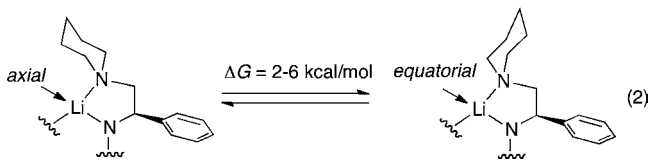
**Table 1.**  $^6\text{Li}$  and  $^{15}\text{N}$  NMR Spectroscopic Data for Mixed Aggregates **6** and **8**

	<b>6</b>			<b>8</b>		
	$\delta$ (ppm)	mult	$J$ (Hz)	$\delta$ (ppm)	mult	$J$ (Hz)
$\text{Li}_1$	1.63	dd	$\text{Li}_1\text{-N}_1 = 2.1$	1.24	dd	$\text{Li}_1\text{-N}_1 = 2.2$
$\text{Li}_2$	2.65	ddd	$\text{Li}_1\text{-N}_2 = 4.3$	2.20	ddd	$\text{Li}_1\text{-N}_2 = 4.3$
$\text{Li}_3$	2.37	d	$\text{Li}_2\text{-N}_2 = 4.9$	2.06	d	$\text{Li}_2\text{-N}_2 = 4.8$
$\text{Li}_4$	---	---	$\text{Li}_2\text{-N}_3 = 4.3$	-0.26	s	$\text{Li}_2\text{-N}_3 = 3.6$
			$\text{Li}_2\text{-N}_4 = 2.1$			$\text{Li}_2\text{-N}_4 = 1.9$
			$\text{Li}_3\text{-N}_3 = 5.8$			$\text{Li}_3\text{-N}_3 = 5.6$
$\text{N}_1$	44.4	t		44.7	t	
$\text{N}_2$	45.4	tt		41.3	tt	
$\text{N}_3$	54.2	tt		45.8	tt	
$\text{N}_4$	46.4	t		46.4	t	

missed the orientation of the three-carbon propanediamine bridge and one of the five-membered chelates. With this additional information in hand, the computations were repeated (Supporting Information).

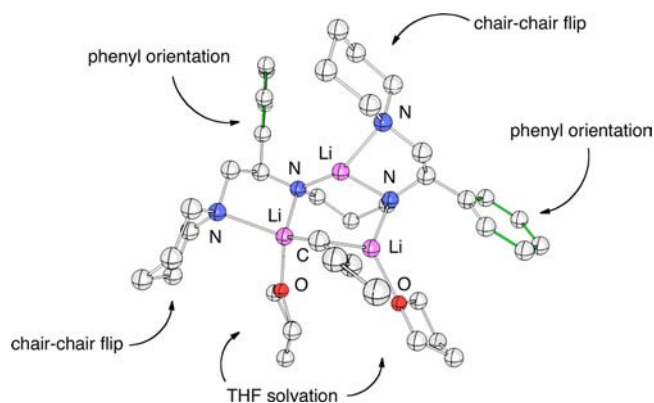
Three important variables are summarized in Figure 5 and described below.

**1. Piperidine Chair–Chair Flip.** Each piperidine ring can exist in two chair conformers, which differ by 2.0–6.0 kcal/mol (for all solvates; eq 2).<sup>34</sup> The preferred conformers have lithiums positioned axially as drawn in Figure 5. This proves to be the overwhelming preference found crystallographically for *N*-alkylpiperidine–lithium complexes.<sup>35,36</sup>



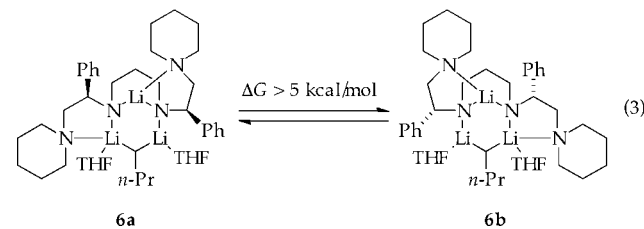
**2. Chelate Conformation.** The five-membered chelate rings show two conformers orienting the phenyl in roughly the equatorial plane and substantially displaced from this plane. They are essentially of equal energy ( $\pm 0.2$  kcal/mol).

**3. *n*-Butyl Orientation.** The *n*-butyl moiety always positions on the opposite face of the six-membered ring from the two THF ligands as drawn, regardless of starting geometry.

**Figure 5.** DFT computed structure of **6** as disolvate (**6a**) showing critical structural variables.

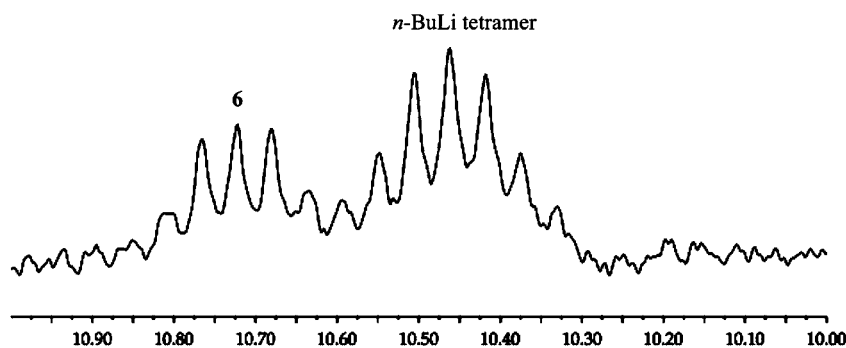
**4. Solvation.** Serial solvation of solvent-free trilitiated fragment **6** shows a strong (8.3 kcal/mol) preference for the di-THF solvate over the monosolvate. Additional solvation was undetectable.<sup>37</sup>

**5. Chelate Orientation.** Reversing the role of the two chelating piperidines (eq 3)—inverting the absolute configuration of the backbone of the structure—revealed a pronounced preference for diastereomer **6a** relative to **6b**.



**6. Dimerization.** The association of **6** to give **5** proved to be very high energy owing largely to a loss of solvation energy. The crystal for X-ray determination of **5** was obtained from hydrocarbon solutions wherein solvation would not be an issue.

**Enediolate–Dilithiated Amide Mixed Aggregate.** **X-ray Crystal Structure.** Addition of 4.0 equiv of *n*-BuLi to a THF solution containing **3** and phenylacetic acid at  $-25$  °C yields a light yellow solution. Crystallization from hexanes, with a small amount of added THF, affords  $[\text{Li}_4(4)(\text{PhCH}=\text{CO}_2)(\text{THF})_2]_2$  (**7**) as a light yellow powder in 48% yield. The composition of **7** was confirmed by X-ray diffraction (Figure 6). Although the data quality is poorer than that observed for **5**, the

**Figure 4.**  $^{13}\text{C}$  NMR spectra of 0.10 M  $[\text{Li}_4^{15}\text{N}]_6$  prepared from  $[\text{N}_4^{15}]_3$  with 4.0 equiv of *n*-BuLi in 6.10 M THF/pentane recorded at  $-90$  °C after aging at  $-78$  °C overnight. The  $^{13}\text{C}$  resonance of the *n*-BuLi dimer is not shown but appears as a 1:2:3:2:1 quintet at 12.6 ppm.



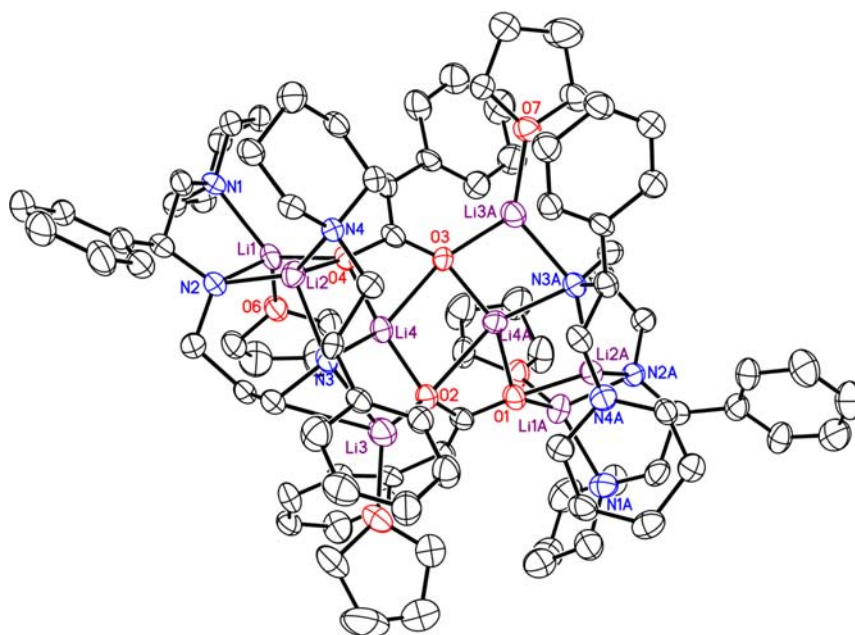


Figure 6. ORTEP of hexalithio enediolate–dilithiated amide mixed aggregate 7.

