J. Am. Chem. Soc. **2001,** *123,* 8039−8046

Solution Structures and Reactivities of the Mixed Aggregates Derived from *n*-Butyllithium and Vicinal Amino Alkoxides

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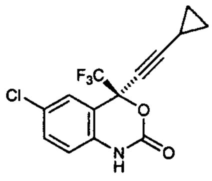
Received January 17, 2001. Revised Manuscript Received May 16, 2001

Abstract: Low-temperature ^{6}Li, ^{13}C, and ^{15}N NMR spectroscopies reveal that mixtures of *n*-BuLi and (1*R*,2*S*)-$R'_2NCH(R)CH(Ph)OLi$ (R*OLi; R = Ph or Me; R'_2N = pyrrolidino or Me_2N) in THF/pentane afford a (n-BuLi)$_3$(R*OLi) (3:1) mixed tetramer and a C_2-symmetric (n-BuLi)$_2$(R*OLi)$_2$ (2:2) mixed tetramer depending on the proportions of the reactants. The corresponding (n-BuLi)(R*OLi)$_3$ (1:3) mixed tetramer is not observed. R*OLi-mediated additions of *n*-BuLi to benzaldehyde proceed with up to 21:1 enantiomeric ratios that depend on the *n*-BuLi/R*OLi stoichiometries. The enantioselectivities are considered in light of a previously posited mechanism involving reaction via the C_2-symmetric 2:2 mixed tetramer.

Introduction

As part of the synthesis of efavirenz (**1**),[1] a powerful reverse transcriptase inhibitor currently marketed under the names Stocrin and Sustiva,[2] investigators at the Merck Research Laboratories developed the highly enantioselective addition shown in eq 1.[3] This highly selective reaction displayed other remarkable properties including pronounced aging effects, modest asymmetric amplification, and a high sensitivity to the structures and proportions of the organolithium reagents. Spectroscopic studies revealed a distribution of 1:3, 2:2, and 3:1 mixed tetramers as single stereoisomers in relative concentrations that could be controlled by adjusting the lithium acetylide (RLi; **3**) and lithium alkoxide (R*OLi; **5b**) ratios. The aggregate−aggregate exchange proved to be *slower* than the 1,2-addition, indicating that deep-seated structural changes could *not* occur on the reaction time scales. Aided by semiempirical computational studies, we concluded that the high enantioselectivity resulted from the reaction of a C_2-symmetric (RLi)$_2$-(R*OLi)$_2$ mixed tetramer. Semiempirical computations also suggested that lithium−acetylene π interactions at the transition structure might be essential. Indeed, the analogous addition of *n*-BuLi to **2** proceeded with mediocre enantioselectivity.



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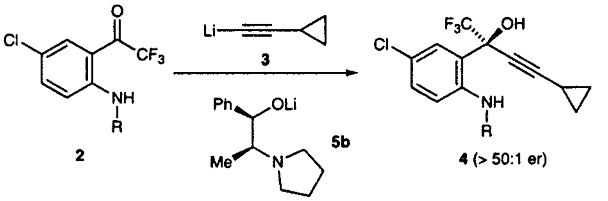

(1)

The modest selectivities obtained from *n*-BuLi/R*OLi mixtures suggested an important question: Does the loss in enantioselectivity resulting from replacing lithium acetylides with *n*-BuLi correlate with the poor control of mixed aggregate stoichiometry and stereochemistry? We describe herein ^{6}Li, ^{13}C, and ^{15}N NMR spectroscopic studies of mixed aggregates derived from alkoxide **5b** and *n*-BuLi.[5−7] The equilibria comprising the *n*-BuLi/R*OLi mixed aggregates display some differences when compared to their lithium acetylide/R*OLi counterparts,[4] but the structural control is quite good nonetheless. We also have

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[1] Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937. Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590. Tan, L.; Chen, C.-Y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 711. Pierce, M. E.; Parsons, R. L., Jr.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C. Y.; Tillyer R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G.; Grabowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536.

[2] Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I.-W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602. Tucker, T. J.; Lyle, T. A.; Wiscount, C. M.; Britcher, S. F.; Young, S. D.; Sanders, W. M.; Lumma, W. C.; Goldman, M. E.; O'Brien, J. A.; Ball, R. G.; Homnick, C. F.; Schleif, W. A.; Emini, E. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994**, *37*, 2437.

[3] Ye, M.; Logaraj, S.; Jackman, L. M.; Hillegass, K.; Hirsh, K. A.; Bollinger, A. M.; Grosz, A. L.; Mani, V. *Tetrahedron* **1994**, *50*, 6109. For other examples, see: Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455. Schön, M.; Naef, R. *Tetrahedron: Asymmetry* **1999**, *10*, 169. Gärtner, P.; Letschnig, M.; Knollmüller, M. *Monatsh. Chem.* **2000**, *131*, 867. Knollmüller, M.; Ferencic, M.; Gärtner, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3969.

[4] (a) 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. (b) 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.

[5] Other asymmetric additions of *n*-BuLi to carbonyl compounds have been effected with high enantioselectivity using chiral amino alkoxides[3] and chiral lithium amides.[6,7]

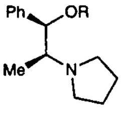
[6] For a related highly enantioselective addition of lithium acetylide to an imine functionality, see: Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L., Jr.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119.

10.1021/ja010136c CCC: \$20.00

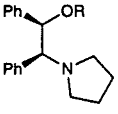
extended Jackman's investigations of the enantioselective *n*-BuLi addition to benzaldehyde.[3,5,8]

Results

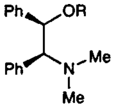
[^{6}Li]*n*-BuLi and [^{6}Li,^{13}C]*n*-BuLi[9] were prepared >98% isotopically labeled and recrystallized from pentane at −95 °C following literature procedures.[10−12] The preparation of ^{15}N-labeled amino alcohol [^{15}N]**5a** has been noted.[4,13] Mixtures of *n*-BuLi and alkoxide **5b** (R*OLi) were generated in situ from



5a; R = H
5b; R = Li



6a; R = H
6b; R = Li



7a; R = H
7b; R = Li

n-BuLi and amino alcohol **5a**, keeping the total lithium titer constant (0.15 M); the *n*-BuLi/R*OLi proportions were calculated by accounting for the consumption of *n*-BuLi. ^{6}Li, ^{13}C, and ^{15}N NMR spectroscopic data are summarized in Table 1. Selected spectra are shown in Figures 1−5 and 7. Additional spectra are included in Supporting Information. Enantioselective 1,2-additions reported by Jackman[3] also prompted us to investigate alkoxides **6b**[14] and **7b**.[15] Because the results from the structural studies using **6b** or **7b** are analogous to those derived from **5b**,[16,17] the spectroscopic details are included only as Supporting Information.

