Lithium Ephedrate-Mediated Addition of a Lithium Acetylide to a Ketone: Solution Structures and Relative Reactivities of Mixed Aggregates Underlying the High Enantioselectivities

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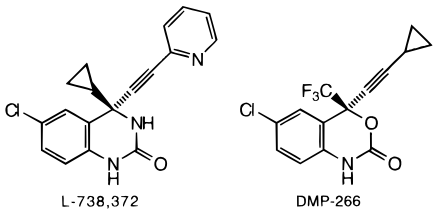
Abstract: Addition of lithium cyclopropylacetylide (RLi) to $ArCOCF_3$ mediated by 1(*R*),2(*S*)-$R_2NCH(CH_3)$-CH(Ph)OLi (ROLi; R_2N = pyrrolidino) occurs with 50:1 enantioselectivity (Thompson, A. S. *et al. Tetrahedron. Lett.* **1995**, *36*, 8937). Low-temperature ^6Li and ^{13}C NMR spectroscopies reveal lithium cyclopropylacetylide in THF to be a dimer−tetramer mixture and the lithium alkoxide to be a complex mixture of oligomers. Mixtures of RLi and ROLi in THF afford stoichiometry-dependent mixtures of 3:1, 2:2, and 1:3 mixed tetramers. The dramatic improvements in the stereochemistry of 1,2-additions caused by aging the reaction at ambient temperatures are shown to coincide with unusually slow aggregate equilibrations. ReactIR studies showed that the previously detected requirement for 2 equiv of lithium acetylide per ketone stems from autoinhibition rather than from a proton abstraction of an NH moiety in the substrate. Semiempirical (MNDO) computational studies support a stereochemical model based upon 1,2-addition via a C_2 symmetric 2:2 mixed tetramer.

Introduction

Two new classes of potent nonnucleoside reverse transcriptase inhibitors were recently reported by the Merck Research Laboratories: the 3,4-dihydroquinazolin-2(1*H*)-ones[1] and the 1,4-dihydro-2*H*-3,1-benzoxazin-2-ones.[2] Efforts to enhance the clinical utility of these inhibitor classes by deriving compounds that express both high levels of antiviral activity and augmented pharmacokinetic profiles led to one promising compound from each class—L-738,372 and DMP-266. DMP-266 was ultimately



chosen for clinical evaluation[2] and has shown excellent preliminary results for the treatment of HIV when used in combination with indinavir.[3,4] The potential importance of DMP-266 and L-738,372 prompted investigations of practical syntheses of both compounds to provide the quaternary carbons with absolute stereocontrol.[5,6]

Previous investigators demonstrated the feasibility of enantioselective 1,2-additions mediated by covalent chiral auxiliaries, chiral solvents, or chiral alkoxides and related chiral lithium salts.[7−11] The synthesis of L-738,372 was achieved using a highly enantioselective lithium acetylide addition to a cyclic imine in the presence of lithiated quinine.[10] However, quinine proved to be unsatisfactory for a conceptually similar asym-

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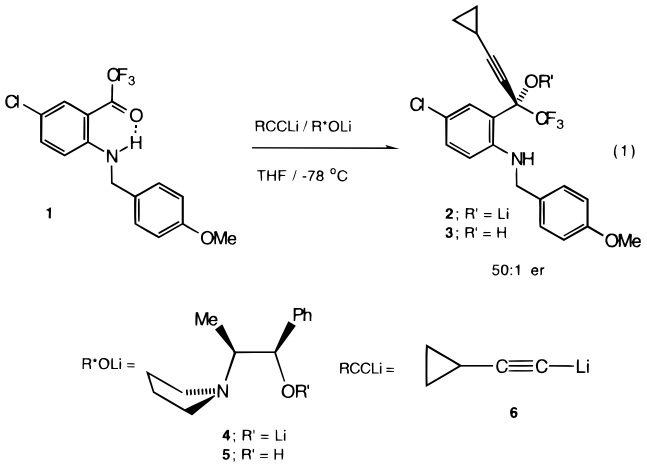
metric ketone addition required to prepare DMP-266. Screening amino alcohols derived from natural sources provided encouraging results from *N*-methylephedrine, consistent with reports by Soai,[10] Mukaiyama,[10] and Jackman.[8] Further investigation of unnatural ephedrine derivatives afforded exceptional enantioselectivities with the pyrrolidino derivative **5** (eq 1). The 50:1 enantioselectivity in eq 1 is remarkably high for the 1,2-addition of such a sterically unhindered nucleophile.



During the development of the ephedrine-based 1,2-addition, several interesting experimental observations shed light on the mixed aggregation effects underlying the high enantioselectivities: (1) Mixtures of **4** and **6** generated and maintained at low temperature afford poor enantioselectivities. In contrast, samples generated at low temperature (<-70 °C), warmed to room temperature, and subsequently cooled and reacted at low temperature provided high enantioselectivities. This "aging" effect implicates an unusually slow aggregate exchange.[12,13] (2) The enantioselectivities erode at **4**/**6** ratios of $<1:1$, indicating that the product determining transition structure may contain the lithium ephedrate and the lithium acetylide in equal proportions.[14] (3) Two equivalents of lithium acetylide **6** and 2 equiv of lithium alkoxide **4** are required to attain full conversion; 1 equiv of each affords 50% conversion at −78 °C. Moreover, ketones such as $PhCOCF_3$ void of the *o*-NHR moiety afford mediocre selectivities. These two observations led us to infer (incorrectly as shall be shown) that the N−H moiety is deprotonated by the lithium acetylide. (4) Mixed aggregates containing the organolithium starting materials and lithium-containing products can cause marked dependencies of reactivities and selectivities on the organolithium:substrate ratios.[15,16] In this instance, however, the selectivity does not change by employing a large excess of the equimolar RLi/ROLi mixture. We concluded (incorrectly again) that mixed aggregates containing adduct **2** are of little mechanistic consequence. (5) The enantioselectivities can exceed the enantiomeric purity of the lithium ephedrate. For example, an equimolar mixture of acetylide **6** and 50% optically pure **4** (3:1 er) affords product **3** with a 7:1 er (enantiomeric ratio). The modest asymmetric amplification[11,17] could stem from a favorable self-aggregation of the alkoxide racemate. (6) The insensitivity of the enantioselectivity to the THF concentration (using hydrocarbon cosolvents) showed that disruption of a pyrrolidine-based chelate by THF does not readily occur or is inconsequential. (7) High enantioselectivities are observed with lithium acetylides, but not with simple alkyllithiums, and are surprisingly sensitive to changes in the substituent on the seemingly remote acetylide β carbon.[10]

Many asymmetric reactions of organolithium derivatives appear to benefit from chelating appendages within the chiral auxiliary or additive.[15] While chelation may accentuate the asymmetric environment of the transition structure, few investigations have probed the importance of the general chelate effect,[18,19] and even fewer have shed light on its importance to stereoselective organolithium reactions.[20] Motivated by the importance of ephedrine-derived chiral auxiliaries[8,9,21,22] and the excellent promise of DMP-266 in the treatment of AIDS,[4] we initiated ^{6}Li, ^{13}C, and ^{15}N NMR spectroscopic studies to establish the existence and structures of putative **4**/**6** mixed aggregates.[23−30] We describe the solution structures and stereochemistries of 3:1, 2:2, and 1:3 mixed aggregates of **4** and **6**. These structural studies show parallels with mixed aggregation studies of Thomas,[25] Klumpp,[27] van Koten,[29] Chabanel,[30a] Duhamel,[30b] and Davidsson.[30c] The slow aggregate exchange