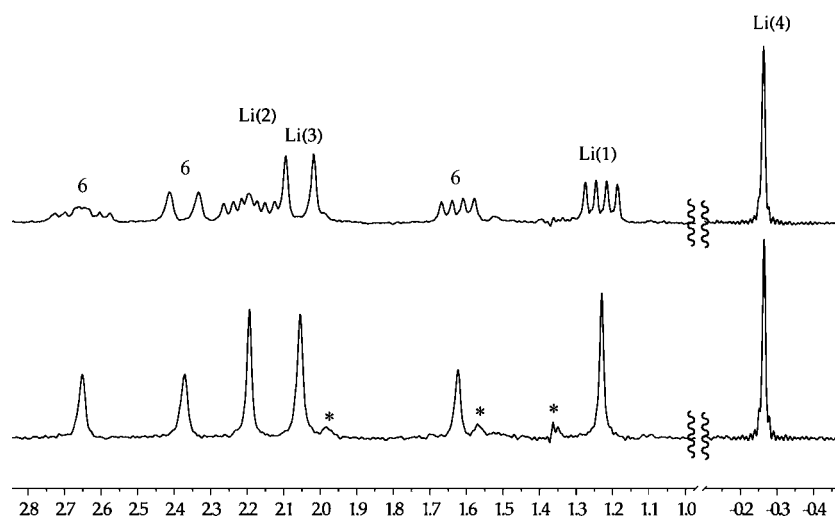
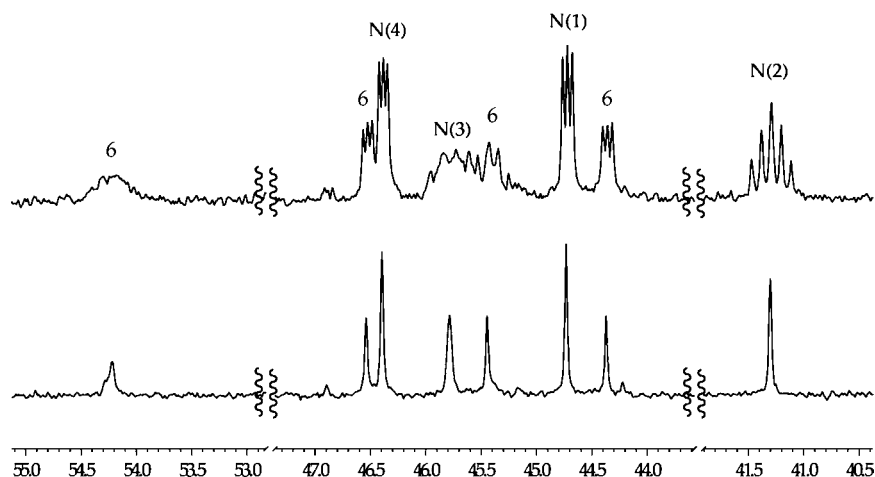


Figure 7.  ${}^6\text{Li}$  NMR spectra of 0.10 M  $[{}^6\text{Li}, {}^{15}\text{N}]\mathbf{8}$  and residual  $[{}^6\text{Li}, {}^{15}\text{N}]\mathbf{6}$  prepared from  $[{}^{15}\text{N}_4]\mathbf{3}$  with 4.0 equiv of *n*-BuLi in 6.1 M THF/pentane recorded at  $-90\text{ }^\circ\text{C}$  after aging at  $-78\text{ }^\circ\text{C}$  for 2.0 h: (A) fully  ${}^{15}\text{N}$  coupled and (B)  ${}^{15}\text{N}$  broadband decoupled. \* indicates unassigned resonances.

connectivity of the atoms in **7** is clearly defined. Complex **7** crystallizes in the orthorhombic space group  $P2_12_12_1$  as the THF solvate  $\mathbf{7}\cdot\text{THF}$ . Complex **7** comprises two tetralithio subunits in the solid state—octalithio overall—with  $C_2$  symmetry. It consists of two chiral dilithiated amides and two enediolates. Four of the eight lithium cations are ligated by THF molecules. The presence of the same dilithium amide core in both **5** and **7** suggests its central importance. Because the molecule is composed of two identical tetralithio subunits, the metrical parameters of only one half are discussed. As was observed for **5**, one lithium atom (Li2) is chelated by three nitrogen atoms from one tetra(amine) ligand: N2, N3, and N4, thereby generating a five-membered ring and a six-membered ring. One lithium atom (Li1) is coordinated by two nitrogen atoms (N1 and N2), generating a five-membered ring. Additionally, two lithium atoms (Li3 and Li4) bridge the chiral amine moiety and the oxygen atoms of the enediolate ligands,  $[\text{PhCH}=\text{CO}_2]^{2-}$ . The Li–N(amide) and Li–N(amine) bond lengths in **7** are

similar to those in **5**. Finally, the Li–Li distances in **7** range from 2.418 to 2.661 Å, in line with structurally related lithium aggregates.<sup>38</sup>

The most interesting structural feature of **7** is the incorporation of the enediolate moiety,  $[\text{PhCH}=\text{CO}_2]^{2-}$ . The atoms within the enediolate ligand are all coplanar, suggesting strong  $\pi$  conjugation. Additionally, each oxygen atom of the enediolate is coordinated to three lithium cations. For instance, one oxygen atom (O4) is coordinated to a triangular face formed by three lithium cations (Li1, Li2, Li4), whereas the other oxygen atom (O2) is ligated by Li3, Li4, and Li4A. The Li–O bond lengths range from 1.857 to 2.245 Å; however, the average Li–O bond length of 1.96 Å is standard.<sup>39</sup> Additionally, there are two independent C=C bonds that exhibit somewhat different C–C bond lengths [C48–C49 = 1.408(8) Å and C40–C41 = 1.356(15) Å]. The C–O bond lengths of the two moieties are comparable [C48–O4 = 1.322(6) Å and



**Figure 8.**  $^{15}\text{N}$  NMR spectra of 0.10 M  $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\mathbf{8}$  and residual  $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\mathbf{6}$  prepared from  $[\text{}^{15}\text{N}_4]\mathbf{3}$ , 4.0 equiv of *n*-BuLi, and phenylacetic acid in 0.10 M THF/pentane recorded at  $-90\text{ }^\circ\text{C}$  after aging at  $-78\text{ }^\circ\text{C}$  for 2.0 h: (A) fully  $^{15}\text{N}$  coupled and (B)  $^6\text{Li}$  broadband decoupled.

C48–O3 = 1.283(7) Å versus C40–O1 = 1.312(7) Å and C40–O2 = 1.326(7) Å].

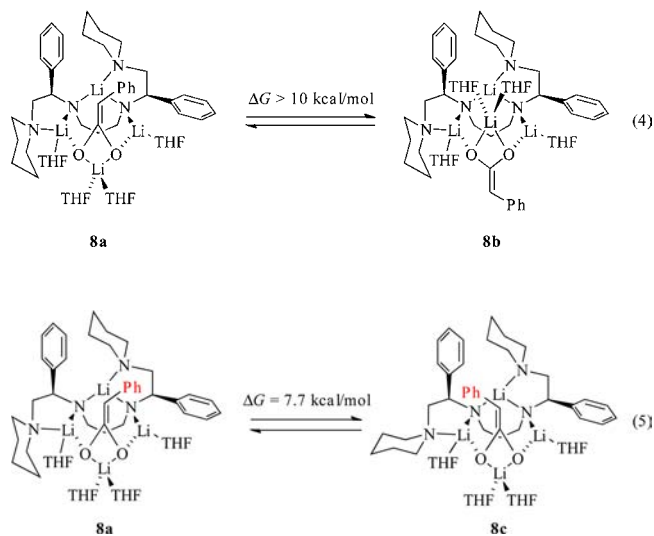
**Solution Structure.** The structure of the centrally important mixed aggregate of dilithiated amide **3** with the dianionic enediolate of phenylacetic acid was studied using the protocols and spectroscopic methods described above. Figure 7 shows  $^6\text{Li}$  NMR spectra recorded on a solution prepared from a 1:4:1 mixture of  $[\text{}^{15}\text{N}_4]\mathbf{3}$ , *n*-BuLi, and phenylacetic acid (**1**) in THF/pentane. Residual *n*-BuLi-derived mixed aggregate **6** is observed along with a new mixed aggregate corresponding to tetralithio mixed aggregate **8**. (The connectivities are highlighted in red in Table 1.) Despite differential broadening, the four resonances integrate to 1:1:1:1, consistent with a 1:1 mixed aggregate constituted from the two dianions. The corresponding fully coupled and broadband decoupled  $^{15}\text{N}$  NMR spectra are illustrated in Figure 8. Single-frequency decoupling and  $[\text{}^6\text{Li}, \text{}^{15}\text{N}]$ -HMQC spectroscopy provided the connectivities and completed the assignments (Table 1). COSY, TOCSY, HSQC, HMBC, and ROESY spectroscopies (Supporting Information) supported the spatial orientations observed computationally (below). Although tetralithio mixed aggregate **8** could have, in theory, dimerized into an octalithio form, neither the physical nor the computational models provided any support for such a severely congested aggregate.

**DFT Computed Structure.** The structure of **8** was examined computationally.<sup>40–42</sup> Many of the structural details such as piperidino chair preferences and chelating side chain orientations were analogous to those outlined above (and provided in detail in the Supporting Information), warranting no additional comment. We also observed no tendency of tetralithio **8** to form an octalithio (dimerized) form. The three significant variables are described in the following.