Structures of Homo Aggregates. NMR spectroscopic data of *n*-BuLi in 1:5 THF/pentane fully show the coexistence of dimer ((*n*-BuLi)$_2$; **8**) and tetramer ((*n*-BuLi)$_4$; **9**) and low concentrations of a mixed tetramer impurity ((*n*-BuLi)$_3$(*n*-BuOLi);[18] **10**). See Figure 1A and Table 1.[19,20] Lithium alkoxides **5b**−**7b** form complex mixtures of aggregates (Figure 1B).[5,21]

Table 1. ^{6}Li, ^{13}C, and ^{15}N NMR Spectral Data[a]

compd	δ ^{6}Li (mult, $J_{\mathrm{Li-C}}$)	(mult, $J_{\mathrm{Li-N}}$)	δ ^{13}C (mult, $J_{\mathrm{C-Li}}$)	δ ^{15}N (mult, $J_{\mathrm{Li-N}}$)
8	2.01 (t, 8.2)		12.32 (qn, 7.9)	
9	1.56 (qt, 5.4)		10.02 (br m)	
10	1.62 (qt, 6.2)		10.21 (br m)	
	0.83 (t, 6.0)			
12	2.25 (t, 6.1)	(d, 2.6)	9.82 (br m)	51.47[b]
	0.96 (d, 4.8)	(s)		
15	2.03 (qt, 6.2)	(s)	9.16 (br m)	51.34[b]
	1.97 (t, 6.0)	(d, 2.7)	10.01 (br m)	
	1.15 (t, 5.5)	(s)	10.06 (br m)	
	1.13 (t, 5.5)	(s)		

[a] The $J_{\mathrm{C-Li}}$ coupling constants were routinely measured from the ^1J(^{6}Li,^{13}C)-resolved spectrum. The multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, qt = quartet, qn = quintet, m = multiplet, br m = broad multiplet. The ^{6}Li, ^{13}C, and ^{15}N chemical shifts are reported relative to 0.3 M ^{6}LiCl/MeOH at −90 °C (δ ^{6}Li = 0.0 ppm), neat dimethylethylamine (δ ^{15}N = 25.7 ppm), and the methyl group of neat toluene (δ ^{13}C = 20.4 ppm), respectively. All *J* values are reported in hertz. [b] Poor resolution stemmed from overlapping resonances.

Structures of Mixed Aggregates. ^{6}Li NMR spectra recorded at −110 °C on solutions of lithium alkoxide [^{6}Li]**5b** and [^{6}Li]*n*-BuLi in 1:5 THF/pentane prepared at −78 °C *without warming* are quite complex, displaying ^{6}Li resonances ascribed to *n*-BuLi/R*OLi mixed aggregates and homo aggregates (Figure 1C). Warming the samples to 0 °C for 5 min then cooling to −110 °C increases the relative concentrations of the mixed aggregates and decreases the concentrations of the homo aggregates (Figure 1D). Additional warm−cool cycles have no measurable effect. These behaviors are consistent with slow aggregate subunit exchange attributed to the strong chelates of the lithium alkoxide fragments.[4] Consequently, all samples were aged for 5 min at 0 °C prior to low-temperature spectroscopic analysis to ensure complete equilibration.[22]

The ^{6}Li NMR spectrum of an aged sample containing a 1:2 mixture of *n*-BuLi/**5b** shows predominantly a pair of resonances at 0.96 and 2.25 ppm in a 1:1 ratio along with resonances of the R*OLi homo aggregates (Figure 1D). The 1:1 ratio is consistent with a mixed dimer (Chart 1; **11**) or any of three possible 2:2 mixed tetramers (**12**−**14**). Spectra recorded on analogous solutions of [^{6}Li,^{13}C]*n*-BuLi/[^{6}Li]**5b** display the ^{6}Li resonance at 2.25 ppm as a triplet, indicating coupling with two *n*-BuLi α-carbons.[23] The ^{6}Li resonance at 0.96 ppm appears as a doublet, indicating coupling to one *n*-BuLi α-carbon (Figure 1E). The ^{13}C NMR spectrum displays predominantly a broad multiplet at 9.82 ppm (Figure 2A), shown by single-frequency decouplings (and ^{6}Li,^{13}C-HMQC spectroscopy; see below) to be coupled to both ^{6}Li resonances. Dimer **11** can be readily excluded because its two ^{6}Li resonances should both appear as doublets. Among the three possible 2:2 mixed tetramers, isomer **12** is the only isomer containing two symmetry-equivalent ^{6}Li nuclei concurrently connected to two carbons *and* coordinated by the pyrrolidine nitrogens. By contrast, isomers **13** and **14** would predict coupling of the pyrrolidine nitrogen to lithiums

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(7) (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) Fressigné, C.; Maddaluno, J.; Marquez, A.; Giessner-Prettre, C. *J. Am. Chem. Soc.* **2000**, *122*, 8899−8907.

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(9) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308.

(10) The original crystallization of *n*-BuLi by Kottke and Stalke[11] has been described in detail for preparative scale.[12b]

(11) Kottke, T.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 580.

(12) (a) Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 5810. (b) Rennels, R. A.; Maliakal, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 421.

(13) Some of the work described herein was carried out with R*OLi additives of the opposite abolute configuration to that depicted. For the sake of clarity, only one antipode is shown.

(14) Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. J. *Synthesis* **1991**, 1453.

(15) Sheng-Jian, L.; Yaozhong, J.; Auqiao, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1467.

(16) The investigations of **6b** and **7b** did not include ^{15}N-labeled R*OLi, however.

(17) We did note, however, that solutions of *n*-BuLi and the diphenyl analogues display measurably more facile aggregate equilibration (aging).

(18) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1984**, *107*, 1805. Further investigations of *n*-BuLi/*n*-BuOLi will be described in due course: Sun, X.; Breslin, S. R.; Winemiller, M. D.; Briggs, T. F.; Xiang, B.; Collum, D. B., unpublished.

(19) For leading references to structural studies of RLi/R′OLi mixed aggregates, see: Thomas, R. D.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 11239. Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, 1115.

(20) For leading references to structural investigations of *n*-BuLi, see refs 9, 12, and 32.

(21) Arnett, E. M.; Nichols, M. A.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 7059. Nichols, M. A.; McPhail, A. T.; Arnett, E. M. *J. Am. Chem. Soc.* **1991**, *113*, 6222. Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

(22) (a) *n*-BuLi was confirmed[22b] to be stable during the aging process. (b) Maercker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972.