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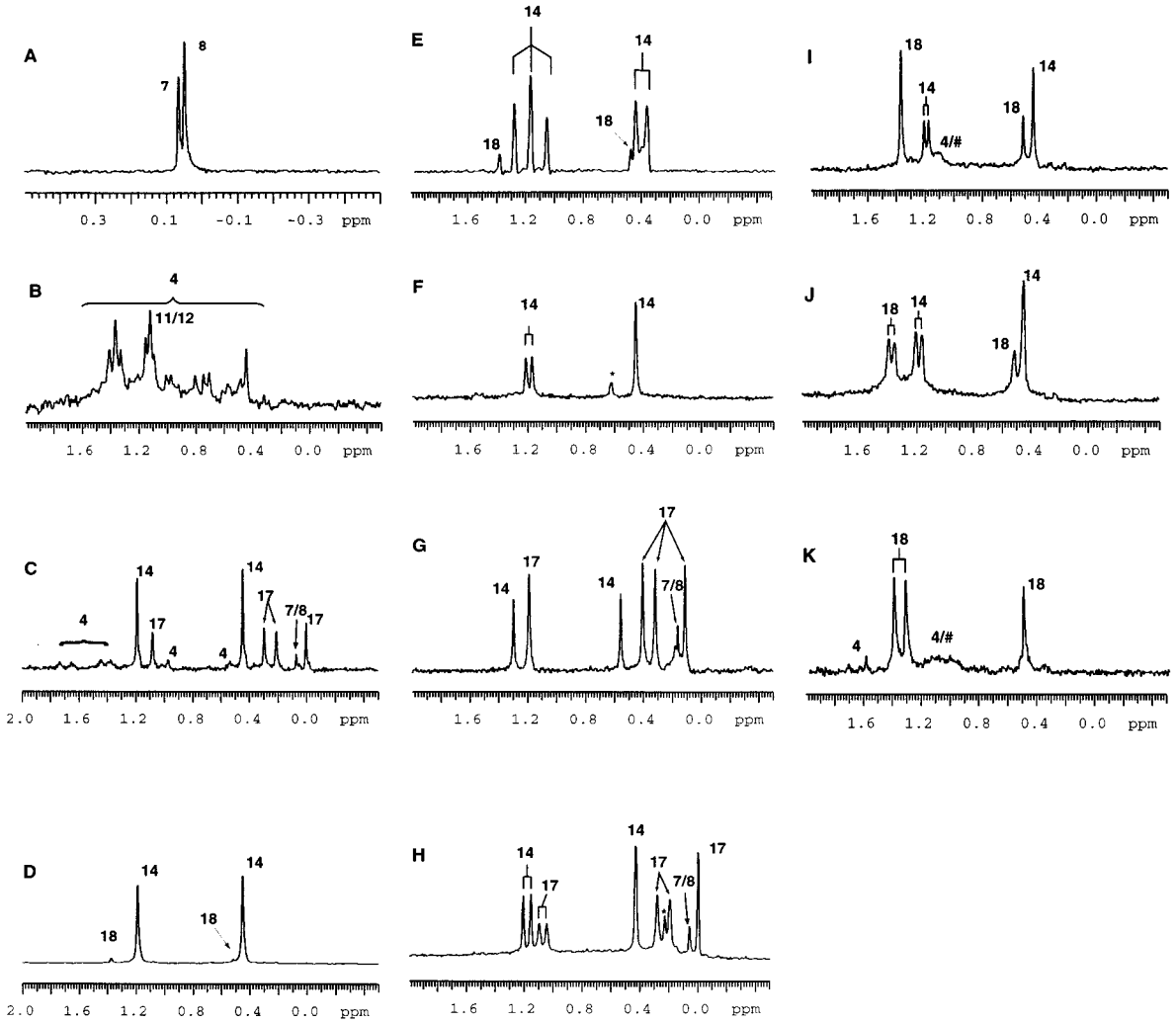

Figure 1. ^{6}Li NMR spectra of samples containing **4** and **6** (0.10 M total lithium titer) in 1:1 THF/pentane at −125 °C. The asterisk (*) denotes an unknown impurity present only in the ^{15}N-labeled **4**, and the pound sign (#) represents an unknown compound observed in the presence of high ratios (>2:1) of **4**/**6**: (A) [^{6}Li]**6**; (B) [^{6}Li,^{15}N]**4**; (C) pre-aged 1:1 mixture of [^{6}Li]**6**:[^{6}Li]**4**; (D) 1:1 mixture of [^{6}Li]**6**/[^{6}Li]**4** after aging for 30 min at RT; (E) 1:1 mixture of [^{6}Li,^{13}C]**6**/[^{6}Li]**4**; (F) 1:1 mixture of [^{6}Li]**6**/[^{6}Li,^{15}N]**4**; (G) 3:1 mixture of [^{6}Li,^{13}C]**6**/[^{6}Li]**4**; (H) 3:1 mixture of [^{6}Li]**6**/[^{6}Li,^{15}N]**4**; (I) ^{6}Li spectrum of a 1:3 mixture of [^{6}Li]**6**/[^{6}Li,^{15}N]**4** with single-frequency ^{15}N decoupling at 60.1 ppm; (J) 1:3 mixture of [^{6}Li]**6**/[^{6}Li,^{15}N]**4**; (K) 1:3 mixture of [^{6}Li,^{13}C]**6**/[^{6}Li]**4**.

on laboratory time scales suggests that the observable aggregates may react with little structural reorganization. FT-IR spectroscopic studies reveal very different reactivities for the different mixed aggregates. Supported by semiempirical (MNDO) computations, a mechanistic rationale for the enantioselectivities in eq 1 is presented.

Results

Lithium ephedrate **4** and lithium acetylide **6** were prepared >98% ^{6}Li enriched and isolated as white solids. The ^{15}N- and ^{13}C-labeled substrates required to prepare [^{6}Li,^{15}N]**4** and [^{6}Li,^{13}C]**6** (^{13}C labeled at the acetylide α-carbon) were synthesized in >98% isotopic purity by literature procedures.[31,32] Unusually slow aggregate subunit exchanges attributable to the lithium ephedrate derivatives (vide infra) mandated aging of all samples for 10 min at 25 °C prior to low-temperature spectroscopic analyses. ^{6}Li, ^{13}C, and ^{15}N NMR spectroscopic

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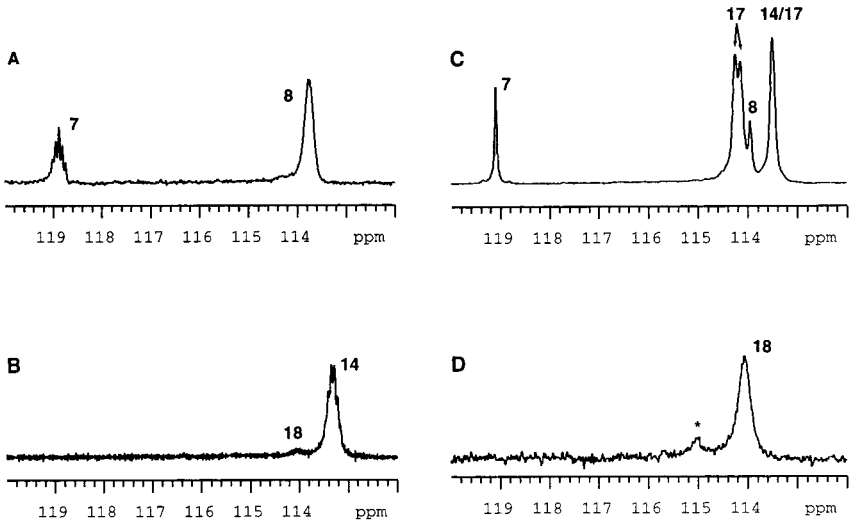


Figure 2. ^{13}C NMR spectra of samples containing 0.10 M Li titer in 1:1 THF/pentane. All spectra were recorded at −125 °C: (A) [^{6}Li,^{13}C]**6**; (B) 1:1 mixture of [^{6}Li,^{13}C]**6**/[^{6}Li]**4**; (C) 3:1 mixture of [^{6}Li,^{13}C]**6**/[^{6}Li]**4**; (D) 1:3 mixture of [^{6}Li,^{13}C]**6**/[^{6}Li]**4**. The asterisk (*) denotes an unassigned resonance that appears in limited intensity at low (1:>2) **6**/**4** ratios.