1. **Solvation.** The serial solvation of the core is exergonic to the tetrasolvation state (7.1 kcal/mol favored over the trisolvate). Additional solvation was undetected without significant structural disruptions.

2. **Enolate Orientation.** The enolate orients favoring **8a** as shown in eq 4, presumably owing to the steric demands of the disolvated lithium nucleus.

3. **Phenyl Orientation.** The orientation of the phenyl moiety on the enediolate fragment is the variable that we believe is at the heart of the enantioselectivity in eq 1. We observe a 7.7 kcal/mol preference for **8a** versus **8c** (eq 5).



#### Calculated Transition Structures and Enantioselectivities.

Aggregates **8a** and **8c** expose the *si* and *re* faces, respectively, of the enediolate to the sterically accessible exterior of the globular aggregate. All that remained was to examine the transition structures for the alkylation and predict the affiliated enantioselectivities. The calculations used methyl chloride. Transition structures **17a** and **17b** correspond to the alkylation of **8a** and **8c**, respectively (Figure 9). We explored cyclic transition structures bearing Li–Cl contacts and found they were only marginally viable.<sup>43–47</sup> The  $\geq 20$  kcal/mol barriers (referenced to common ground state **8a**) do not trouble us; barriers of alkylations are routinely overestimated.<sup>48</sup> More importantly, the 6.4 kcal/mol preference for **17a** suggests a  $\gg 99.9\%$  ee. Although this value exceeds the experimental value of 98% ee for allyl bromide,<sup>6</sup> the model is impressively robust, especially given possible sources of erosion experimentally. Equilibration of the aggregates on the time scales of alkylation is by no means certain.

## DISCUSSION

**Summary.** The studies of the mixed aggregates derived from dilithiated amide **4** and the coordination chemistry underlying the enantioselective alkylation of carboxylic acid enediolates in eq 1<sup>6</sup> reveal a remarkably coherent picture

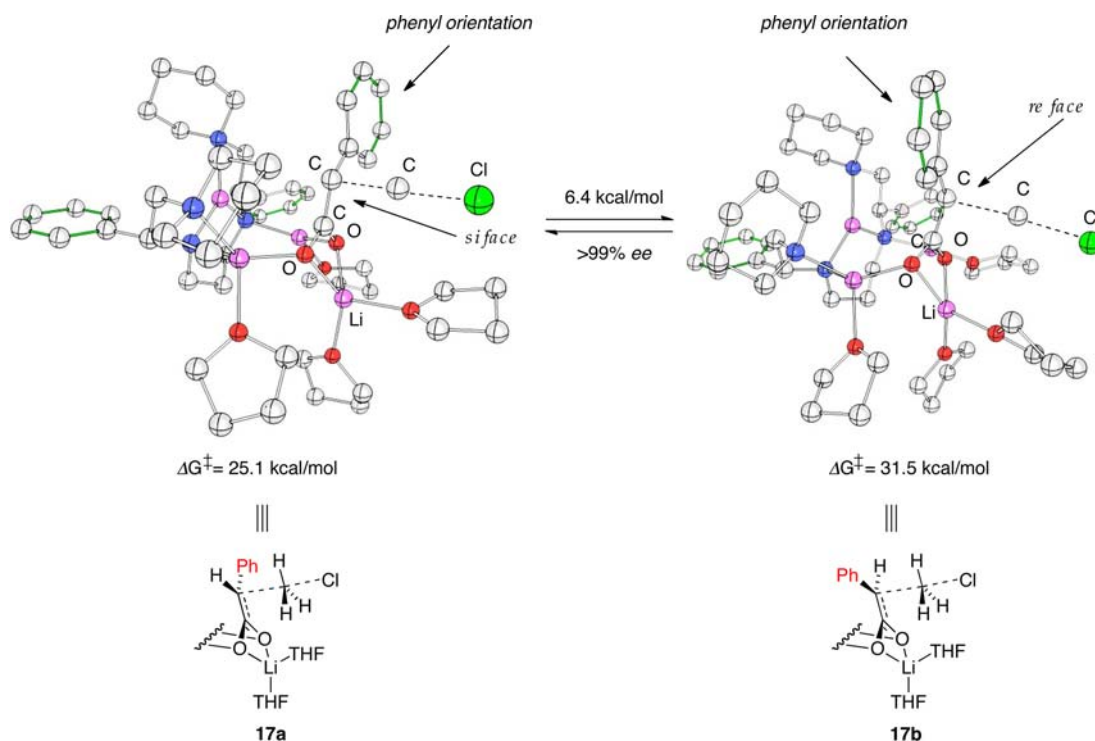
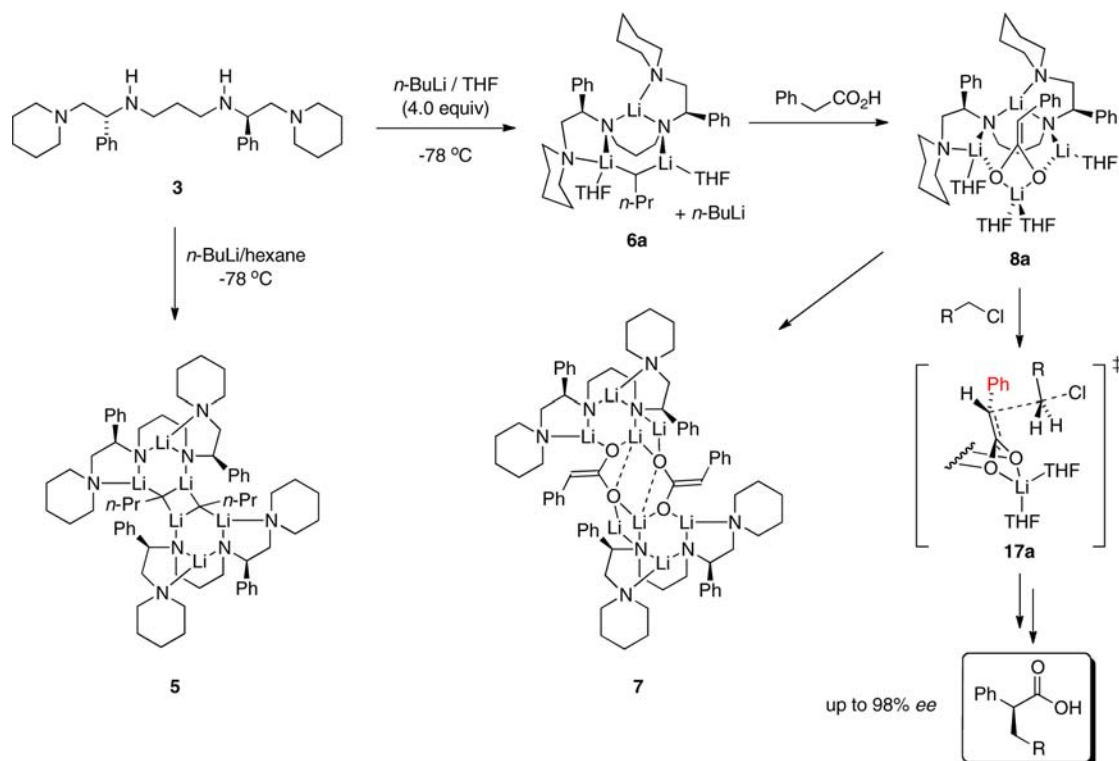


Figure 9. Calculated transition structures 17a and 17b showing selectivity for alkylation from the *si* and *re* enolate faces, respectively.

#### Scheme 2



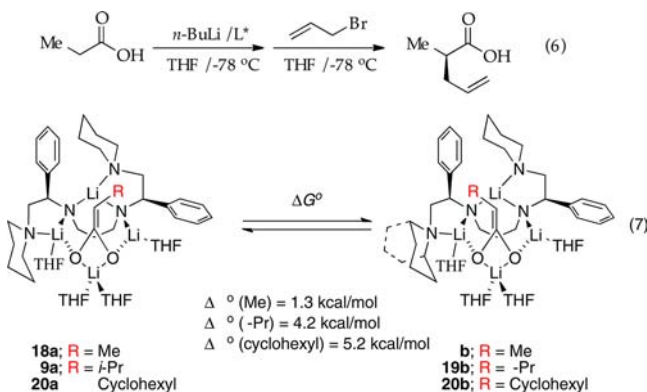
(Scheme 2). In the absence of coordinating ligand, dilithiated amide **3** and *n*-BuLi affords a crystalline mixed aggregate shown by X-ray crystallography to be an exceedingly complex hexalithiated form, **5**, comprising two *n*-BuLi–dilithiated amide trilithio subunits. Analogous metalation in THF solution affords trilithio form **6** as a single diastereomer, suggested by computations to be disolvate **6a** (vide supra).<sup>49</sup>

Mixing diamine **3**, 4.0 equiv of *n*-BuLi, and phenylacetic acid (**1**) affords octalithio mixed aggregate **7** comprising two dilithiated amides and two enediolate dianions in a  $C_2$ -symmetric dimerized form. Analogous mixtures in THF solution afford the corresponding tetralithio mixed aggregate **8** composed of a dilithiated amide and enediolate dianions and suggested by computations to be tetrasolvated (**8a**). Once again, the structural

and stereocontrol are predicted to be very high. Computations of **8a** also indicate a strong (7.7 kcal/mol) preference for a single orientation of the enediolate relative to the dilithium amide fragment.