(23) The nuclear spins of ^{6}Li, ^{13}C, and ^{15}N are 1, $^1/_2$, and $^1/_2$, respectively.

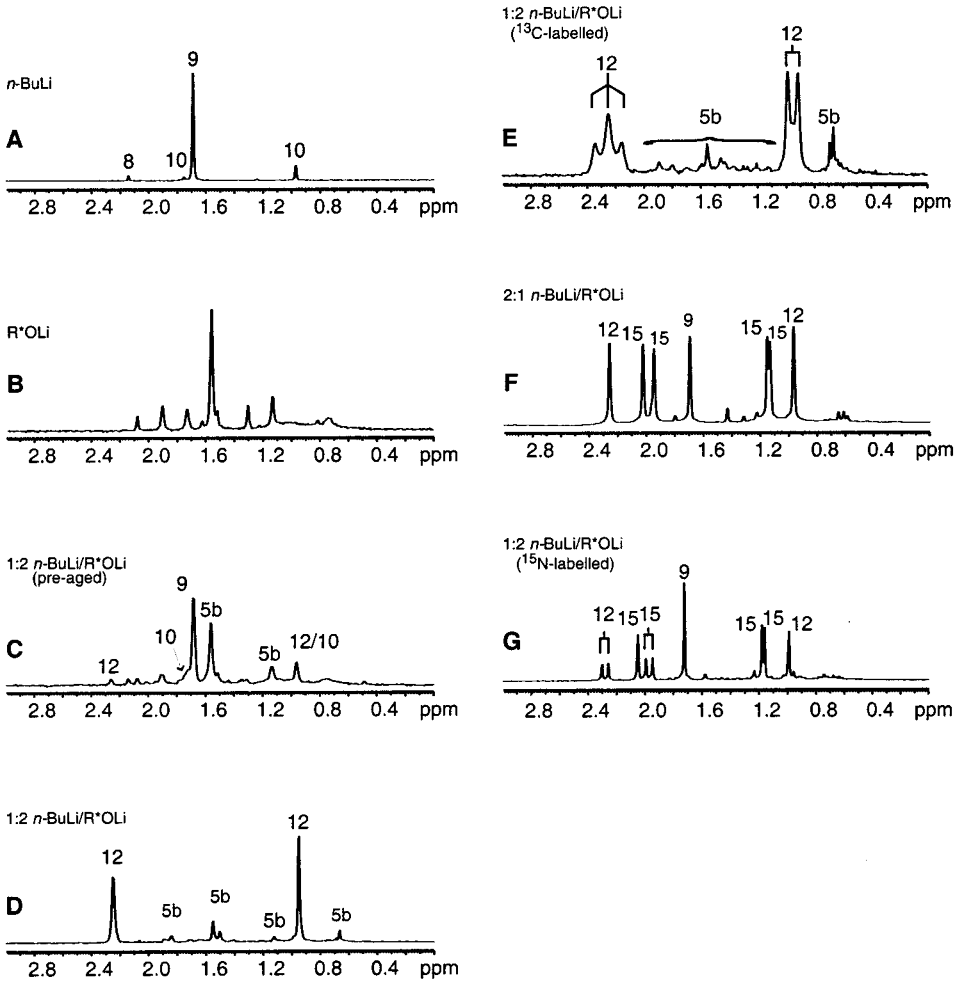
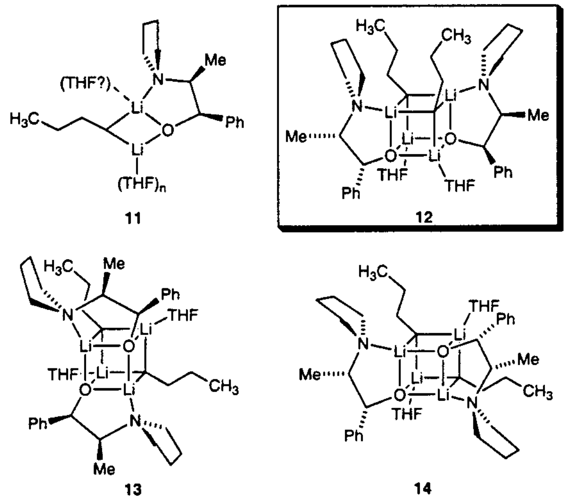


Figure 1. ^{6}Li NMR spectra of samples containing *n*-BuLi and **5b** (0.15 M total lithium titer) in 1:5 THF/pentane at −110 °C: (A) [^{6}Li]*n*-BuLi; (B) [^{6}Li]**5b**; (C) pre-aged 1:2 mixture of [^{6}Li]*n*-BuLi/[^{6}Li]**5b**; (D) 1:2 mixture of [^{6}Li]*n*-BuLi/[^{6}Li]**5b** after aging at 0 °C for 5 min; (E) 1:2 (aged) mixture of [^{6}Li,^{13}C]*n*-BuLi/[^{6}Li]**5b**; (F) 2:1 (aged) mixture of [^{6}Li]*n*-BuLi/[^{6}Li]**5b**; (G) 2:1 (aged) mixture of [^{6}Li]*n*-BuLi/[^{6}Li,^{15}N]**5b**.

Chart 1. Possible 1:1 Mixed Dimer and 2:2 Mixed Tetramers of *n*-BuLi/**5b**



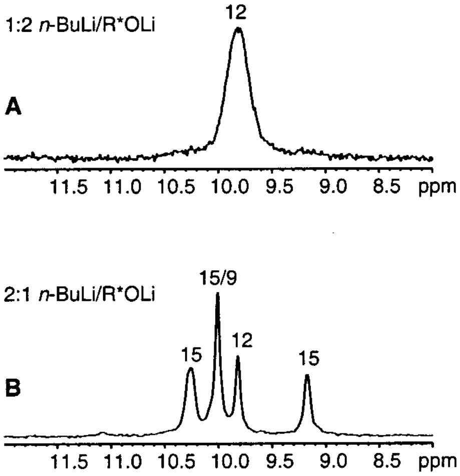


Figure 2. ^{13}C NMR spectra of solutions containing [^{6}Li,^{13}C]*n*-BuLi and [^{6}Li]**5b** (0.15 M total lithium titer) in 1:5 THF/pentane at −110 °C: (A) 1:2 mixture of [^{6}Li,^{13}C]*n*-BuLi/[^{6}Li]**5b**; (B) 2:1 mixture of [^{6}Li,^{13}C]*n*-BuLi/[^{6}Li]**5b** with ^{6}Li broad-band decoupling.

bearing only one neighboring *n*-butyl fragment. A combination of ^{15}N NMR spectroscopy and ^{6}Li,^{15}N-heteronuclear multiple quantum correlation (HMQC) spectroscopy[24] showed ^{15}N coupling to the ^{6}Li resonance at 2.25 ppm—the resonance also showing coupling to *two* *n*-Bu fragments (Figure 1G). The spectral data establish C_2-symmetric isomer **12** as the observable 2:2 mixed tetramer.[23]

A 2:1 mixture of [^{6}Li]*n*-BuLi/[^{6}Li]**5b** to *n*-BuLi in 1:5 THF/pentane yields a pair of ^{6}Li resonances attributed to 2:2 mixed tetramer **12** along with four ^{6}Li resonances in approximate 1:1:

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[24] Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *Magn. Reson. Chem.* **1992**, *30*, 855. Review: Gudat, D. *Ann Rep. NMR Spectrosc.* **1999**, *38*, 139.