Table 1. NMR Spectroscopic Data[a]

species	δ ^{6}Li (m, J_{C-Li})[b] (m, J_{N-Li})[b]	δ ^{13}C (m, J_{C-Li})[b]	δ ^{15}N (m)[b]
7	0.07 (t, 8.4) (—)	118.9 (q, 8.6)	
8	0.05 (qt, 6.0) (—)	113.7 (br m)	
11 (or **12**)	1.10 (s) (t, 2.4)		61.6 (t, 2.4)
14	1.19 (t, 6.6) (d, 3.1)	113.4 (br m)	60.8 (t, 3.1)
	0.45 (d, 4.7) (s)		
17	1.08 (dd) (d, 3.0)	114.0 (br m)	60.7 (t, 3.0)
	0.30 (m) (s)	113.9 (br m)	
	0.21 (m) (s)	113.3 (br m)	
	0.00 (m) (s)		
18 (or **19**)	1.36 (d, 5.9) (d, 3.0)	114.0 (br m)	60.1 (t, 3.0)
	0.51 (s) (s)		

[a] The chemical shifts derive from spectra recorded on 0.1 M solutions in 1:1 pentane/THF at −125 °C. [b] The C−Li couplings derive from samples enriched in ^{6}Li and ^{13}C, and the N−Li couplings derive from samples enriched in ^{6}Li and ^{15}N. The multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, qt = quartet, q = 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}Li/MeOH at −75 °C (δ ^{6}Li = 0.0 ppm), neat dimethylethylamine (δ ^{15}N = 25.7 ppm), and THF in 1:1 THF/pentane (δ $^{13}C_{\alpha}$ = 67.4 ppm), respectively. All *J* values are reported in hertz.

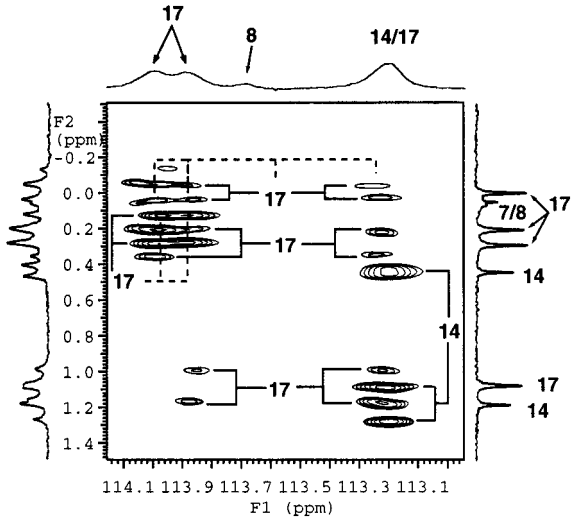


Figure 3. ^{6}Li,^{13}C-HMQC spectrum of a sample containing 3:1 [^{6}Li,^{13}C]-**6**/[^{6}Li]**4** (0.10 M total Li titer) in 1:1 THF/pentane at −125 °C. The ^{6}Li NMR spectrum is on the left axis, the $^{6}Li\{^{13}C\}$ NMR spectrum appears on the right axis, and the $^{13}C\{^{6}Li\}$ NMR spectrum is displayed on top.

data are summarized in Table 1. Selected NMR spectra are included in Figures 1−3. Additional spectra and results from MNDO calculations are included as Supporting Information.

Structures of Lithium Acetylide and Lithium Alkoxide Homonuclear Aggregates. The spectroscopic data of lithium acetylide **6** in THF solution are fully consistent with the coexistence of dimer **7** and tetramer **8** as previously observed for related lithium acetylides.[33−36] The ^{6}Li NMR spectra

(28) (a) For an example of a LiBr/chelating alkoxide mixed aggregate, see: van der Schaaf, P. A.; Hogerheide, M. P.; Grove, D. M.; Spek, A. L.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1703. (b) For an example of a lithium acetylide/LiBr mixed aggregate, see: Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7791.

(29) 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.

(30) (a) Goralski, P.; Legoff, D.; Chabanel, M. *J. Organomet. Chem.* **1993**, *456*, 1. (b) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Prigent, Y.; Davoust, D.; Duhamel, D. *J. Am. Chem. Soc.* **1997**, *119*, 10042. (c) Hilmersson, G.; Ahlberg, P.; Davidsson, O. *J. Am. Chem. Soc.* **1996**, *118*, 3539.

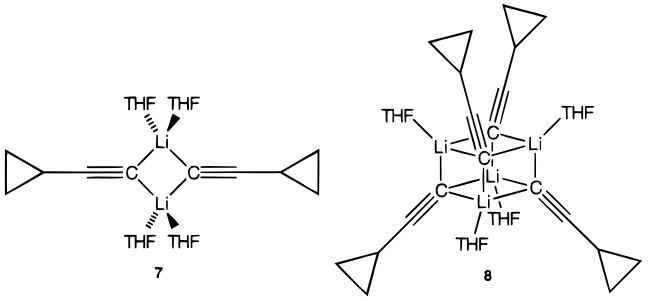
(31) [1-^{13}C]cyclopropylacetylene was prepared as described in the Supporting Information.

(32) Labeled norephedrine ([^{15}N]**3b**) was prepared as described in the Supporting Information.

(33) For solution structural studies of lithium acetylide, see: (a) Fraenkel, G.; Stier, M. *Prepr. Am. Chem. Soc., Div. Pet. Chem.* **1985**, *30*, 586. (b) Fraenkel, G.; Pramanik, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1527. (c) Hässig, v. R.; Seebach, D. *Helv. Chim. Acta* **1983**, *66*, 2269. (d) Bauer, W.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1972. (e) Jackman, L. M.; Scarmoutzos, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1987**, *109*, 5355. (f) Gareyev, R.; Streitwieser, A. *J. Org. Chem.* **1996**, *61*, 1742. (g) See also ref 30.

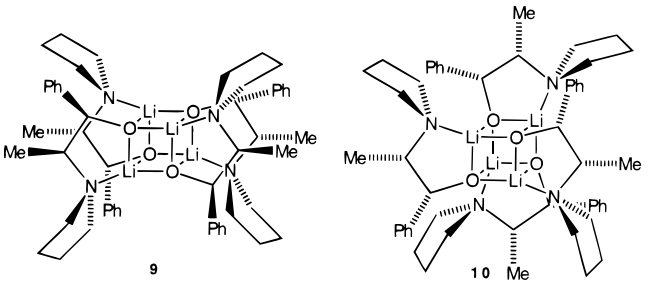
(34) For lithium acetylide X-ray crystal structures, see: Schubert, B.; Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 496. Schubert, B.; Weiss, E. *Chem. Ber.* **1983**, *116*, 3212. Seebach, D.; Hässig, v. R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308. Geissler, M.; Kopf, J.; Schubert, B.; Weiss, E.; Neugebauer, W.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 587.

(35) For theoretical studies of lithium acetylides, see: Bachrach, S. M.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 2283. Bühl, M.; van Eikema Hommes, N. J. R.; Schleyer, P. v. R.; Fleischer, U.; Kutzelnigg, W. *J. Am. Chem. Soc.* **1991**, *113*, 2459. Ritchie, J. P. *Tetrahedron Lett.* **1982**, *23*, 4999. Jemmis, E. D.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1979**, *101*, 2848. Dorigo, A. E.; van Eikema Hommes, N. J. R.; Krogh-Jespersen, K.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1602. Also, see refs 33f and 52.

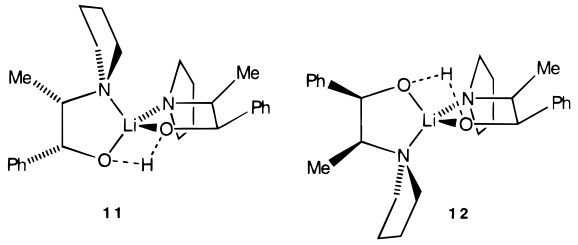


recorded on 0.10 M [^{6}Li]**6** in 1:1 THF/pentane at −125 °C display resonances at 0.05 and 0.07 ppm (Figure 1A). The relative intensity of the downfield resonance increases at low lithium acetylide concentrations and high THF concentrations, implicating a relatively low aggregation number and high per-lithium solvation number expected for dimer **7**.[37] Using [^{6}Li,^{13}C]**6**, the resonances at 0.05 and 0.07 ppm appear as a quartet (J_{C-Li} = 6.0 Hz) and a triplet (J_{C-Li} = 8.4 Hz), respectively. The corresponding ^{13}C NMR spectrum recorded at −110 °C on [^{6}Li,^{13}C]**6** displays a quintet (118.9 ppm, J = 8.6 Hz) as well as an unresolved multiplet (113.7 ppm) resulting from coupling to two and three (or even four[38]) spin 1 ^{6}Li nuclei, respectively (Figure 2A). Single-frequency ^{13}C decoupling[39] and ^{6}Li−^{13}C heteronuclear multiple quantum correlation (HMQC) spectroscopy[39,40] confirm the Li−C connectivities inferred from the concentration dependencies and coupling patterns.