**Stereochemical Model: Predictions.** In essence, the dilithium amide fragment concurrently controls the orientation of the enediolate and blocks one of two enantiotopic enediolate faces, ensuring a highly enantioselective alkylation. Computed product-determining transition structures **17a** and **17b** (Figure 9) do not contain Cl–Li interactions. Importantly, the computations predict the correct facial selectivity and an enantioselectivity of >99% ee compared with the experimental values of up to 98% ee. This satisfying theory-experiment correlation attests to a potentially robust stereochemical model. One should note, however, that the predicted selectivity based on reactant preference or transition structure preference will depend critically on whether the aggregates equilibrate on the time scale of the alkylation. Instantaneous alkylation could be construed as evidence of non-equilibrium kinetics. Given the enormous energetic bias, this would not measurably affect the observed selectivities.

Of course, many variables had to be controlled to obtain the highly enantioselective alkylations. Ultimately, however, the orientation of the enediolate phenyl moiety appears to be the central variable (eq 5). The robustness of this model is easily tested. The data showed a priori that the propionate enediolate is poorly selective (eq 6). Computations confirmed the inferior (1.3 kcal/mol) selectivity of the enediolate geometry (eq 7). The corresponding computed transition structures for isopropyl and cyclohexyl-substituted enolates are akin to the 4.2 and 5.2 kcal/mol facial preference of the phenyl-substituted enediolate. The cyclohexyl- and isopropyl-substituted enolates force a conformational flip of the piperidine (dotted line in **19b** and **20b**).



## CONCLUSIONS

Only in a few instances has stereocontrol been correlated with the underlying organolithium aggregation.<sup>12,13</sup> We suspect, however, that high stereocontrol is often affiliated with high structural control.<sup>13</sup> To borrow a familiar phrase, “what you see is what you get” (WYSIWYG). The structural studies described herein certainly are supportive. The emergent model appears to be highly predictive. Ongoing studies may reveal why certain electrophiles are poorly selective owing to specific steric interactions. At this time we do not know the relative rates of alkylations and aggregate exchanges.<sup>50</sup> We suspect, however, that highly reactive electrophiles—those most likely to react

directly with the mixed aggregate without intervening deaggregations and other structural changes—are amenable to computational prediction. For sluggish electrophiles, intervening deaggregations could cause stereochemical leakage. Of course, alkylations are a small subset of the reactions of lithium enolates, so this story may be only in its infancy.

## EXPERIMENTAL SECTION

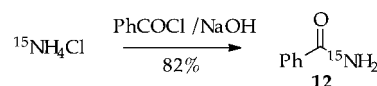
**Reagents and Solvents.** THF and hexanes were distilled from blue or purple solutions containing sodium benzophenone ketyl. The hexane contained 1% tetraglyme to dissolve the ketyl. *n*-BuLi was prepared and recrystallized as described previously.<sup>21</sup> Solutions of *n*-BuLi were titrated using a literature method.<sup>51</sup> Amine **3** was prepared as described previously.<sup>8</sup> [<sup>15</sup>N<sub>4</sub>]**1** was prepared as described below.

**NMR Spectroscopic Analyses.** All NMR tubes were prepared using stock solutions and sealed under partial vacuum. Standard <sup>6</sup>Li, <sup>13</sup>C, and <sup>15</sup>N NMR spectra were recorded on a 500 MHz spectrometer at 73.57, 125.79, and 50.66 MHz, respectively. The <sup>6</sup>Li, <sup>13</sup>C, and <sup>15</sup>N resonances are referenced to 0.30 M [<sup>6</sup>Li]LiCl/methanol at –90 °C (0.0 ppm), the CH<sub>2</sub>O resonance of THF at –90 °C (67.57 ppm), and neat Me<sub>3</sub>NiEt at –90 °C (25.76 ppm), respectively.

**Computations.** DFT computations were optimized at B3LYP/6-31G(d) level<sup>33</sup> with single-point calculations at the MP2 level of theory.

**Synthesis of [<sup>15</sup>N<sub>4</sub>]**3**: General.** Unless the reaction procedure states otherwise, all reactions requiring inert atmosphere were carried out with dry argon in oven or flame-dried glassware. THF and diethyl ether were distilled from sodium/benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, diisopropylamine, pyridine, triethylamine, and chlorotrimethylsilane were distilled from calcium hydride in a continuous still under an atmosphere of argon. Chlorotriethylsilane (TESCl) and diisopropylethylamine (Hunig's base) were distilled from calcium hydride under an inert atmosphere of dry argon and stored over calcium hydride. Room temperature reactions were carried out between 22 and 24 °C. Analytical thin-layer chromatography was visualized using combinations of ultraviolet, anisaldehyde, ceric ammonium molybdate, potassium permanganate, and iodine staining. Flash chromatography was performed using 40–63 mm silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. Proton magnetic resonance spectra were recorded at 400, 500, or 600 MHz. Carbon magnetic resonance spectra were recorded at 100, 125, or 150 MHz. All chemical shifts were reported in δ units relative to tetramethylsilane. High-resolution mass spectroscopic data were obtained at the Mass Spectrometry Laboratory at the University of California, Santa Barbara.

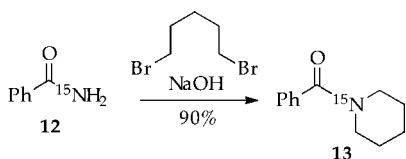
**Benzamide-<sup>15</sup>N (**12**).**<sup>52</sup> Sodium hydroxide (10 M in water, 16.7 mL, pre-cooled to 0 °C) was added to a solution of benzoyl chloride (12.55 mL, 0.108 mol) and ammonium-<sup>15</sup>N chloride (2.50 g, 45.88 mmol) in water (8.3 mL) and diethyl ether (12.5 mL) at 0 °C. After 15 min, the solids were filtered, collected, and dried under high vacuum to deliver benzamide-<sup>15</sup>N (4.62 g, 37.83 mmol, 82%) which was used directly without further purification. <sup>1</sup>H NMR (600 MHz; CDCl<sub>3</sub>): δ 7.81–7.80 (m, 2H), 7.54–7.51 (m, 1H), 7.45 (m, 2H), 5.91 (m, 2H).



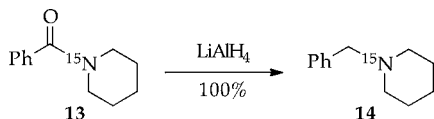
**1-Benzoylpiperidine-<sup>15</sup>N (**13**).** 1,5-Dibromopentane was added to a mixture of benzamide-<sup>15</sup>N (4.62 g, 37.83 mmol), tetrabutylammonium hydrogen sulfate (1.41 g, 4.16 mmol), potassium carbonate (7.37 g, 53.34 mmol), and sodium hydroxide (7.41 mol, 0.185 mol) in dry toluene (162 mL). The solution was heated at reflux for 18 h. After cooling to room temperature (rt), the solids were filtered off and the residue was purified via flash chromatography (silica, 30% → 70% ethyl acetate/hexanes) to deliver 1-benzoylpiperidine-<sup>15</sup>N (6.41 g,



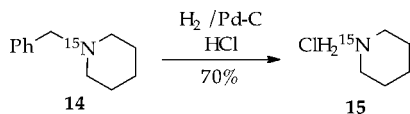
33.69 mmol, 90%).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.52–7.21 (m, 5H), 3.75–3.68 (m, 2H), 3.38–3.31 (m, 2H), 1.72–1.48 (m, 6H).



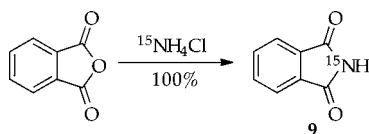
**1-Benzylpiperidine- $^{15}\text{N}$  (14).** A solution of 1-benzylpiperidine- $^{15}\text{N}$  (6.41 g, 33.69 mmol) in diethyl ether (50 mL total with rinses) was added to a suspension of lithium aluminum hydride (5.11 g, 0.135 mol) in diethyl ether (122 mL) at 0 °C. After the addition of 1-benzylpiperidine- $^{15}\text{N}$  was complete, the solution was refluxed for 18 h. The reaction was cooled to 0 °C, and water (5.10 mL) was added carefully. After 5 min 3 M NaOH (5.10 mL) was added and the reaction was stirred for an additional 5 min. Water (15.30 mL) was added, and the reaction was stirred for 5 min at 0 °C before warming to rt. After 3 h the solids were filtered and rinsed with diethyl ether. The filtrate was concentrated under reduced pressure to deliver 1-benzylpiperidine- $^{15}\text{N}$  (5.94 g, 33.69 mmol, 100%), which was used directly without further purification.  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.32–7.21 (m, 5H), 3.49–3.47 (m, 2H), 2.41–2.32 (m, 4H), 1.60–1.52 (m, 4H), 1.45–1.38 (m, 2H).