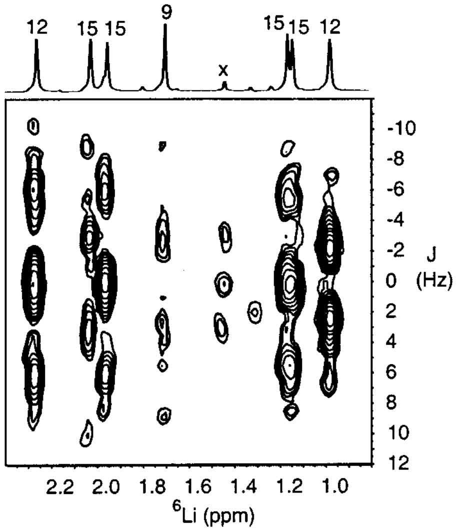
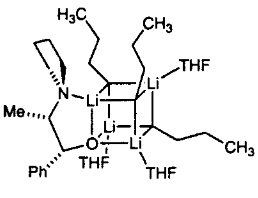


Figure 3. $^1J(^6\mathrm{Li},^{13}\mathrm{C})$-resolved ^{6}Li NMR spectrum recorded on a solution containing 2:1 [^{6}Li,^{13}C]*n*-BuLi and [^{6}Li]**5b** (0.15 M total lithium titer) in 1:5 THF/pentane at −110 °C. X represents an unknown species present only in this sample.

1:1 intensities (Figure 1F) anticipated for the 3:1 mixed tetramer **15**. The ^{6}Li and ^{13}C NMR spectra recorded on an analogous sample containing [^{6}Li,^{13}C]*n*-BuLi and [^{6}Li]**5b** are complex due to the severely overlapping multiplets. Fortunately, several two-dimensional NMR spectroscopic methods provided the requisite resolution. The $^1J(^6\mathrm{Li},^{13}\mathrm{C})$-resolved spectrum[25] displays the multiplets consistent with a mixture of 2:2 and 3:1 mixed aggregates **12** and **15** (Figure 3). The ^{6}Li,^{13}C-HMQC spectrum[26] (Figure 4) shows the anticipated cross-peaks consistent with the proposed ^{6}Li−^{13}C connectivities. The ^{6}Li−^{6}Li exchange (EXSY)[27] spectrum recorded at −110 °C (Figure 5) reveals cross-peaks between the three ^{6}Li resonances assigned as proximal to the alkoxide oxygen of **15**, implicating a rapid 3-fold degenerate exchange of the chelate as shown in eq 2



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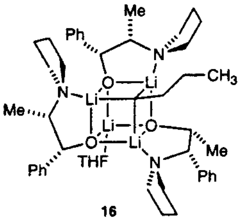

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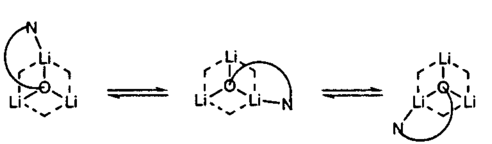

(degenerate chelate exchange in 15)

(2)

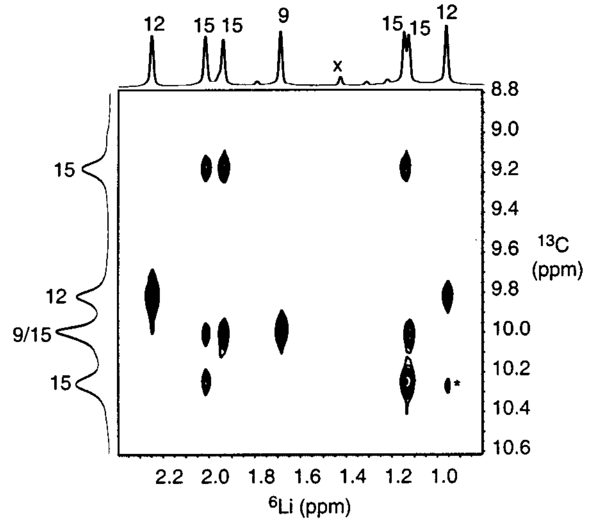

Figure 4. ^{6}Li,^{13}C-HMQC spectrum recorded on a solution containing 2:1 [^{6}Li,^{13}C]*n*-BuLi and [^{6}Li]**5b** (0.15 M total lithium titer) in 1:5 THF/pentane at −110 °C showing *n*-BuLi tetramer **9**, 3:1 *n*-BuLi/R*OLi mixed tetramer **15**, and 2:2 *n*-BuLi/R*OLi mixed tetramer **12**. The ^{6}Li{^{13}C} and ^{13}C{^{6}Li} NMR spectra are shown on the top and left, respectively. The asterisk (*) denotes the 3:1 mixed aggregate of *n*-BuLi and *n*-BuOLi impurity. X represents an unknown species present only in this sample.

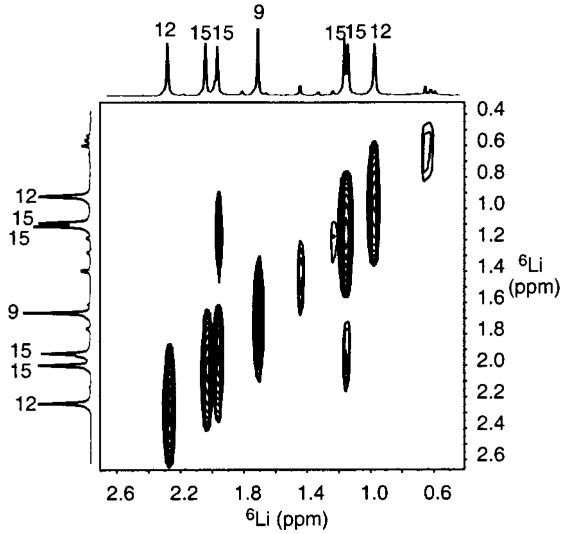

Figure 5. ^{6}Li,^{6}Li-EXSY spectrum recorded on a solution containing 2:1 [^{6}Li]*n*-BuLi and [^{6}Li]**5b** (0.15 M total lithium titer) in 1:5 THF/pentane at −110 °C. The spectrum was recorded with a mixing time of 2 s.