The ^{6}Li NMR spectra recorded on 0.1 M solutions of [^{6}Li]**4** in 1:1 THF/pentane reveal a complex envelope of resonances (Figure 1B) that did not simplify upon aging the sample at 25 °C (see below). A similar spectral complexity was noted by Arnett and co-workers for the Me_2N analogue of **4**.[19] The complexity of the ^{6}Li spectra precludes detailed structural assignments. Literature analogies[18b,19] and the results described below implicate stereoisomeric tetramers (such as **9** and **10**, for example).[41,42] We did, however, note a marked (and greatly

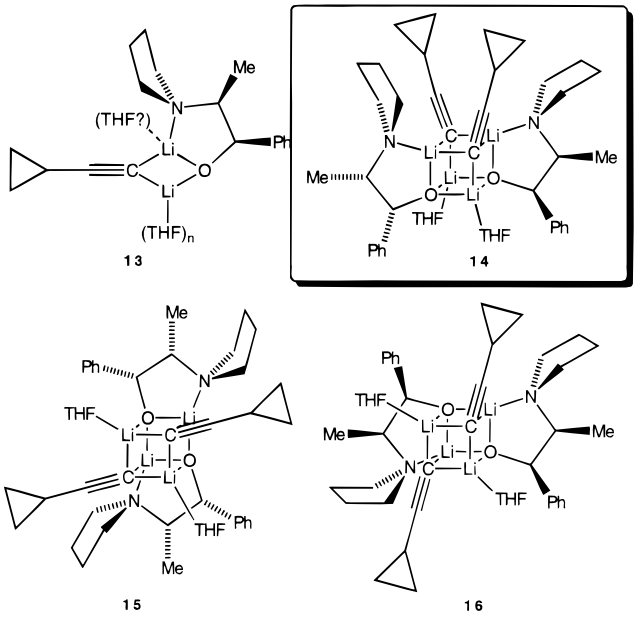


simplifying) dependence of the spectra on the presence of unlithiated amino alcohol due to formation of **11** or **12**. Incremental addition of the ephedrine alcohol causes the appearance of a new ^{6}Li resonance at 1.10 ppm that becomes the dominant resonance (>90%) at 1.0 equiv. At >1.0 equiv of added alcohol, the ^{13}C NMR spectrum shows free and coordinated alcohol in the slow exchange limit, confirming the 1:1 alkoxide/alcohol stoichiometry. Using the ^{15}N-labeled



ephedrine, the ^{6}Li resonance exhibits coupling from two magnetically equivalent ^{15}N nuclei and a singular ^{15}N resonance exhibits coupling from one ^{6}Li nucleus, consistent with monomers **11** or **12**. MNDO calculations suggest that **11** and **12** are of equal energy (±0.2 kcal/mol), yet show no evidence of hydrogen bridging.[43]

Chart 1. Possible $(ROLi)_n(RLi)_n$ (n = 1 or 2) Mixed Aggregates of Lithium Ephedrate **4** and Lithium Acetylide **6**



Structures of Lithium Acetylide−Lithium Alkoxide Mixed Aggregates. Mixing stock solutions of [^{6}Li]**4** and [^{6}Li]**6** in 1:1 THF/pentane at −78 °C affords ^{6}Li resonances ascribable to mixed aggregates along with resonances of the homonuclear aggregates of **4** and **6** (Figure 1C). When the sample is warmed to 25 °C for 30 min and then cooled back to −110 °C, the ^{6}Li resonances of the homonuclear aggregates are no longer observable (Figure 1D). Instead, the ^{6}Li NMR spectrum displays a pair of resonances in a 1:1 ratio consistent with a mixed dimer (**13**) or any of three possible 2:2 mixed tetramers (**14**−**16**; Chart 1). Dimer **13** is readily excluded by spectroscopic analysis of equimolar mixtures of [^{6}Li]**4** and [^{6}Li,^{13}C]**6**. Whereas the ^{6}Li resonance at 0.45 ppm shows coupling to one acetylide carbon, the ^{6}Li resonance at 1.19 ppm appears as a triplet indicating coupling to two acetylide carbons (Figure 1E).

(36) For a general discussion of metal acetylides, see: Manna, J.; John, K. D.; Hopkins, M. D. *Adv. Organomet. Chem.* **1995**, *38*, 79.

(37) Trisolvated dimers have been observed, but seem unlikely. For leading references, see: Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5518. Legzdins, P.; Sayers, S. F. *Organometallics* **1996**, *15*, 3907.

(38) Rapid intra-aggregate exchange can cause coupling to all nuclei within the aggregate. For leading references, see: Bauer, W. *J. Am. Chem. Soc.* **1996**, *118*, 5450. See also ref 25.

(39) Günther, H.; Moskau, D.; Bast, P.; Schmalz, D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1212.

(40) Mons, H.-E.; Günther, H.; Maercker, A. *Chem. Ber.* **1993**, *126*, 2747.

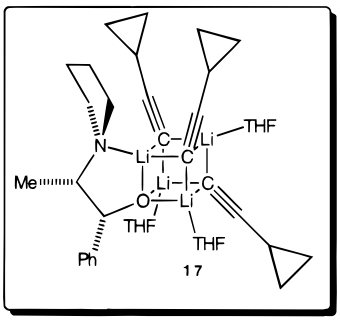
(41) Williard, P. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 1, p 1. Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353. Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1501.

(42) (a) Arnett and co-workers observed complex ^{6}Li NMR spectra for lithium *N*-methylephedrate.[15] (b) Prismatic hexamers are also possible.[25,41]

(43) Amino alcohol/amino alkoxide complexes analogous to **11** and **12** may be important in asymmetric protonations: Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996** *35*, 2567.

The corresponding ^{13}C spectrum recorded on the 1:1 mixture of [^{6}Li]**4** and [^{6}Li,^{13}C]**6** at −110 °C (Figure 2B) reveals a broadened six-line multiplet shown through single-frequency ^{6}Li irradiations to be a triplet of quintets. Of the three possible 2:2 mixed tetramers, isomer **14** is uniquely defined by two symmetry equivalent ^{6}Li nuclei flanked by two acetylene carbons *and* coordinated by pyrrolidines. Indeed, ^{6}Li NMR spectra recorded on mixtures of [^{6}Li,^{15}N]**4** and [^{6}Li]**6** reveal ^{6}Li−^{15}N coupling only in the resonance at 1.19 ppm (Figure 1F), establishing **14** as the only detectable 2:2 mixed tetramer.

Incremental addition of lithium ephedrate **4** to lithium acetylide **6** affords cubic mixed aggregates of both $(ROLi)(RLi)_3$ and $(ROLi)_3(RLi)$ stoichiometries. For example, addition of 0.33 equiv of **4** to **6** with requisite sample aging at ambient temperature affords four ^{6}Li resonances in approximate 1:1:1:1 intensities (Figure 1G), consistent with the formation of mixed tetramer **17**. The ^{6}Li and ^{13}C NMR spectra recorded on