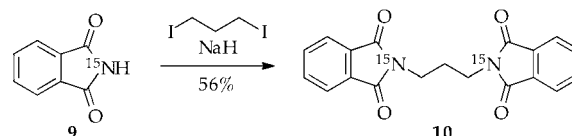
**Piperidine-HCl- $^{15}\text{N}$  (15).** Following a literature protocol<sup>53a</sup> hydrogen gas was bubbled through a solution of 1-benzylpiperidine- $^{15}\text{N}$  (2.97 g, 16.85 mmol) and palladium on carbon (0.297 g) in methanol (112 mL) and dichloromethane (56 mL), which generates HCl in situ under the reaction conditions.<sup>53b</sup> After 15 min the hydrogen needle was removed from the solution, and the reaction was allowed to stir under a hydrogen atmosphere for 24 h. The solution was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to deliver piperidine- $^{15}\text{N}$  (1.45 g, 11.83 mmol, 70%) as its hydrochloride salt, which was used directly without further purification.  $^1\text{H}$  NMR (500 MHz;  $\text{D}_2\text{O}$ ):  $\delta$  3.27–3.09 (m, 4H), 1.90–1.74 (m, 4H), 1.74–1.62 (m, 2H).



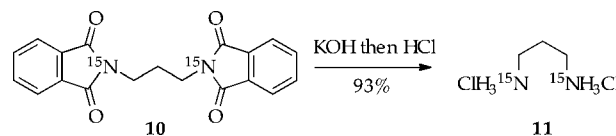
**Phthalimide- $^{15}\text{N}$  (9).**<sup>54</sup> Ammonium- $^{15}\text{N}$  chloride (2.50 g, 45.88 mmol) and sodium hydroxide were combined in a flask and connected via cannula to a separate flask containing phthalic anhydride (6.80 g, 45.88 mmol) in methanol (113 mL) cooled to –10 °C. The flask containing ammonium- $^{15}\text{N}$  chloride and sodium hydroxide was heated with a propane torch, and the resulting gas was bubbled through the mentholic solution of phthalic anhydride. After gas evolution ceased the solution was stirred for an additional hour. The methanol was distilled at atmospheric pressure. The crude residue was heated to 230 °C for 10–15 min. After cooling, phthalimide- $^{15}\text{N}$  (6.80 g, 45.88 mmol, 100%) was obtained and used directly without further purification.  $^1\text{H}$  NMR (500 MHz;  $\text{DMSO}-d_6$ ):  $\delta$  11.33 (d,  $J = 93.9$  Hz, 1H), 7.85–7.82 (m, 4H).



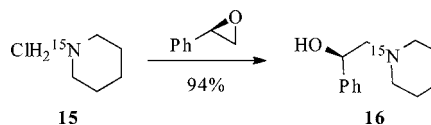
**$N,N'$ -Trimethylenedipthalimide- $^{15}\text{N}$  (10).**<sup>55</sup> Phthalimide- $^{15}\text{N}$  (6.80 g, 45.88 mmol) was added to a suspension of sodium hydride (3.30 g, 82.58 mmol) in dimethylformamide (91.8 mL) at rt. After 15 min 1,3-diiodopropane (2.63 mL, 22.94 mmol) was added and the reaction stirred at rt for 15 min and then heated in a sealed flask at 100 °C for 3 h. The reaction was cooled to rt and diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with water (2 × 300 mL) and brine, dried with sodium sulfate, and concentrated. The residue was dissolved in ethyl acetate and dichloromethane, and silica gel was added. The solution was evaporated to dryness. The residue, absorbed onto the silica gel was purified via flash chromatography (silica, 10% → 30% ethyl acetate/dichloromethane) to give the desired product (4.35 g, 12.93 mmol, 56%).  $^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.87–7.82 (m, 4H), 7.74–7.69 (m, 4H), 3.79–3.75 (m, 4H), 2.14–2.07 (m, 2H).



**1,3-Diaminopropane- $^{15}\text{N}$  (11).** Potassium hydroxide (5.81 g, 0.104 mol) was added to a suspension of  $N,N'$ -trimethylenedipthalimide- $^{15}\text{N}$  (4.35 g, 12.93 mmol) in water (18 mL) and heated at 70 °C for 18 h, at which point the reaction became clear and homogeneous. The reaction was distilled into a flask containing 2.15 mL of 12.1 M hydrochloric acid. After distilling to dryness, water (45 mL) was added to the reaction flask and again distilled to dryness. This process was repeated twice with water (45 mL) and once with methanol (45 mL). The combined distillates were concentrated under reduced pressure to deliver 1,3-diaminopropane- $^{15}\text{N}$  as its hydrochloride salt (1.78 g, 11.94 mmol, 92%), which was used without further purification.  $^1\text{H}$  NMR (600 MHz;  $\text{CD}_3\text{OD}$ ):  $\delta$  3.05 (m, 4H), 2.05 (m, 2H).  $^{13}\text{C}$  NMR (150 MHz;  $\text{CD}_3\text{OD}$ ):  $\delta$  36.4, 25.1.  $^{15}\text{N}$  NMR (60.5 MHz;  $\text{CD}_3\text{OD}$ ):  $\delta$  31.8. LRMS (ESI) calcd for  $\text{C}_3\text{H}_{13}^{15}\text{N}_2$  [ $\text{M}+\text{H}$ ] 77.09, found 76.98.

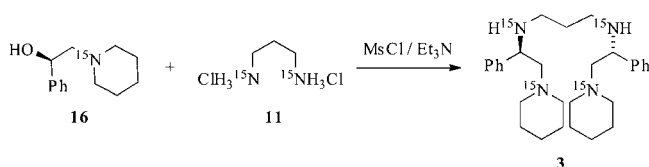


**(1S)-1-(1-Phenyl)-2-(1-piperidinyloxy)ethanol- $^{15}\text{N}$  (16).** Sodium hydroxide (0.437 g, 11.83 mmol) was added to a solution of piperidine- $^{15}\text{N}$  (1.45 g, 11.83 mmol) and (*S*)-styrene oxide (1.29 mL, 11.26 mmol) in ethanol (28.2 mL) and heated at 120 °C for 4 h. After cooling to rt, the reaction was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated. The residue (2.29 g, 11.08 mmol, 94%) was used directly without further purification.  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.41–7.15 (m, 5H), 4.73–4.69 (m, 1H), 3.70–3.57 (m, 1H), 2.76–2.64 (m, 2H), 2.60–2.52 (m, 1H), 2.53–2.45 (m, 1H), 2.43–2.32 (m, 2H), 1.74–1.41 (m, 6H).



**Tetraamine- $^{15}\text{N}$  (3).** Methanesulfonyl chloride (2.10 mL, 26.58 mmol) was added to a solution of (1S)-1-(1-phenyl)-2-(1-piperidinyloxy)ethanol- $^{15}\text{N}$  (4.57 g, 22.15 mmol) and triethylamine (9.30 mL, 66.45 mmol) in diethyl ether (74 mL) at 0 °C. After 30 min the solution was warmed to rt and stirred for an additional hour. Then,

triethylamine (12.4 mL, 88.6 mmol), 1,3-diaminopropane-<sup>15</sup>N hydrochloride (1.65 g, 11.08 mmol), and water (12.8 mL) were added to the reaction, and the solution was allowed to stir for 2 days at rt. The reaction was diluted with water and diethyl ether. The aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated, and the residue was purified via flash chromatography (silica, 5% → 10% → 20% triethylamine/ethyl acetate). The product was then recrystallized from isopropanol:water (1.1:1) to deliver the purified tetraamine-<sup>15</sup>N (2.10 g, 4.64 mmol, 42%) as a white solid and 1.25 g (2.76 mmol, 25%) of tetraamine-<sup>15</sup>N 3 from the mother liquors as an oil. <sup>1</sup>H NMR (600 MHz; CDCl<sub>3</sub>): δ 7.34 (d, J = 7.2 Hz, 4H), 7.30 (t, J = 7.6 Hz, 4H), 7.22 (t, J = 7.2 Hz, 2H), 3.72 (dd, J = 11.0, 3.1 Hz, 2H), 2.52–2.22 (m, 18H), 1.66 (t, J = 5.6 Hz, 2H), 1.57–1.49 (m, 8H), 1.41 (d, J = 5.1 Hz, 4H). <sup>13</sup>C NMR (150 MHz; CDCl<sub>3</sub>): δ 143.3, 128.2, 127.3, 126.9, 66.6, 60.2, 54.6, 46.3, 30.5, 26.1, 24.5. HRMS (ESI) calcd for C<sub>29</sub>H<sub>45</sub><sup>15</sup>N<sub>4</sub> [M+H] 453.3518, found 453.3526.