Addition of 1.0 equiv of lithium alkoxide **5b** to *n*-BuLi affords 2:2 mixed tetramer **12** along with appreciable concentrations of both mixed tetramer **15** and free R*OLi (**5b**). The coexistence of **15** and R*OLi—departs significantly from the behavior of the lithium acetylide/**5b** mixtures in which the existence of the 1:3, 2:2, and 3:1 mixed aggregates could be rigorously controlled through control of RLi/R*OLi stoichiometry.[4] Addition of >1.5 equiv of lithium alkoxide **5b** eliminates mixed tetramer **15**, providing 2:2 mixed tetramer **12** along with free R*OLi. The absence of an (*n*-BuLi)(R*OLi)$_3$ (1:3) mixed tetramer such as **16**[28] also contrasts with the results from lithium acetylides,[4] in which the corresponding lithium acetylide analogue of **16** was formed quantitatively with an excess (≥3.0 equiv) of alkoxide **5b**.

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[28] There are two possible C_3-symmetric forms of (RCCLi)(R*OLi)$_3$ mixed tetramers. An X-ray crystal structure of the (lithium cyclopropylacetylide)(**5b**)$_3$ mixed tetramer supports the form depicted (**16**)[4b] whereas computations support the alternative.[4a]

Table 2. Enantiomeric Ratios (er) for the Addition of *n*-BuLi to PhCHO (eq 3)[a]

entry	R*OLi	*n*-BuLi/R*OLi	selectivity (er)
1	**5b**	3:1	1.4:1
2	**5b**	2:1	1.7:1
3	**5b**	1:1	2.4:1
4	**5b**	1:1.5	2.5:1
5[b]	**5b**	1:1.5	1.1:1
6	**5b**	1:2	2.5:1
7	**5b**	1:3	2.5:1
8	**6b**	5:1	1.1:1
9	**6b**	3:1	1.2:1
10	**6b**	2:1	1.5:1
11	**6b**	1:1	4.0:1
12	**6b**	1:1.5	8.5:1
13	**6b**	1:2	8.5:1
14[b]	**6b**	1:2	3.3:1
15	**6b**	1:3	7.2:1
16	**6b**	1:5	7.2:1
17	**7b**	3:1	1.7:1
18	**7b**	2:1	2.2:1
19	**7b**	1:1	5.5:1
20	**7b**	1:1.5	10:1
21[b]	**7b**	1:1.5	4.9:1
22	**7b**	1:2	10:1
23	**7b**	1:3	8.0:1
24[c]	**7b**	1:1.5	21:1

[a] PhCHO was added to aged mixtures of *n*-BuLi/R*OLi at −78 °C. [b] PhCHO was added to a *n*-BuLi/R*OLi mixture at −78 °C without prior aging at 0 °C. [c] Addition at −105 °C.

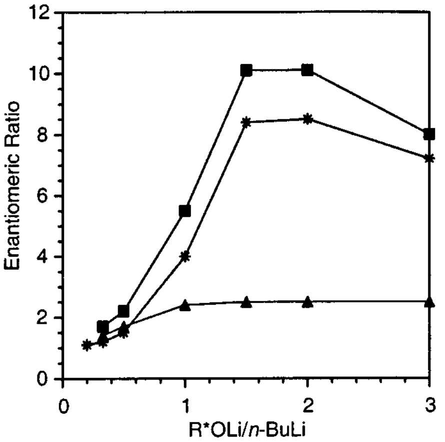
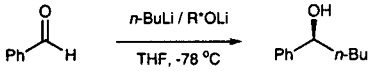


Figure 6. Enantiomeric ratio of 1-phenyl-1-pentanol versus R*OLi/*n*-BuLi for the addition of *n*-BuLi to benzaldehyde in the presence of amino alkoxides **5b** (▲), **6b** (∗), and **7b** (■) at −78 °C.

Enantioselective 1,2-Additions to Benzaldehyde. To understand how structure correlates with reactivity, we investigated the enantioselective addition of *n*-BuLi to benzaldehyde (eq 3).



(3)

The enantioselectivity was probed as a function of the structure and stoichiometry of added R*OLi additives **5b**−**7b** (Table 2; Figure 6). Additives **5b**−**7b** behave similarly in that maximum enantioselectivity is attained at >1.5 equiv of R*OLi per *n*-BuLi. The optimum enantioselectivities coincide with the formation of the C_2-symmetric mixed tetramers (e.g., **12**). We do note, however, that replacing the methyl group of **5b** with a phenyl (**6b** or **7b**) imparts measurably higher stereocontrol.

Several experiments molded our general ideas about mechanism and how aging effects on the aggregate structures correlate with the enantioselectivities of 1,2-addition: (1) samples that were not aged at 0 °C to achieve aggregate equilibration prior to addition of benzaldehyde displayed poor enantioselectivities (Table 2, entries 5 and 14) when compared with their aged counterparts (entries 4 and 13, respectively); (2) the enantioselectivities for the addition of 0.1 equiv of PhCHO and 0.9 equiv of PhCHO are indistinguishable within experimental error; and (3) addition of 0.45 equiv of PhCHO at −78 °C, aging at 0 °C, followed by addition of a second 0.45 equiv of PhCHO afford enantioselectivities that were indistinguishable from normal runs where 0.9 equiv of PhCHO was added in one part at −78 °C. These three experiments are discussed below.