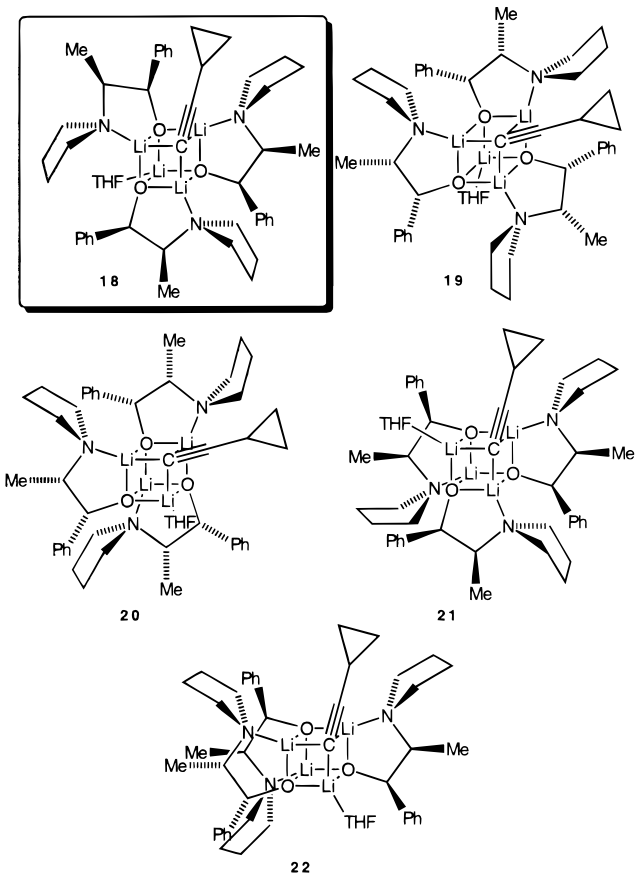
analogous solutions of [^{6}Li]**4** and [^{6}Li,^{13}C]**6** (Figures 1H and 2C) display the complex multiplets of **17** obscured by resonances of **7**, **8**, and **14**.[44] The resonance correlations in the ^{6}Li−^{13}C HMQC spectrum[39] (Figure 3) are consistent with our assignments. ^{6}Li NMR spectra recorded on 1:3 mixtures of [^{6}Li,^{15}N]-**4** and [^{6}Li]**6** below −100 °C reveal ^{15}N coupling ($^{1}J_{Li-N} = 3.0$ Hz) to one ^{6}Li resonance, confirming the nonfluctional chelation within **17**. Spectra recorded above −100 °C show time averaging of three of the four ^{6}Li resonances. In principle, the resulting time-averaged resonance should exhibit ^{6}Li−^{15}N coupling at one-third of the magnitude, but peak broadening obscures the coupling.[45]

Addition of >1.0 equiv of alkoxide **4** to lithium acetylide **6** provides a mixed aggregate, which gives rise to two ^{6}Li resonances in a 3:1 ratio (Figure 1I) consistent with the C_3 symmetric isomers **18** or **19**. ^{6}Li NMR spectra recorded on analogous mixtures containing [^{6}Li,^{13}C]**6** display the major ^{6}Li resonance as a doublet ($J_{C-Li} = 5.9$ Hz). ^{6}Li NMR spectra recorded on mixtures of [^{6}Li,^{15}N]**4** and [^{6}Li]**6** reveal the major and minor ^{6}Li resonances to be a doublet ($J_{N-Li} = 3.0$ Hz) and a singlet, respectively (Figure 1J). Of the five possible stereoisomers (**18**−**22**, Chart 2), isomers **20**−**22** can be excluded since each would afford four ^{6}Li resonances of equal intensities. Although rapid chelate exchange in conjunction with slow Li−Li exchange could cause **20**−**22** to display higher symmetry on NMR time scales, the ^{6}Li−^{15}N coupling patterns would be very complex. Assignment of the mixed aggregate as **18** rather than **19** is based on MNDO calculations revealing a substantially greater stability of **18** vs **19** (vide infra).

(44) For example, each of the three ^{13}C nuclei in **17** are flanked by three chemically and magnetically inequivalent spin 1 lithium nuclei, causing them to display up to 27 lines each. Similarly, the four ^{6}Li resonances will appear as multiplets, manifesting from two to eight lines.

(45) For example, see: Reich, H. J.; Gudmundsson, B. Ö. *J. Am. Chem. Soc.* **1996**, *118*, 6074.

Chart 2. Possible $(ROLi)_3(RLi)$ Mixed Aggregates of Lithium Ephedrate **4** and Lithium Acetylide **6**



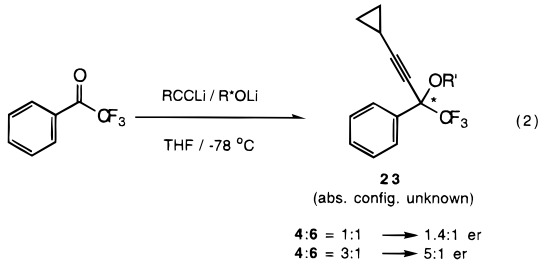
1,2-Additions: NMR Spectroscopic Studies. ^{6}Li NMR spectra recorded on mixtures of the 2:2 mixed aggregate **14** and ketone **1** are too complex for detailed interpretation at this time. However, one observation is pertinent: The ^{6}Li NMR spectra recorded on solutions of [^{6}Li,^{13}C]**14** containing ≥1.0 equiv of ketone **1** (per lithium acetylide unit) contain residual resonances displaying ^{13}C−^{6}Li coupling as confirmed by broadband ^{13}C decoupling. This provided preliminary evidence that the 50% conversion observed for mixtures containing 1:1:1 proportions of **1**:**4**:**6** is *not* due to deprotonation of the N−H moiety on either **1** or **2** by the lithium acetylide. Further corroboration by low-temperature IR studies is described below.

1,2-Additions: Infrared Spectroscopic Studies. Since the 1,2-additions proved difficult to follow by NMR spectroscopy, we turned to FT-IR spectroscopy. The reaction described by eq 1 proved to be too fast to monitor on laboratory time scales ($t_{1/2} < 25$ s). Nonetheless, IR spectroscopic studies at −90 °C employing a ReactIR fitted with an ATR immersible DiComp probe provided important information. Upon slow addition of ketone **1** to an equimolar solution of **4** and **6** (0.38 M each) in THF, the characteristic carbonyl absorbance of **1** at 1660 cm^{-1} becomes visible after 0.5 equiv of ketone **1** per lithium acetylide has been added. This is consistent with previous studies showing that the reaction proceeds to only 50% conversion (based on active lithium acetylide). The absence of a measurable frequency change in the carbonyl absorbance suggests that the remaining ketone does not complex to a lithium cation.[46]

(46) For leading references to detectable organolithium−substrate precomplexation, see: ref 18d. For a general discussion of ketone−lithium complexation and related ketone−Lewis acid complexation, see: Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 1, p 283.

More importantly, two spectral features show that the excess lithium acetylide **6** does *not* deprotonate the NHR moiety of **1**. First, the spectra recorded after addition of >0.5 equiv of **1** display weak but discernible N−H stretching bands at 3432 and 3339 cm^{-1}. The absorbance at 3432 cm^{-1} is readily ascribed to the starting ketone **1** while the stretch at 3339 cm^{-1} is tentatively attributed to the N−H of the alkoxide product **2**. Second, the C−H stretch of cyclopropylacetylene is absent. In a separate experiment, addition of 0.5 equiv of cyclopropylacetylene confirmed that the acetylene C−H stretch at 3261 cm^{-1} is distinguishable from other high-frequency stretches. Thus, although the reaction proceeds to only 50% conversion at −90 °C, this is not caused by N−H deprotonation. When warmed to 0 °C, the reaction proceeds from 50 to 90% after 5.0 h. The resulting 10:1 er overall indicates that the final 40% conversion afforded product in 6:1 er.

We suspected that the 1,2-addition of the first acetylide might produce a mixed tetramer containing lithium acetylide **6**, lithium ephedrate **4**, and adduct **2** in a 1:2:1 ratio. We further surmised that the presence of a third potentially chelating alkoxide (**2**) might be the source of the dramatic reduction in reactivity of the remaining lithium acetylide. Although the NMR spectroscopic studies of the 1,2-addition are not interpretable at present, these suppositions prompted us to explore the rates of 1,2-addition using 3:1 mixtures of lithium ephedrate **4** and lithium acetylide **6**. In particular, the THF-bearing lithium and the acetylide fragments of **18** are not proximate. We wished to determine whether the spectroscopically observable C_3 symmetric mixed tetramer **18** would display reduced reactivity. Indeed, monitoring the addition of ketone **1** to solutions containing 0.6 M **4** and 0.2 M **6** by IR spectroscopy showed no appreciable reaction at −60 °C. Warming the sample to −30 °C caused slow consumption of **1**. A reaction run to 70% conversion affords **3** in >100:1 er (eq 1). Furthermore, addition of $PhCOCF_3$ to a 3:1 mixture of **4** and **6** (eq 2) affords adduct **23** in 5:1 er (unknown absolute configuration).