## ■ ASSOCIATED CONTENT

### Supporting Information

Spectroscopic, crystallographic, and computational data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) (a) Ojima, I. *Catalytic Asymmetric Synthesis*; Wiley: New York, 2010. (b) Corey, E. J.; Kürti, L. *Enantioselective Chemical Synthesis*; Direct Book Publishing LLC: New York, 2010.
- (2) For discussion of the challenges of ligand-catalyzed organolithium reactions and an attempt to accumulate a comprehensive bibliography, see: Ramirez, A.; Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 10326.
- (3) (a) Paull, D. H.; Wolfer, J.; Grebinski, J. W.; Weatherwax, A.; Lectka, T. *Chimia* **2007**, *61*, 240. (b) Kawabata, T.; Fujii, K. *Top. Stereochem.* **2003**, *23*, 175. (c) Kawabata, T. *Rev. Heteroat. Chem.* **2000**, *22*, 33.
- (4) A comprehensive survey of scaled procedures used by Pfizer over two decades shows that 68% of all C–C bond formations are carbanion based and 44% of these involve enolates: Dugger, R. W.; Ragan, J. A.; Ripin, D. H. *Org. Process Res. Dev.* **2005**, *9*, 253.
- (5) (a) Green, J. R. *Science of Synthesis*; Georg Thieme Verlag: New York, 2005; Vol. 8a, pp 427–486. (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506. (c) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917. (d) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1989; Vol. 1, p 1. (e) Martin, S. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1989; Vol. 1, p 475. (f) Plaquevent, J.-C.; Cahard, D.; Guillen, F.; Green, J. R. *Science of Synthesis*; Georg Thieme Verlag: New York, 2005; Vol. 26, pp 463–511. (g) *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, 1995; pp 834–835. (h) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569.
- (6) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2011**, *133*, 11936.
- (7) (a) Dang, T. T.; Kelzhanova, N. K.; Abilov, Z. A.; Turmukhanova, M. Zh.; Langer, P. *Synlett* **2012**, *23*, 1283. (b) Johnson, C. R.; Bade, T. R. *Synthesis* **1982**, *4*, 284. (c) Miyashita, M.; Yamaguchi, R.; Yoshikoshi, A. *Chem. Lett.* **1982**, 1505. (d) Miyashita, M.; Yamaguchi, R.; Yoshikoshi, A. *J. Org. Chem.* **1984**, *49*, 2857. (e) Mulzer, J.; De Lasalle, P.; Chucholowski, A.; Blaschek, U.; Bruentrup, G.; Jibril, I.; Huttner, G. *Tetrahedron* **1984**, *40*, 2211. (f) Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969. (g) Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284. (h) Larson, G. L.; Cruz de Maldonado, V.; Berrios, R. R. *Synth. Commun.* **1986**, *16*, 1347. (i) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1987**, *52*, 2549. (j) Gil, S.; Parra, M.; Rodriguez, P. *ARKIVOC* **2009**, 172. (k) Bellassoued, M.; Dubois, J. E.; Bertounesque, E. *Bull. Soc. Chim. Belges* **1988**, *97*, 263. Shtelman, A. V.; Becker, J. Y. *Tetrahedron* **2011**, *67*, 1135. Thompson, C. M.; Green, D. L. C. *Tetrahedron* **1991**, *47*, 4223.
- (8) (a) Yamashita, Y.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1999**, *40*, 2803. (b) Yamashita, Y.; Emura, Y.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **2000**, *41*, 209.
- (9) For other applications of diamine 3 in asymmetric synthesis, see: (a) Swingle, N. M.; Reddy, K. V.; Rossiter, B. E. *Tetrahedron* **1994**, *50*, 4455. (b) Frizzle, M. J.; Nani, R. R.; Martinelli, M. J.; Moniz, G. A. *Tetrahedron Lett.* **2011**, *52*, 5613. (c) Fehr, C.; Galindo, J.; Farris, I.; Cuenca, A. *Helv. Chim. Acta* **2004**, *87*, 1737.
- (10) (a) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140. (b) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596. (c) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734. (d) Rathman, T. L.; Bailey, W. F. *Org. Process Res. Dev.* **2009**, *13*, 144. (e) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: New York, 2002.
- (11) For leading references and discussions of mixed aggregation effects and their applications in synthesis, see: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Tchoubar, B.; Loupy, A. *Salt Effects in Organic and Organometallic Chemistry*; VCH: New York, 1992; Chapters 4, 5, and 7. (c) Briggs, T. F.; Winemiller, M. D.; Xiang, B.; Collum, D. B. *J. Org. Chem.* **2001**, *66*, 6291. (d) Caubère, P. *Chem. Rev.* **1993**, *93*, 2317. (e) Gossage, R. A.; Jastrzebski, J. T. B. H.; van Koten, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 1448. (f) Seebach, D. In *Proceedings of the Robert A. Welch Foundation Conferences on Chemistry and Biochemistry*; Wiley: New York, 1984; p 93. (g) Luderer, M. R.; Bailey, W. F.; Luderer, M. R.; Fair, J. D.; Dancer, R. J.; Sommer, M. B. *Tetrahedron: Asymmetry* **2009**, *20*, 981. (h) Reich, H. J. *J. Org. Chem.* **2012**, *77*, 5471.
- (12) (a) Briggs, T. F.; Winemiller, M. D.; Collum, D. B.; Parsons, R. L., Jr.; Davulcu, A. K.; Harris, G. D.; Fortunak, J. D.; Confalone, P. N. *J. Am. Chem. Soc.* **2004**, *126*, 5427. (b) Dinca, E.; Hartmann, P.; Smrcek, J.; Dix, I.; Jones, P. G.; Jahn, U. *Eur. J. Org. Chem.* **2012**, 4461. (c) Casey, B. M.; Flowers, R. A. *J. Am. Chem. Soc.* **2011**, *133*, 11492. (d) Lecachey, B.; Duguet, N.; Oulyadi, H.; Fressigné, C.; Harrison-Marchand, A.; Yamamoto, Y.; Tomioka, K.; Maddaluno, J. *Org. Lett.* **2009**, *11*, 1907.
- (13) (a) Gessner, V. H.; Koller, S. G.; Strohmman, C.; Hogan, A. M.; O'Shea, D. F. *Chem.—Eur. J.* **2011**, *17*, 2996. (b) Ruiz, M.; Ojea, V.; Quintela, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 1863. (c) Hilmersson, G.; Davidsson, O. *J. Organomet. Chem.* **1995**, *489*, 175. (d) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277. (e) Hilmersson, G.; Ahlberg, P.; Davidsson, O. *J. Am. Chem. Soc.* **1996**, *118*, 3539. (f) Gallagher, D. J.; Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1992**, *114*, 5872. (g) Byrne, L. T.; Engelhardt, L. M.; Jacobsen, G. E.; Leung,