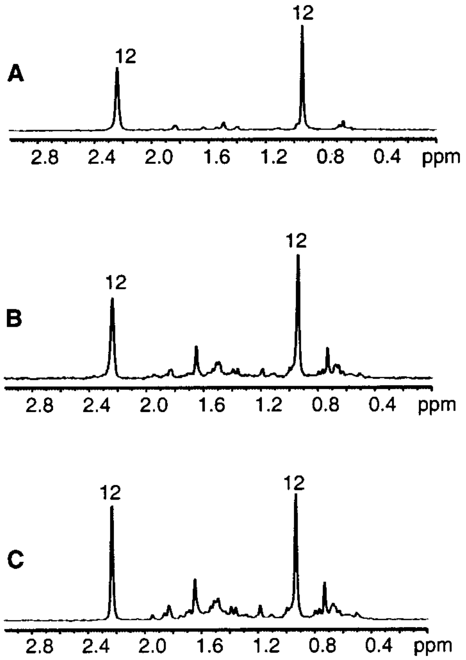
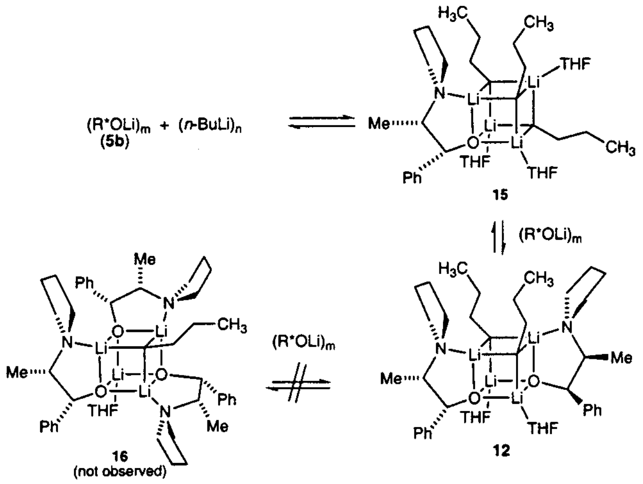


Figure 7. ^{6}Li NMR spectra of samples containing *n*-BuLi and **5b** (0.15 M total lithium titer) in 1:5 THF/pentane at −110 °C: (A) 1:2 mixture of [^{6}Li]*n*-BuLi/[^{6}Li]**5b**; (B) 1:2 mixture of [^{6}Li]*n*-BuLi/[^{6}Li]**5b** with added PhCHO (0.5 equiv per *n*-BuLi); (C) 1:2 mixture of [^{6}Li]*n*-BuLi/[^{6}Li]**5b** with added PhCHO (0.5 equiv per *n*-BuLi) after aging at 0 °C for 3 min.

We investigated the enantioselective additions using ^{6}Li NMR spectroscopy to understand the aging effects noted above. Previous studies of the effectively instantaneous 1,2-addition in eq 1 had revealed a mixed aggregate comprised of lithium acetylide **3**, R*OLi **5b**, and the lithium salt of adduct **4** in a 1:2:1 ratio that equilibrated slowly on *laboratory* time scales.[4] We expected that an analogous 1:2:1 (*n*-BuLi)(R*OLi)$_2$(PhCH(OLi)*n*-Bu) mixed aggregate would be detectable prior to equilibration with other structural forms. Nevertheless, treating a THF solution containing a 1:2 mixture of *n*-BuLi and **5b** (Figure 7A) with 0.5 equiv of PhCHO (per *n*-BuLi), rigorously maintaining the sample below −110 °C to minimize aggregate equilibration, revealed only 2:2 mixed tetramer **12** along with a complex distribution of resonances (Figure 7B). Aging the sample at 0 °C and recording another spectrum at −110 °C (Figure 7C) revealed no significant changes, indicating that the mixture had equilibrated prior to warming. Using [^{6}Li,^{13}C]*n*-BuLi to show C−Li connectivities revealed that virtually all of the remaining 0.5 equiv of *n*-BuLi resides in the mixed tetramer **12** rather than in the complex envelope of newly generated aggregates. This rapid aging and the regeneration of C_2-symmetric mixed dimer **12** are critical observations that may be required to explain the insensitivity of the enantioselectivity to percent conversion (points 2 and 3 noted above).

Scheme 1



Discussion

Previous NMR spectroscopic studies of lithium acetylide/R*OLi mixtures (R*OLi = lithium ephedrate **5b**) reveal equilibria comprised of 3:1, 2:2, and 1:3 mixed aggregates. To ascertain the role that the acetylenic group plays in controlling structure and reactivity, we expanded the structural studies to include *n*-BuLi/R*OLi mixtures for three chiral additives (R*OLi = **5b**−**7b**); alkoxide **5b** is emblematic (Scheme 1).[29] At >2:1 *n*-BuLi/**5b**, mixed tetramer **15** is the dominant form. The connectivities within the cubic structure as well as the presence of the chelate are readily discerned from a combination of ^{6}Li−^{13}C and ^{6}Li−^{15}N coupling patterns. As the *n*-BuLi/R*OLi ratio approaches 1:1, C_2-symmetric 2:2 mixed tetramer **12** becomes significant. Tetramer **12** forms to the exclusion (<10%) of three other possible stereoisomers (Chart 1).[30] However, the *n*-BuLi/R*OLi series shows distinctly different behaviors from the analogous lithium acetylide/R*OLi series. Tetramer **12** is formed quantitatively only with an approximate 0.5 equiv excess R*OLi. Also, whereas lithium acetylides readily afford the C_3-symmetric 1:3 mixed tetramers, we found no evidence of the analogous C_3-symmetric mixed tetramer **16**.[28] A seemingly related relative instability of (*n*-BuLi)(*n*-BuOLi)$_3$ was noted by McGarrity and Ogle.[18]

Mixtures of *n*-BuLi and either alkoxide **6b** or **7b** afford analogous equilibria comprising the 3:1 and 2:2 mixed aggregates. Because of the high structural homology, the detailed spectroscopic results for **6b** and **7b** are relegated to the Supporting Information. However, comparison of the enantioselective additions mediated by **5b**−**7b** revealed some interesting differences as discussed below.

Enantioselective 1,2-Additions to Benzaldehyde. The lithium ephedrate-mediated 1,2-additions of alkyllithiums to aldehydes reported by Jackman and co-workers[3] formed the basis of the highly enantioselective synthesis of efavirenz. We reinvestigated the addition of *n*-BuLi to benzaldehyde (eq 3, Table 2, and Figure 6) in an effort to correlate structure with reactivity. Four structurally and mechanistically important trends emerged.

(1) The enantioselectivities display a significant dependence on the *n*-BuLi/R*OLi stoichiometries. As shown in Figure 6, the enantioselectivities reach plateaus at ≥1.5 equiv of R*OLi per *n*-BuLi—stoichiometries favoring the C_2-symmetric mixed tetramer (e.g., **12**). The eroded selectivities at lower R*OLi concentrations correlate with the formation of 3:1 mixed tetramer **15**.

(2) Although the selectivities do not appear to be particularly sensitive to the substituents on the dialkylamino group (Figure 6), we noted a measurable increase in enantioselectivity by replacing the methyl of **5b** with a phenyl (**6b** or **7b**). Because these substitutions are not accompanied by substantial changes in the aggregate structures or concentrations, they may stem from subtle differences at the otherwise isostructural product-determining transition structures (below).