MNDO Studies of Mixed Aggregates: Reactants. We addressed several experimentally elusive questions using semiempirical (MNDO) computational methods. We began with highly simplified structures and added substituents and solvents systematically. Coordinated THF was modeled by dimethyl ether (Me_2O) and the cyclopropyl substituent on the lithium acetylide by a CH_3. We note at the outset that the tendency of MNDO to overestimate van der Waals interactions[47] and carbon−lithium bond strengths[48] is particularly acute. Since the complex structures are difficult to visualize, the structures, Cartesian coordinates, and heats of formation ($\Delta H_f°$) are included as Supporting Information. Selected results are summarized as follows:

(1) There are two conformational isomers of C_2 symmetric 2:2 mixed aggregates corresponding to **14**: the conformer with the Ph moiety protruding out of the chelate plane and the Me moiety in a pseudoequatorial position is the more stable by 3−4 kcal/mol.

(2) The 2:2 mixed aggregates analogous to **14** are predicted to be moderately more stable than the lowest energy conformers of the alternative diastereomers corresponding to **15** and **16**. The three diastereomers are predicted to be of equal stability when the phenyl and methyl substituents along the chelate backbone are omitted.

(3) Replacement of the pyrrolidine by a dimethylamine has little influence on the relative stabilities noted in (1) and (2); MNDO-calculated reactant structures do not reflect the optimal enantioselective additions observed for the pyrrolidine-based ephedrate **4**.

(4) Substitutions of a pyrrolidino or dimethylamino ligand on tetramers analogous to **14** by Me_2O with concomitant opening of the chelate ring are modestly endothermic. The unfavorable chelate opening is consistent with experimental results of Reich,[49] Koga,[50] Hilmersson,[51] Klumpp,[18b] and Arnett[19] attesting to the stability of internally coordinated structures. The improved enantioselectivities observed with the pyrrolidine substituent do *not* appear to correlate with a chelate stability in the reactants. However, experimental investigations of trialkylamine-, diamine-, and aminoether-solvated lithium amides show the relative binding of the Me_2N and pyrrolidino moieties to be highly environment-dependent.[18a,49,52,53]

(5) The single $(ROLi)_3RLi$ mixed aggregate was shown by NMR spectroscopy to be one of two C_3 symmetric isomers **18** and **19**; MNDO calculations reveal transition structures analogous to **18** to be more stable than the analogues of **19** by 3−4 kcal/mol.

(6) Conversion of tetramer **14** to two molecules of even the most stable analogues of mixed dimer **13** is endothermic by >10 kcal/mol. However, due to the limitations of MNDO noted above, such a nonisodesmic comparison is highly suspect.

(7) Substitution of the ethereal ligand on **14** by $PhCOCH_3$ is suggested to be moderately exothermic. The reaction of **1** with mixed tetramer **14** is too rapid to show whether such a precomplex attains an appreciable concentration. However, the carbonyl absorbance of **1** in the IR spectrum does not measurably shift in the presence of the kinetically less-reactive mixed tetramer **18**, arguing against *spectroscopically observable* precomplexation in *neat* THF.[46]

MNDO Studies of Mixed Aggregates: Transition Structures. The most pressing unresolved issues pertain to the relative stabilities of the transition structures underlying the high enantioselectivity in eq 1. We considered mechanistic models based upon mixed dimers and mixed tetramers.

All mixed dimer-based transition structures show the four-membered ring characteristic of a cyclic dimer (**24**);[54] mixed "open dimer"[55,56] transition structures of general form **25** were not found. Figure 4 summarizes six modes of ketone coordina-

(47) Scano, P.; Thomson, C. *J. Comput. Chem.* **1991**, *12*, 172. Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9187. Stewart, J. J. P. *J. Comput.-Aided Mol. Design* **1990**, *4*, 1.

(48) Glaser, R.; Streitwieser, A., Jr. *THEOCHEM* **1988**, *163*, 19. Schleyer, P. v. R. *Pure Appl. Chem.* **1984**, *56*, 151.

(49) For leading references, see: Reich, H. J.; Kulicke, K. *J. Am. Chem. Soc.* **1996**, *118*, 273.

(50) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761.

(51) Hilmersson, G.; Davidsson, O. *Organometallics* **1995**, *14*, 912.

(52) For a superb discussion and extensive leading references to lithium acetylene π interactions, see: Goldfuss, B.; Schleyer, P. v. R.; Hampel, F. *J. Am. Chem. Soc.* **1997**, *119*, 1072. See also: Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217 and ref 33f.

(53) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5517.

(54) Bachrach, S. M.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 3946. See also: ref 55.

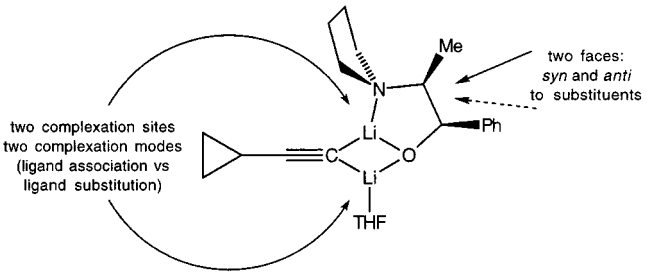
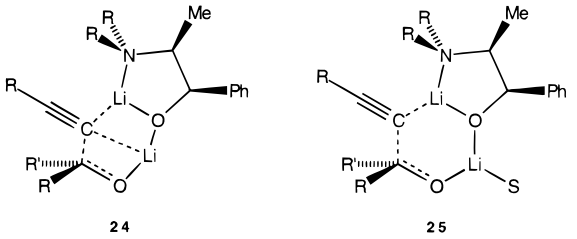
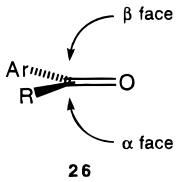


Figure 4.



24 **25**

tion to mixed dimers involving complexation to (i) the ether-solvated vs amine-solvated lithium, (ii) the chelate faces syn or anti to the Ph and Me ephedrine substituents, and (iii) the lithium nuclei with and without ancillary ligand displacement. For each of the six addition modes, we evaluated transition structures involving addition of the acetylide fragment to either the α or β faces of the ketone (**26**).[57]



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Many mixed dimer-based transition structures displayed prominent CF_3-Li[58] or Ph−Li interactions that appeared to offer provisions for highly enantioselective additions to ketone **1**. However, the ephedrine substituents do not provide sufficient steric control over substrate entry. Accordingly, for every β-selective transition structure resulting from substrate approach anti to the ephedrine substituents there is an α-selective transition structure *of equal stability* resulting from approach syn to the ephedrine substituents. Since MNDO tends to overestimate steric effects, a stereochemical model based upon mixed dimers does not account for the experimental observations.

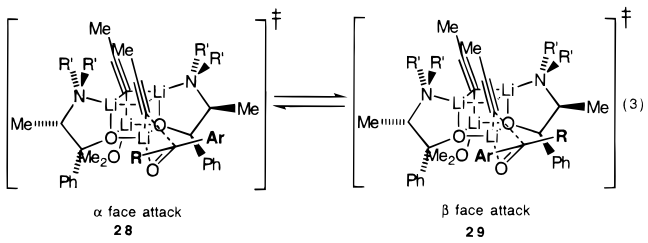
Calculated transition structure energies for 2:2 mixed tetramers produced more satisfying results. Substrate-dependent facial selectivities[57] (**26**) and affiliated theoretical enantioselectivities (eq 3) are summarized in Table 2.

(55) Open dimer-based mechanisms for 1,2-additions of alkyllithiums have been investigated computationally: 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.

(56) For leading references to other investigations and discussions of open dimer-based mechanisms, see: Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9187. 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.

(57) We denote the faces as α and β as depicted in **26** rather than using the more common *si-re* designations since changes from CH_3 to CF_3 cause a confusing reversal in the *si-re* notations.

(58) For a discussion and leading references to F−Li interactions, see: Barbarich, T. J.; Handy, S. T.; Miller, S. M.; Andersen, O. P.; Grieco, P. A.; Strauss, S. H. *Organometallics* **1996**, *15*, 3776.