- W.-P.; Papasergio, R. I.; Raston, C. L.; Skelton, B. W.; Twiss, P.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1989**, 105. (h) Gais, H.-J.; Dingerdissen, U.; Krüger, C.; Angermund, K. *J. Am. Chem. Soc.* **1987**, *109*, 3775. (i) Zaegel, F.; Gallucci, J. C.; Meunier, P.; Gautheron, B.; Sivik, M. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 6466. (j) Cramer, C. J.; Denmark, S. E.; Miller, P. C.; Dorow, R. L.; Swiss, K. A.; Wilson, S. R. *J. Am. Chem. Soc.* **1994**, *116*, 2437. (k) Williard, P. G.; Tata, J. R.; Schlessinger, R. H.; Adams, A. D.; Iwanowicz, E. J. *J. Am. Chem. Soc.* **1988**, *110*, 7901. (l) Kahne, D.; Gut, S.; DePue, R.; Mohamadi, F.; Wanat, R. A.; Collum, D. B.; Clardy, J.; Van Duyne, G. *J. Am. Chem. Soc.* **1984**, *106*, 4865. (m) Wanat, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **1985**, *107*, 2078. (n) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 3546. (o) Seebach, D.; Bauer, W.; Hansen, J.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Chem. Soc., Chem. Commun.* **1984**, 853. (p) Enders, D.; Bachstädter, G.; Kremer, K. A. M.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1522. (q) Williard, P. G.; Liu, Q.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 3380. (r) Marsch, M.; Harms, K.; Zschage, O.; Hoppe, D.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 321. (s) Ahlbrecht, H.; Boche, G.; Harms, K.; Marsch, M.; Sommer, H. *Chem. Ber.* **1990**, *123*, 1853. (t) Hoppe, L.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2158. (u) Gawley, R. E.; Zhang, P. *J. Org. Chem.* **1996**, *61*, 8103. (v) Hilmersson, G.; Arvidsson, P. I.; Davidsson, Ö; Håkansson, M. *Organometallics* **1997**, *16*, 3352. (w) Glaser, R.; Hadad, C. M.; Wiberg, K. B.; Streitwieser, A. *J. Org. Chem.* **1991**, *56*, 6625. (x) Glaser, R.; Streitwieser, A. *J. Org. Chem.* **1991**, *56*, 6612. (y) Fraser, R. R.; Chuaqui-Offermanns, N.; Houk, K. N.; Rondan, N. G. *J. Organomet. Chem.* **1981**, *206*, 131. (z) Houk, K. N.; Strozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chuaqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426.
- (14) For studies of reactivities of alkyllithium–lithium amide mixed aggregates, see: (a) Arvidsson, A. I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10*, 527. (b) Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *25*, 5187. (c) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1519. (d) Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Prigent, Y.; Davoust, D.; Duhamel, P. *J. Am. Chem. Soc.* **1997**, *119*, 10042. (e) Williard, P. G.; Sun, C. *J. Am. Chem. Soc.* **1997**, *119*, 11693. (f) Arvidsson, P. I.; Ahlberg, P.; Hilmersson, G. *Chem.—Eur. J.* **1999**, *5*, 1348. (g) Johansson, A.; Pettersson, A.; Davidsson, Ö. *J. Organomet. Chem.* **2000**, *608*, 153. (h) Lecachey, B.; Fressigné, C.; Oulyadi, H.; Harrison-Marchand, A.; Maddaluno, J. *Chem. Commun.* **2011**, 47, 9915.
- (15) Spectroscopic studies of lithium salts of dianions: (a) Li, D.; Keresztes, I.; Hopson, R.; Williard, P. G. *Acc. Chem. Res.* **2009**, *42*, 270. (b) Gareyev, R.; Ciula, J. C.; Streitwieser, A. *J. Org. Chem.* **1996**, *61*, 4589. (c) Gruver, J. M.; West, S. P.; Collum, D. B.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 13212. (d) Brand, H.; Capriotti, J. A.; Arnold, J. *Inorg. Chem.* **1994**, *33*, 4334. (e) Günther, H. *J. Braz. Chem. Soc.* **1999**, *10*, 241. (f) Li, D.; Keresztes, I.; Hopson, R.; Williard, P. G. *Acc. Chem. Res.* **2009**, *42*, 270. (g) Jacobson, M. A.; Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2005**, *127*, 4965. (h) Cohen, Y.; Roelofs, N. H.; Reinhardt, G.; Scott, L. T.; Rabinovitz, M. *J. Org. Chem.* **1987**, *52*, 4207. (i) Matsuo, T.; Mizue, T.; Sekiguchi, A. *Chem. Lett.* **2000**, 896.
- (16) For representative examples of X-ray crystal structures of dianions, see: (a) Selinka, C.; Stalke, D. *Z. Naturforsch., B: Chem. Sci.* **2003**, *58*, 291. (b) Konrad, T. M.; Grunwald, K. R.; Belaj, F.; Mosch-Zanetti, N. *C. Inorg. Chem.* **2009**, *48*, 369. (c) Williard, P. G.; Jacobson, M. A. *Org. Lett.* **2000**, *2*, 2753. (d) Brooks, J. J.; Rhine, W.; Stucky, G. D. *J. Am. Chem. Soc.* **1972**, *94*, 7346. (e) Sekiguchi, A.; Ebata, K.; Kabuto, C.; Sakurai, H. *J. Am. Chem. Soc.* **1991**, *113*, 7081. (f) Sekiguchi, A.; Ichinohe, M.; Kabuto, C.; Sakurai, H. *Organometallics* **1995**, *14*, 1092. (g) Wilhelm, D.; Dietrich, H.; Clark, T.; Mahdi, W.; Kos, A. J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1984**, *106*, 7279. (h) Henderson, K. W.; Dorigo, A. E.; MacEwan, G. J.; Williard, P. G. *Tetrahedron* **2011**, *67*, 10291. (i) Brask, J. K.; Chivers, T.; Yap, G. P. A. *Inorg. Chem.* **1999**, *38*, 5588. (j) Wilhelm, D.; Clark, T.; Schleyer, P. v. R.; Dietrich, H.; Mahdi, W. *J. Organomet. Chem.* **1985**, *280*, C6. (k) Lappert, M. F.; Raston, C. L.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1982**, 14.
- (17) We cannot find crystallographic studies of dilithium salts of enediolates; however, several probes of their physical properties have been reported: (a) Kaneti, J. *Bulg. Chem. Commun.* **1995**, *28*, 458. (b) Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745. (c) Aurell, M.; Gil, S.; Mestres, R.; Parra, M.; Tortajada, A. *Tetrahedron* **1994**, *50*, 5109. (d) Bongini, A.; Orena, M.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1986**, 50. (e) Sini, G.; Bellassoued, M.; Brodie, N. *Tetrahedron* **2000**, *56*, 1207. (f) Domingo, L. R.; Gil, S.; Mestres, R.; Picher, M. T. *Tetrahedron* **1996**, *52*, 11105.
- (18) After surveying a subset of the community, we have chosen to refer to  $(\text{LiX})_n$  and  $(\text{LiX})_m(\text{LiX}')_n$  as a “homoaggregate” and “heteroaggregate”, respectively, and reserve the term “mixed aggregate” for  $(\text{LiX})_m(\text{LiY})_n$ .
- (19) Leading references to  $\text{RLi}/\text{R}_2\text{NLi}$  mixed aggregates: (a) Balamraju, Y.; Sharp, C. D.; Gammill, W.; Manuel, N.; Pratt, L. M. *Tetrahedron* **1999**, *54*, 7357. (b) Arvidsson, P. I.; Hilmersson, G.; Davidsson, O. *Chem.—Eur. J.* **1999**, *5*, 2348. (c) Paté, F.; Duguet, N.; Oulyadi, H.; Harrison-Marchand, A.; Fressigné, C.; Valnot, J.-V.; Lasne, M. C.; Maddaluno, J. *J. Org. Chem.* **2007**, *72*, 6982. (d) Pratt, L. M.; Le, L. T.; Truong, T. N. *J. Org. Chem.* **2005**, *70*, 8298. (e) Johansson, A.; Pettersson, A.; Davidsson, O. *J. Organomet. Chem.* **2000**, *608*, 153. (f) Arvidsson, P. I.; Hilmersson, G.; Davidsson, O. *Helv. Chim. Acta* **2002**, *85*, 3814.
- (20) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761.
- (21) (a) Kottke, T.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 580. (b) Rennels, R. A.; Maliakal, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 421.
- (22) Dilithium amides showing structural analogies with **4** and their mixed aggregates have been studied computationally: Pratt, L. M.; Mu, R.; Carter, C.; Woodford, B. *Tetrahedron* **2007**, *63*, 1331.
- (23) Addition of *n*-BuOH to a solution of **6** affords a mixed aggregate that is isostructural to **6** but is not observable under normal conditions.
- (24) (a) Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47. (b) Mulvey, R. E. *Chem. Soc. Rev.* **1991**, *20*, 167. (c) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227. (d) Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *32*, 1035.
- (25) Crystallographic studies of dilithium amides: (a) Daniele, S.; Drost, C.; Gehrhus, B.; Hawkins, S. M.; Hitchcock, P. B.; Lappert, M. F.; Merle, P. G.; Bott, S. G. *J. Chem. Soc., Dalton Trans.* **2001**, 3179. (b) Hellmann, K. W.; Galka, C. H.; Gade, L. H.; Steiner, A.; Wright, D. S.; Kottke, T.; Stalke, D. *Chem. Commun.* **1998**, 549. (c) Galka, C. H.; Trösch, D. J. M.; Rüdener, J.; Gade, L. H.; Scowen, I.; McPartlin, M. *Inorg. Chem.* **2000**, *39*, 4615. (d) Drost, C.; Hitchcock, P. B.; Lappert, M. F. *J. Chem. Soc., Dalton Trans.* **1996**, 3595. (e) Gauvina, R. M.; Kyritsakas, N.; Fischer, J.; Kress, J. *Chem. Commun.* **2000**, 965. (f) Westerhausen, M.; Kneifel, A. N.; Mayer, P. *Z. Anorg. Allg. Chem.* **2006**, *632*, 634. (g) Martínez, P. H.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221.
- (26) (a) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308. (b) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1984**, *107*, 1805. (c) Sun, X.; Winemiller, M. D.; Xiang, B.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 8039. (d) Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 10228 and references cited therein.
- (27) Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 4069.
- (28) Xiang, B.; Winemiller, M. D.; Briggs, T. F.; Fuller, D. J.; Collum, D. B. *Magn. Reson. Chem.* **2001**, *39*, 137.
- (29)  ${}^6\text{Li}$  is spin 1. For a review of  ${}^6\text{Li}$  NMR spectroscopy, see: Günther, H. *J. Braz. Chem.* **1999**, *10*, 241.
- (30) For theoretical investigations of  ${}^6\text{Li}$ – ${}^{15}\text{N}$  coupling constants, see: (a) Parisel, O.; Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C. *J. Org. Chem.* **2003**, *68*, 1290. (b) Koizumi, T.; Morihashi, K.; Kikuchi, O. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 305.
- (31) (a) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 3529. (b) Waldmüller, D.; Kotsatos, B. J.; Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1997**, *119*, 5479. (c) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761. (d) Reich, H. J.; Goldenberg, W. S.;



Gudmundsson, B. O.; Sanders, A. W.; Kulicke, K. J.; Simon, K.; Guzei, I. A. *J. Am. Chem. Soc.* **2001**, *123*, 8067. (e) Johansson, A.; Davidsson, O. *Chem.—Eur. J.* **2001**, *7*, 3461.

(32) In the C–Li–C subunit of hexalithio aggregate **5** the two carbons are chemically equivalent but magnetically inequivalent (couple differentially to  $^6\text{Li}$ ). Doubling of the  $^6\text{Li}$  satellites in the  $^6\text{Li}$  spectrum of **5** would have confirmed the C–Li–C connectivity, but no such doubling was observed. The absence of evidence, however, does not connote evidence of absence.

(33) Frisch, M. J.; et al. *Gaussian 09*, revision A.1; Gaussian, Inc.: Wallingford, CT, 2009.

(34) Review of piperidine conformational analysis: Blackburne, I. D.; Katritzky, A. R.; Takeuchi, Y. *Acc. Chem. Res.* **1975**, *8*, 300.

(35) Of 22 *N*-alkylpiperidine–lithium complexes characterized crystallographically, all but one shows axial disposition of lithium (ref 35a). For representative examples, see: (a) Nichols, M. A.; Sobinsky, R. M.; Hunter, A. D.; Zeller, M. J. *Chem. Crystallogr.* **2007**, *37*, 433. (b) Strohmman, C.; Schildbach, D.; Auer, D. *J. Am. Chem. Soc.* **2005**, *127*, 7968. (c) Aoki, K.; Tomioka, K.; Noguchi, H.; Koga, K. *Tetrahedron* **1997**, *53*, 13641. (d) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761. (e) Colquhoun, V. P.; Strohmman, C. *Dalton Trans.* **2012**, *41*, 1897.