(3) The enantioselective addition in eq 3 exhibits aging effects; solutions of *n*-BuLi/R*OLi that were kept at −78 °C displayed low enantioselectivities when compared with analogous samples that had been aged at 0 °C prior to adding the PhCHO substrate. Similar effects were noted in the efavirenz synthesis (eq 1).[1,4] These aging effects correlate with the slow equilibration of the mixed aggregates on *laboratory* time scales, and they substantially influence our mechanistic interpretation (below).

(4) The enantioselectivities are insensitive to the percent conversion as shown by adding 0.1−0.9 equiv of PhCHO. To the extent that new mixed aggregates intervene, they do not appear to influence the stereocontrol.

Mechanistic Hypotheses. One might legitimately question attempts to correlate structure with reactivity. The discussion has brushed against the assumption that the observable aggregate is also the reactive form. In most instances, such an assumption would be highly suspect. Reactions that are slow enough to be monitored on laboratory time scales are at least several orders of magnitude slower than most aggregate exchanges, which are typically observed as coalescences in the low-temperature NMR spectra. Detailed rate studies often show that deep-seated structural changes precede the rate-limiting steps.[31,32] In the studies described herein, however, we have the opposite situation. The pronounced aging effects suggest that the aggregate exchanges are slow on laboratory time scales whereas the 1,2-addition in eq 3 is, practically speaking, instantaneous. Consequently, the observable aggregates appear to react faster than they undergo deep-seated structural changes.

We now reiterate the model in Scheme 2 presented earlier.[4a] Facile[33] substitution of a THF by benzaldehyde in the observable C_2-symmetric mixed tetramer **12** would provide precomplex **17**. The subsequent 1,2-addition via a four-centered (Li_2OC) transition structure[34] can proceed by placing a phenyl group of PhCHO toward the less hindered chelate face (as drawn) or toward the more hindered chelate face; placing the phenyl group toward the less hindered face is consistent with the observed enantioselectivity. The improved enantioselectivities using diphenyl-substituted ligands **6b** or **7b** (cf., entries 7, 15, and 23 in Table 2) might stem from the enhanced steric demand.

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[29] For a related crystal structure of (*n*-BuLi)(R*OLi)$_3$ and (*n*-BuLi)$_2$-(R*OLi)$_2$ mixed aggregates, see: Goldfuss, B.; Khan, S. I.; Houk, K. N. *Organometallics* **1999**, *18*, 2927. Goldfuss, B.; Steigelmann, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 4133. Donkervoort, J. G.; Vicario, J. L.; Rijnberg, E.; Jastrzebski, J. T. B. H.; Kooijman, H.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **1998**, *550*, 463.

[30] An alternative to **12** involving a ladder structure corresponding to cleavage of the Li_2O_2 ring cannot be excluded.

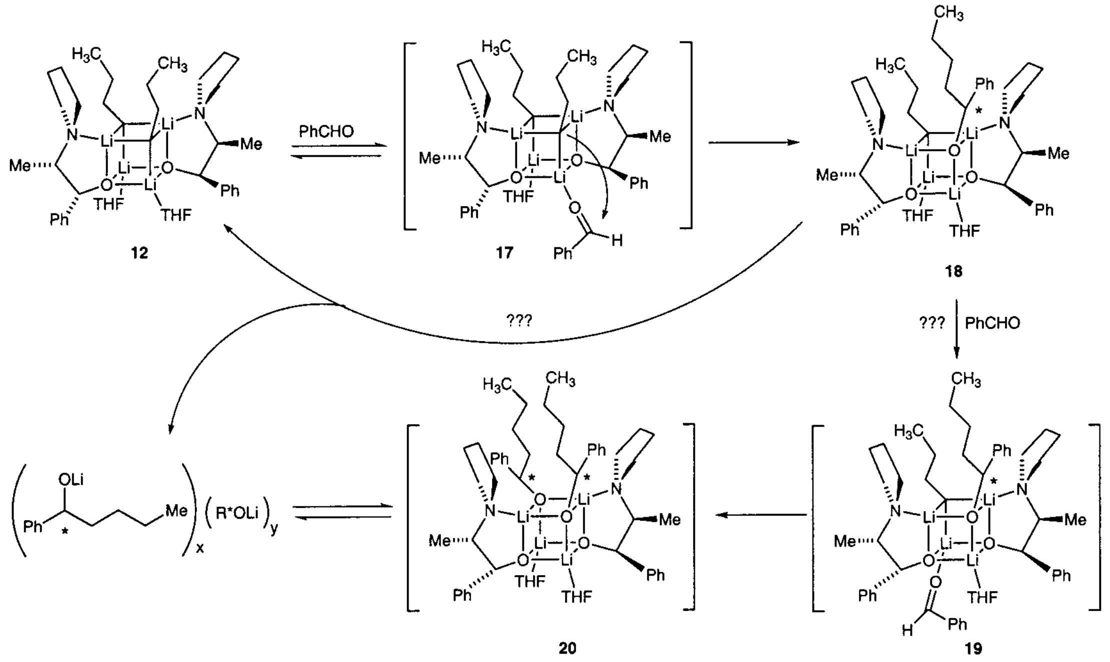
[31] Leading references: Wardell, J. L. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abels, F. W., Eds.; Pergamon: New York, 1982; Vol. 1, Chapter 2. *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley: New York, 1972; Vols. 1 and 2. Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

[32] McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1810. Also, see: Ogle, C. A.; Wang, X. L.; Carlin, C. M.; Strickler, F. H.; Gordon, B. *J. Polym. Sci.* **1999**, *37*, 1157.

[33] Ligand−ligand exchanges are extremely fast for monodentate ligands. Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *32*, 1035 and references therein.

[34] Bachrach, S. M.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 3946. Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. Nakamura, E.; Nakamura, M.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016.

Scheme 2



The mechanism delineated in Scheme 2 includes the implicit assumption that adduct **18** does not equilibrate before reacting further via precomplex **19**. We can defend this assumption using four key observations: (1) The numerous examples of slow aging of *n*-BuLi/R*OLi mixtures on laboratory time scales suggests that slow exchanges of *n*-BuLi/R*OLi aggregates may be prevalent. (2) Previous investigations of the 1,2-addition in eq 1 revealed an adduct analogous to **18** prior to equilibration to give other forms.[4b] (3) In a compelling study, McGarrity and Ogle used rapid injection NMR spectroscopy to show that the dimers and tetramers of *n*-BuLi react with PhCHO faster than the aggregates exchange, affording mixed aggregates in a "nonequilibrated state".[32] (4) The independence of the enantioselectivity in eq 3 to the percent conversion would be consistent with reaction of the remaining *n*-BuLi fragment of **18** before the essential elements of the C_2 symmetry are lost via an aggregate equilibration.