α face attack **28** β face attack **29**

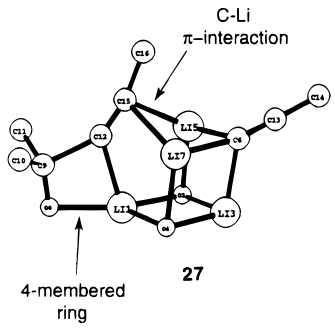
(3)

Table 2. Calculated Relative Activation Enthalpies and Affiliated Enantiomeric Excesses for Addition of Lithium Acetylides to Aryl Ketones According to Eq 2

entry	Ar	R	NR_2	$H_f°_\beta - H_f°_\alpha$ [a]	er[b]
1	Ph	CH_3	$N(CH_2)_4$	−0.52	3.3:1
2	Ph	CH_3	NMe_2	−0.42	2.6:1
3	*o*-(NHMe)Ph	CH_3	$N(CH_2)_4$	−1.25	19:1
4	*o*-(NHMe)Ph	CH_3	NMe_2	−1.24	19:1
5	*p*-(NHMe)Ph	CH_3	$N(CH_2)_4$	−0.67	4.6:1
6	*o*-($NHMe_2$)Ph	CH_3	$N(CH_2)_4$	−0.77	5.7:1
7	*o*-(NHMe)Ph	CF_3	$N(CH_2)_4$	−1.98	100:1
8	*o*-(NHMe)Ph	CF_3	NMe_2	−1.65	40:1

[a] The α and β faces of ArCOR are defined in **26**. [b] Enantiomeric ratio (er) was calculated for addition at −50 °C. The product of addition to the ketone β face (via **29**) is preferred.

Transition structure **27** (in which the ephedrate chelate has been omitted for clarity) displays two prominent and potentially important features that are *common to all calculated mixed tetramer-based transition structures*: (i) a LiC_2O ring common to previous depictions of such 1,2-additions[54] and (ii) an interaction of the acetylenic β carbon with two lithium nuclei of the aggregate cube. Although this π interaction could be an



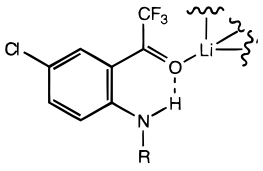
27

artifact of overestimated C−Li bond strengths by MNDO,[48] it is both plausible and potentially very important. Substantial negative charge on the β carbon of acetylide anion has been noted previously,[35,59] and lithium acetylene π interactions are well documented.[52] The π interactions in the mixed tetramer-based transition structures allow for maximum coordinative saturation to be maintained at the lithiums as the acetylenic α carbon forfeits the two C−Li bonds. The acetylene cants back over the face of the cube, placing the acetylene substituent proximate to the two chelating R_2N moieties. Although we have not explored the full consequences of the acetylene-dialkylamine interaction, it is interesting given the dependence of the enantioselectivities on the acetylene and amine substituents.[5] The lithium acetylene π interactions also appear to orient the LiC_2O ring in the transition structure rigidly and symmetrically along what was the edge of the cube in the reactant. This places the two ketone substituents proximate to the two chelate rings with little latitude for relaxation to avoid significant steric interactions.

(59) Bickelhaupt, F. M.; Hoffmann, R. Unpublished results.

Transition structures **28** and **29** (see Table 2) bearing the full complement of substituents along the ephedrine chelate and acetophenone afford a relatively simple stereochemical analysis. Transition structure **29** corresponds to a β facial approach consistent with the experimental findings. The phenyl moiety resides in a sterically uncongested pocket with the substituents along the ephedrate backbone oriented away from the ketone phenyl moiety while the ketone methyl group is situated above the ephedrate chelate with syn-oriented substituents. The α-face-selective transition structure **28** with the alternative ketone alignment is 0.52 kcal/mol less stable (Table 2, entry 1). The predicted moderate β facial selectivity is in reasonable agreement with the experimentally observed 1.4:1 er for the addition to acetophenone.

Substrate changes reveal trends that further correlate strongly with experiment (Table 2). Electron-donating amino groups in the ortho and para positions on the substrate enhance the predicted β facial selectivity. The *o*-NHMe moiety (Table 2, entry 7) affords the largest bias. This may be due to a structurally important N−H···O hydrogen bond implicated by the 2.36 Å NH···O═C bond distance.[60] Although we initially surmised that the hydrogen bond would preclude complexation of lithium to one of the two lone pairs as illustrated by **30**, the MNDO calculations show that the lithium is positioned normal to the plane defined by the carbonyl for all substrates. Thus, it



30

seems that the hydrogen bond, if important, enhances the poorly understood electronic effects, or it orients the aromatic fragment to maximize the steric interactions with the ephedrate substituents. Replacement of the CH_3 on the acetophenones with CF_3 groups also enhances the β facial selectivity. *o*-(NHMe)-$PhCOCF_3$ is predicted to afford an optimal (2.0 kcal/mol) preference.

Thus, the mechanistic model based upon mixed tetramers nicely accounts for the experimentally observed enantioselectivities. The calculations also suggest that the CF_3 and *o*-(NHR)-Ph substituents on substrate **1** and the π system of acetylide **6** are important for attaining the high enantioselectivity.[10]

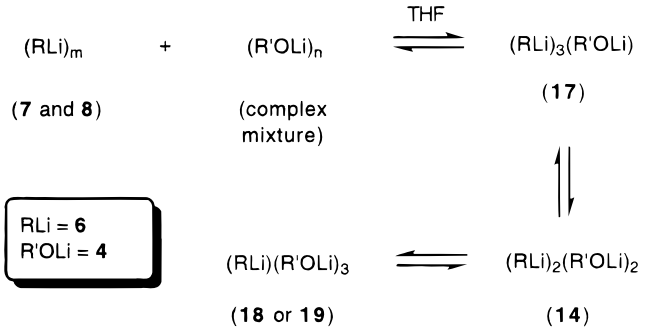
Discussion

We described studies to determine the structural and mechanistic basis for the highly enantioselective addition of lithium acetylides to ketone **1** (eq 1). NMR spectroscopy, IR spectroscopy, and semiempirical computations have afforded detailed solution structure assignments summarized in Scheme 1 and a self-consistent stereochemical model detailed in Scheme 2. The model accounts for the condition-dependent stereoselectivities outlined in the Introduction. Throughout the Discussion, we will refer to the substrate faces as α and β as designated in **26**.[57]

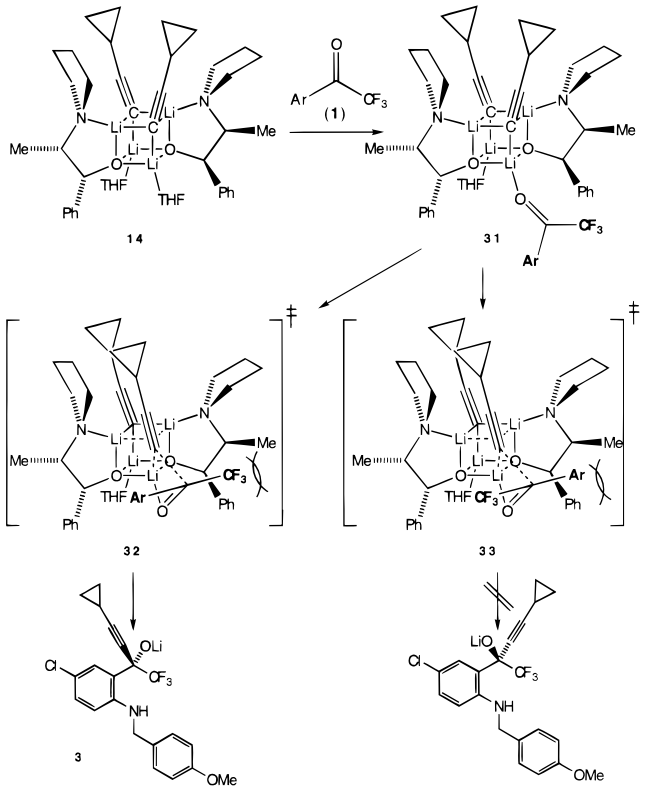
RLi−ROLi Mixed Aggregate Structures. Lithium cyclopropylacetylide in THF was shown to be a mixture of dimer **7**

(60) For an interesting discussion of and leading references to hydrogen bonding in organometallic complexes, see: Kapteijn, G. M.; Dervisi, A.; Grove, D. M.; Kooijman, H.; Lakin, M. T.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1995**, *117*, 10939.