(36) Zhou, M.-S.; Huang, S.-P.; Weng, L.-H.; Sun, W.-H.; Liu, D.-S. *J. Organomet. Chem.* **2003**, *665*, 237.

(37) The computations use the Gaussian standard state of 1.0 atm. If the THF concentration is corrected to neat THF (approximately 12 M), each solvation step benefits from approximately 2.0 kcal/mol of additional stabilization at  $-78\text{ }^\circ\text{C}$  (195 K). Pratt, L. M.; Merry, S.; Nguyen, S. C.; Quan, P.; Thanh, B. T. *Tetrahedron* **2006**, *62*, 10821.

(38) Wijkens, P.; van Koten, E. M.; Janssen, M. D.; Jastrzebski, T. B. H.; Spek, A. L.; van Koten, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 219.

(39) (a) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403. (b) Williard, P. G. *Comprehensive Organic Synthesis*; Pergamon: New York, 1991; Vol. 1, p 1. (c) Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353.

(40) Lithium enolates and their mixed aggregates have been examined computationally: (a) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255. (b) Weiss, H.; Yakimansky, A. V.; Müller, A. H. E. *J. Am. Chem. Soc.* **1996**, *118*, 8897. (c) Pratt, L. M.; Khan, I. M. *J. Comput. Chem.* **1995**, *16*, 1067. (d) Dybal, J.; Křiž, J. *Collect. Czech. Chem. Commun.* **1994**, *59*, 1699. (e) Rosi, M.; Sgamellotti, A.; Floriani, C. *J. Mol. Struct. (THEOCHEM)* **1998**, *431*, 33. (f) Pratt, L. M.; Streitwieser, A. *J. Org. Chem.* **2003**, *68*, 3830. (g) Pratt, L. M.; Nguyen, N. V.; Ramachandran, B. *J. Org. Chem.* **2005**, *70*, 4279. (h) Streitwieser, A.; Reyes, J. R.; Singhapricha, T.; Vu, S.; Shah, K. *J. Org. Chem.* **2010**, *75*, 3821. (i) Pugh, J. K.; Streitwieser, A. *J. Org. Chem.* **2001**, *66*, 1334. (j) Kwan, E. E.; Evans, D. A. *Org. Lett.* **2010**, *12*, 5124. (k) Streitwieser, A. *J. Org. Chem.* **2009**, *74*, 4433.

(41) Lithium enolate–lithium amide mixed aggregates have been examined computationally: (a) Pratt, L. M.; Newman, A.; Cyr, J. S.; Johnson, H.; Miles, B.; Lattier, A.; Austin, E.; Henderson, S.; Hershey, B.; Lin, M.; Balamraju, Y.; Sammonds, L.; Cheramie, J.; Karnes, J.; Hymel, E.; Woodford, B.; Carter, C. *J. Org. Chem.* **2003**, *68*, 6387. (b) Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339. (c) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9187. (d) Pratt, L. M.; Streitwieser, A. *J. Org. Chem.* **2003**, *68*, 2830. (e) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 2166.

(42) Spectroscopic studies of lithium enolate–lithium amide mixed aggregates: (a) Kim, Y.-J.; Streitwieser, A. *Org. Lett.* **2002**, *4*, 573. (b) Sun, C. Z.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7829. (c) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602. (d) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539.

(43) Calculations of the alkylation of a lithium enolate with MeBr display the absence of Li–Br contacts in exo transition structures: (a) Ikuta, Y.; Tomoda, S. *Org. Lett.* **2004**, *6*, 189. By contrast, enolate

alkylations with methyl chloride show computational evidence of a cyclic transition structure analogous to **17a** and **17b**: (b) Streitwieser, A.; Jayasree, E. G. *J. Org. Chem.* **2007**, *72*, 1785. (c) Streitwieser, A.; Jayasree, E. G.; Hasanayn, F.; Leung, S. S.-H. *J. Org. Chem.* **2008**, *73*, 9426.

(44) For computed cyclic transition structures for enolate alkylations, see: (a) Ando, K.; Morokuma, K. *Theor. Chem. Acc.* **2011**, *130*, 323. (b) Streitwieser, A. *J. Mol. Model.* **2006**, *12*, 673.

(45) For examples showing that halogen leaving groups require no metal assistance during the alkylation of lithium-based nucleophiles, see: (a) Zuend, S. J.; Ramirez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 5939. (b) Ikuta, Y.; Tomoda, S. *Org. Lett.* **2004**, *6*, 189. For a general discussion of lithium-assisted departure of the leaving group, see: (c) Reich, H. J.; Sanders, A. W.; Fiedler, A. T.; Bevan, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 13386.

(46) Theoretical studies of  $\text{S}_{\text{N}}2$  reactions involving lithium-containing species: (i) *No solvent*: (a) Ren, Y.; Gai, J.-G.; Xiong, Y.; Lee, K.-H.; Chu, S.-Y. *J. Phys. Chem. A* **2007**, *111*, 6615. (b) Streitwieser, A.; Jayasree, E. G.; Leung, S. S.-H.; Choy, G. S.-C. *J. Org. Chem.* **2005**, *70*, 8486. (c) Pomelli, C. S.; Bianucci, A. M.; Crotti, P.; Favero, L. *J. Org. Chem.* **2004**, *69*, 150. (d) Ren, Y.; Chu, S. Y. *J. Comput. Chem.* **2004**, *25*, 461. (e) Xiong, Y.; Zhu, H.; Ren, Y. *J. Mol. Struct.* **2003**, *664–665*, 279. (f) Leung, S. S.-H.; Streitwieser, A. *J. Comput. Chem.* **1998**, *19*, 1325. (ii) *Dielectric solvation models*: (g) Streitwieser, A.; Jayasree, E. G.; Hasanayn, F.; Leung, S. S.-H. *J. Org. Chem.* **2008**, *73*, 9426. (h) Ren, Y.; Li, M.; Wong, N.-B.; Chu, S.-Y. *J. Mol. Model.* **2006**, *12*, 182. (i) Ren, Y.; Chu, S. Y. *J. Phys. Chem. A* **2004**, *108*, 7079. (j) Zhu, H.; Ren, Y.; Ren, J. *J. Mol. Struct.* **2004**, *686*, 65. (iii) *Microsolvation models*: (k) Ando, K. *J. Org. Chem.* **2006**, *71*, 1837. (l) Ando, K. *J. Am. Chem. Soc.* **2005**, *127*, 3964.

(47) For leading references to theoretical studies of O-lithiated species, see: (a) Khartabi, H. K.; Gros, P. C.; Fort, Y.; Ruiz-Lopez, M. F. *J. Org. Chem.* **2006**, *73*, 9393. (b) Streitwieser, A. *J. Mol. Model.* **2006**, *12*, 673. (c) Pratt, L. M.; Nguyen, S. C.; Thanh, B. T. *J. Org. Chem.* **2008**, *73*, 6086. (d) Pratt, L. M.; Kwon, O. H.; Chi, T. *Tetrahedron* **2008**, *64*, 5314.

(48) (a) Gupta, L.; Ramirez, A.; Collum, D. B. *J. Org. Chem.* **2010**, *74*, 8392. (b) See also refs 25b and 45a.

(49) By definition, any organolithium equilibrium containing two or more species is inadequately represented by a single X-ray crystal structure. On two occasions, for example, we have characterized species crystallographically that were undetectable in solution. (a) Xu, F.; Reamer, R. A.; Tillyer, R.; Cummins, J. M.; Grabowski, E. J. J.; Reider, P. J.; Collum, D. B.; Huffman, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11212. (b) See ref 13l.

(50) For examples of reactions that are fast relative to the rates of aggregate–aggregate exchanges, see: (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1810. (b) Jones, A. C.; Sanders, A. W.; Bevan, M. J.; Reich, H. J. *J. Am. Chem. Soc.* **2007**, *129*, 3492. (c) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028. (d) Jones, A. C.; Sanders, A. W.; Sikorski, W. H.; Jansen, K. L.; Reich, H. J. *J. Am. Chem. Soc.* **2008**, *130*, 6060. (e) Reich, H. J. *J. Org. Chem.* **2012**, *77*, 5471. (f) Hoepker, A. C.; Gupta, L.; Ma, Y.; Faggini, M. F.; Collum, D. B. *J. Am. Chem. Soc.* **2011**, *133*, 7135.

(51) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

(52) Aubrecht, K. B.; Lucht, B. L.; Collum, D. B. *Organometallics* **1999**, *18*, 2981.

(53) (a) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem.* **2005**, *70*, 1897. (b) Prati, L.; Rossi, M. *Appl. Catal., B* **1999**, *23*, 135.

(54) (a) Kozminski, W.; Philipsborn, W. *J. Magn. Reson. A* **1995**, *116*, 262. (b) Samejima, K.; Takeda, Y.; Kawase, M.; Okada, M.; Kyogoku, Y. *Chem. Pharm. Bull.* **1984**, *32*, 3428.

(55) Scherer, G.; Limbach, H.-H. *J. Am. Chem. Soc.* **1994**, *116*, 1230.