While aggregate equilibration may be very slow relative to reaction with PhCHO, several experiments indicate that the equilibration of mixed aggregate **18** could be fast relative to sample mixing (sample preparation): (1) Addition of 0.5 equiv did not afford detectable concentrations of **18** despite efforts to keep the sample cold during the addition of PhCHO, and (2) spectra recorded on mixtures of *n*-BuLi, R*OLi, and PhCHO were essentially identical before and after aging the samples, indicating that we were unsuccessful at observing a preequilibrated mixture. Failure to observe mixed aggregate **18** does not undermine the mechanism in Scheme 2; equilibration on the laboratory time scales does not mean that **18** equilibrates faster than it reacts with another PhCHO. It did, however, lead to an important question: *Why wouldn't aggregate equilibration erode the enantioselectivities?* The simple answer stems from an interesting quirk of the thermochemistry: *the equilibration of* ***18*** *regenerates* C_2*-symmetric mixed tetramer* ***12*** *as the only n-BuLi containing species*. Therefore, whether **18** is kinetically trapped and reacts via precomplex **19** or regenerates **12** has no stereochemical consequence—the key elements of stereocontrol appear to be essentially identical in precomplexes **17** and **19**.

Conclusion and Summary

Mixed aggregates derived from *n*-BuLi and three nonracemic amino alkoxides (R*OLi) have been characterized by NMR spectroscopy. $(n\text{-BuLi})_3(\text{R*OLi})$ and $(n\text{-BuLi})_2(\text{R*OLi})_2$ are formed with control of both stoichiometry and stereochemistry. In contrast to the lithium acetylide/R*OLi series described previously,[4] no $(n\text{-BuLi})(\text{R*OLi})_3$ (1:3) mixed tetramers are observed. In conjunction with aging effects on both structure and reactivity, enantioselective additions to benzaldehyde are interpreted in the context of a mechanistic model based on reaction via a C_2-symmetric mixed tetramer. It is rather extraordinary that an alkoxide containing two stereogenic centers and an achiral alkyllithium could spontaneously assemble to afford aggregates with control of up to 12 stereogenic centers. It is less extraordinary, however, that C_2 symmetry is implicated as the key control element given the prevalence of C_2 symmetry in asymmetric synthesis.[35]

Experimental Section

Reagents and Solvents. The pentane and THF used were vacuum transferred from degassed blue or purple stills containing sodium benzophenone ketyl. The pentane still contained 1% tetraglyme to dissolve the ketyl. Air- and moisture-sensitive materials were manipulated using vacuum line and syringe techniques. Amino alcohols **5a**–**7a** as well as [^{15}N]**5a** were prepared by literature procedures.[4a,14,15] [^{6}Li]*n*-BuLi and [^{6}Li,^{13}C]*n*-BuLi were prepared from *n*-BuCl and [^{13}C-1]*n*-BuCl,[36] respectively. [^{6}Li]*n*-BuLi was recrystallized from pentane,[10–12] whereas [^{6}Li,^{13}C]*n*-BuLi was used without further purification. Solutions of *n*-BuLi were titrated using a literature method.[37] Lithium alkoxides **5b**–**7b** were generated in situ by adding the appropriate amounts of stock solutions of amino alcohols **5a**–**7a** to *n*-BuLi solution to obtain the desired ratio of *n*-BuLi/R*OLi.

NMR Spectroscopic Analyses. All NMR tubes were prepared using stock solutions and sealed under vacuum. Standard ^{6}Li, ^{15}N, and ^{13}C NMR spectra were recorded on a Varian XL-400 spectrometer operating at 58.84, 40.52, and 100.58 MHz (respectively) or on a Varian Unity

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[35] *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, Y., Eds; Springer-Verlag: Heidelberg, 1999.

[36] Westaway, K. C.; Lai, Z.-g. *Can. J. Chem.* **1988**, *66*, 1263.

[37] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

500 spectrometer operating at 73.57, 58.84, and 125.76 MHz (respectively).[38] The ^{6}Li, ^{15}N, and ^{13}C resonances are referenced to 0.3 M [^{6}Li]LiCl/MeOH at −100 °C (0.0 ppm), neat Me_2NEt at −100 °C (25.7 ppm), and the toluene methyl resonance at −100 °C (20.4 ppm), respectively. The ^{6}Li−^{15}N HMQC spectra were recorded on the Varian Unity 500 spectrometer equipped with a 3-channel probe designed to accommodate lithium and nitrogen pulses custom-built by Nalorac (www.nalorac.com). ^{6}Li−^{6}Li exchange spectroscopy (EXSY),[27] ^{6}Li,^{13}C-HMQC spectroscopy,[26] and ^{6}Li,^{15}N-HMQC spectroscopy[24] are well-established methods. The $^1J(^6\text{Li},^{13}\text{C})$-resolved spectroscopy has also been reported, but is relatively untested. The $^1J(^6\text{Li},^{13}\text{C})$-resolved spectra were recorded using existing protocols with some modification.[25] The ^{6}Li is observed and the ^{13}C pulses employed a separate Rf-channel. The first decoupling[25b] was replaced by a 180° pulse on ^{6}Li. The phases of the two 180° pulses are the same. Due to this specific implementation, the splittings in the $^1J(^6\text{Li},^{13}\text{C})$-resolved spectra are identical to those in the standard ^{6}Li spectra instead of $1/2J$ as described.[25b]

The Addition of *n*-BuLi to Benzaldehyde. A representative run is as follows: To a solution of 1.6 M *n*-BuLi in hexane (125 μL, 0.20 mmol) was added THF (140 μL), pentane (375 μL), and a 0.4 M solution of amino alcohol in THF solution (333 μL, 0.13 mmol), all at −78 °C. The mixture was warmed to 0 °C for 5 min in an ice bath and then cooled to −78 °C. A 2.4 M solution of PhCHO (25 μL, 0.060 mmol) in THF was added slowly to the reaction mixture. The reaction was stirred at −78 °C for 5 min, quenched with 1.0 N HCl, and extracted with ether. The two enantiomers of the product are baseline-resolved by a GC fitted with a commercial chiral Cyclodex-B column. The configurations of the two adducts were assigned by analogy with Jackman's results.[3]

Acknowledgment. We thank the National Institutes of Health for direct support of this work as well as Dupont Pharmaceuticals, Merck, Pfizer, and Boehringer-Ingelheim for indirect support. We also acknowledge the National Science Foundation Instrumentation Program (CHE 7904825 and PCM 8018643), the National Institutes of Health (RR02002), and IBM for support of the Cornell Nuclear Magnetic Resonance Facility.

Supporting Information Available: ^{6}Li, ^{13}C, and ^{15}N NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010136C

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[38] Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575.