Scheme 1



Scheme 2



and tetramer **8** in accordance with previous studies.[33−35] Lithium ephedrate **4** forms a complex mixture of oligomers, also in accordance with literature reports.[19] Incremental addition of lithium ephedrate **4** to lithium cyclpropylacetylide affords (in order) a 3:1 mixed aggregate (**17**), a 2:2 mixed aggregate (**14**), and a 1:3 mixed aggregate (**18**). The stereogenic centers on the ephedrate cause the ^{6}Li NMR spectra to be surprisingly informative due to the symmetries of the mixed aggregates. The remaining structural details derive from a combination of ^{13}C labeling of **6** and ^{15}N labeling of the pendent pyrrolidine in **4**. (The distinction of **18** from isomer **19** is supported by MNDO calculations.) The complete control of stereochemistry in **14** and **18** may be of considerable consequence to their reactivity (vide infra).

Previous investigations showed that the enantioselective addition of lithium acetylide **6** to ketone **1** displays unusual aging effects;[13] samples of **4** and **6** mixed and maintained at −78 °C afford mediocre selectivities, whereas samples mixed cold, warmed to ambient temperature, and then cooled back to −78 °C prior to substrate addition afford exceptional selectivities. A structural basis of this effect is clearly evidenced by the presence of complex mixtures of homo- and heteronuclear

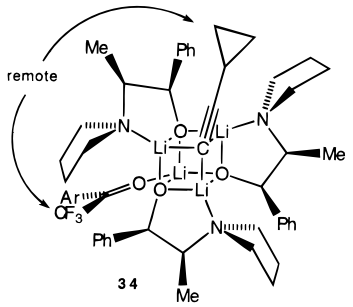
aggregates of **4** and **6** that require warming to ambient temperature to establish equilibrium. *Complete aggregate equilibration is substantially slower than the 1,2-addition.* It is possible that the mixed aggregates exchange quickly and that the equilibration is slowed by a rate-limiting exchange of the homonuclear lithium ephedrate aggregates. However, $^{6}Li-^{13}C$ and $^{6}Li-^{15}N$ couplings observable at ambient temperature attest to the slow subunit exchange within the mixed aggregates. The mere *possibility* that the 2:2 mixed aggregate **14** is structurally robust on the time scale of the 1,2-addition dramatically influences our thinking.

MNDO Calculations and a Self-Consistent Mechanistic Model. The calculated transition structure stabilities and stereochemistries proved central to the development of a predictive mechanistic model. The MNDO calculations indicate that mixed dimer-based transition structures do not include provisions for highly enantioselective additions to **1**. The model based upon mixed dimers is problematic due to a large number of possible variables (Figure 4). A nonselective substrate approach either syn or anti to the substituents on the ephedrate chelate proves to be the Achilles heel. *For every β-selective transition structure resulting from attack anti to the ephedrate substituents there exists an equally stable* α*-selective transition structure resulting from approach of the electrophile from the opposite chelate face.*

A model based upon 2:2 mixed tetramers proved far more fruitful, leading to the mechanistic hypothesis summarized in Scheme 2. The experimentally observed C_2 symmetric tetramer **14** is an optimal template to control the 1,2-addition. The two lithium nuclei on **14** bearing substitutionally labile THF ligands are symmetry equivalent; the single precomplex **31** reduces the absolute stereocontrol in eq 1 to control of rotation about the carbonyl oxygen−lithium bond. The calculated transition structures based upon C_2 symmetric mixed tetramers, as exemplified by transition structure **27** with chelates omitted for clarity, display two important features: (1) four-center LiC_2O rings often associated with 1,2-additions[54] and (2) prominent π interactions between the acetylene β carbons and two neighboring lithium nuclei. The two combine to provide possible explanations for a high sensitivity of the enantioselectivities to the acetylene and dialkylamino groups. The π interactions impose rigidity, forcing the aryl and CF_3 substituents to orient over two sterically quite distinct faces of the cube as illustrated in **32** and **33** (Scheme 2). Transition structure **32**, corresponding to the experimentally observed β-selective addition, places the ketone CF_3 group over the sterically congested chelate face containing the phenyl and methyl substituents syn while placing the aryl moiety above the sterically less-congested chelate face with the ephedrate substituents anti. In contrast, **33** places the sterically demanding ketone phenyl substituent above the sterically congested chelate face. The computations reveal a general β facial selectivity consistent with the experimental findings. Systematic substituent variations in the substrate (Table 2) also reveal that substrate **1** is optimal. The CF_3 and *o*-ArNHR moieties (and affiliated N−H···O hydrogen bond, **30**) substantially enhance the predicted β facial selectivity, affording predicted enantioselectivities of 100:1 er at −50 °C. This agrees well with the experimentally observed 50−100:1 er for the addition to ketone **1**.

According to the MNDO calculations, there are substantial conformational preferences within the ephedrate chelate rings of reactant **14** and transition structures **31** and **32** that place the methyl groups protruding above the plane of the chelate and the phenyl groups approximately in the plane. The stereochemically consequential interactions in transition structures **32** and **33** appear to be between the ketone substituent and the ephedrate methyl group. While we have not explored chelate substituent effects in detail, it is not difficult to imagine why chiral alkoxides derived from valine and related amino alcohols bearing a single substituent provided mediocre enantioselectivities.[5]

Origins of 50% Conversion. The previous studies showed that additions of 1:1 mixtures of **4** and **6** to ketone **1** require 2 equiv of active lithium acetylide. We reasoned that 1 equiv of lithium acetylide might deprotonate the N−H moiety of **1**; however, NMR and IR studies show that the N−H moiety of **1** and the second equivalent of lithium acetylide **6** remain intact. Reinvestigation revealed that the first 50% conversion occurs immediately at −90 °C while the second 50% conversion requires several hours at 0 °C and proceeds with a markedly lower enantioselectivity. It is interesting in this context that conditions favoring mixed tetramer **18** also afford ketone **1**, but very slowly near ambient temperature. The lithium nucleus of **18** bearing a substitutionally labile THF ligand and the acetylide fragment are remote, precluding any possibility that precomplex **34** derived from **18** could proceed to the product without substantial structural reorganization. Since product **2** is also a potentially chelating alkoxide, the mixed aggregates formed from the 1:2:1 **2**:**4**:**6** mixtures could inhibit the reaction in much the same way that mixed tetramer **18** is unreactive.



The remarkably lower reactivity of **18** when compared with **14** (estimated to be $>10^5$ assuming a 2-fold rate change with every 10 °C) attests to substantial structural changes en route to the rate-limiting transition structure. These results do not, however, directly implicate either a mixed dimer or a mixed tetramer intermediate. The high enantioselectivities for the addition of **6** to ketone **1** observed under conditions favoring the formation of either the 1:3 mixed tetramer **18** or the 2:2 mixed tetramer **14** could be construed as evidence of a common intermediate. However, one experiment suggests that the changes in stoichiometry and affiliated changes in mixed aggregate structure lead to fundamental changes in the mechanism; 1,2-addition to $PhCOCF_3$ at stoichiometries favoring **14** is marginally enantioselective while addition at RLi−ROLi stoichiometries favoring **18** is more enantioselective.

Summary and Conclusions

The highly enantioselective 1,2-addition in eq 1 has been investigated using NMR and IR spectroscopies and semiempirical (MNDO) computational methods. Mixtures of RLi and ROLi in THF afford a stoichiometry-dependent distribution of 3:1, 2:2, and 1:3 mixed tetramers with complete stereocontrol for each aggregate. We find it remarkable that an achiral lithium acetylide and a lithium ephedrate containing two stereogenic

centers could self-assemble into mixed tetramers containing up to 14 stereogenic centers with essentially complete stereocontrol. The C_2 symmetry of tetramer **14** is interesting given the prevalence of absolute stereocontrol based upon C_2 symmetry.[61] The semiempirical computational studies support a stereochemical model based upon 1,2-addition via such a C_2 symmetric 2:2 mixed tetramer. While the proposed model is self-consistent, it is not fully established. The burden of proof will rest heavily upon the projected rate studies.[62]

(61) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, 1994.

(62) For rate studies of 1,2-additions, see: Smith, S. G. *J. Org. Chem.* **1985**, *50*, 2715 and references therein.

Acknowledgment. This paper is dedicated to Professor Dieter Seebach on the occasion of his 60th birthday. D.B.C. and J.F.R. acknowledge the National Institutes of Health (RR02002) for support of the Cornell Nuclear Magnetic Resonance Facility and the National Science Foundation for direct support of this work.

Supporting Information Available: General experimental procedures, ^{6}Li and ^{13}C NMR spectra, and results from MNDO computations (70 pages). See any current masthead page for ordering and Internet access instructions.

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