Highly Enantioselective 1,2-Addition of Lithium Acetylide-Ephedrate Complexes: Spectroscopic Evidence for Reaction Proceeding via a 2:2 Tetramer, and X-ray Characterization of Related Complexes

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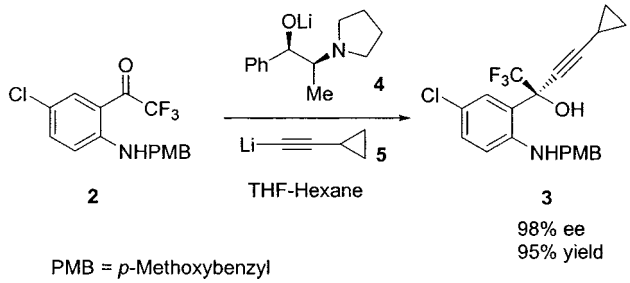
Abstract: The key step in the manufacturing process for the HIV reverse transcriptase inhibitor efavirenz (Sustiva) involves addition of the 2:2 tetrameric complex **6** [formed from lithium cyclopropylacetylide (**5**) and lithium (*1R,2S*)-*N*-pyrrolidinylnorephedrate (**4**)] to ketone **2**, to give **3** in 95% yield and 98% enantioselectivity. Studies of acetylide-alkoxide complexes in solution by NMR spectroscopy and in the solid state by X-ray crystallography are described. Studies of the asymmetric addition reaction involving 2:2 tetramer **6** using low-temperature NMR spectroscopy provide conclusive evidence for formation of 2:1:1 tetramer **9** containing the product alkoxide **3**. Observation of this reaction intermediate strongly supports the proposed reaction mechanism involving the tetramer **6** in the stereo-determining step.

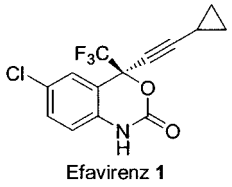
Introduction

Recent efforts within the Merck Research Laboratories to discover new compounds for the treatment of HIV infection have resulted in indinavir (Crixivan), a protease inhibitor, as well as efavirenz (**1**)[1−3] (Sustiva),[4] a nonnucleoside reverse transcriptase inhibitor. Efavirenz has shown excellent potency against a variety of HIV-1 mutants when used in combination with Crixivan or with other reverse transcriptase inhibitors, and was recently approved for use by the FDA. A practical asymmetric synthesis[5] of efavirenz has been implemented for large scale manufacture.[6] The key step in this process (Scheme 1) involves the 1,2-addition of lithium cyclopropylacetylide (**5**)

Scheme 1. Highly Enantioselective 1,2-Addition Reaction



to trifluoromethyl ketoaniline **2** using stoichiometric amounts of lithium (*1R,2S*)-*N*-pyrrolidinylnorephedrate (**4**) as chiral mediator.[7]



Efavirenz **1**

Optimal enantioselectivity (98% ee) and full conversion (95% isolated yield)[6] are obtained using THF as solvent and require

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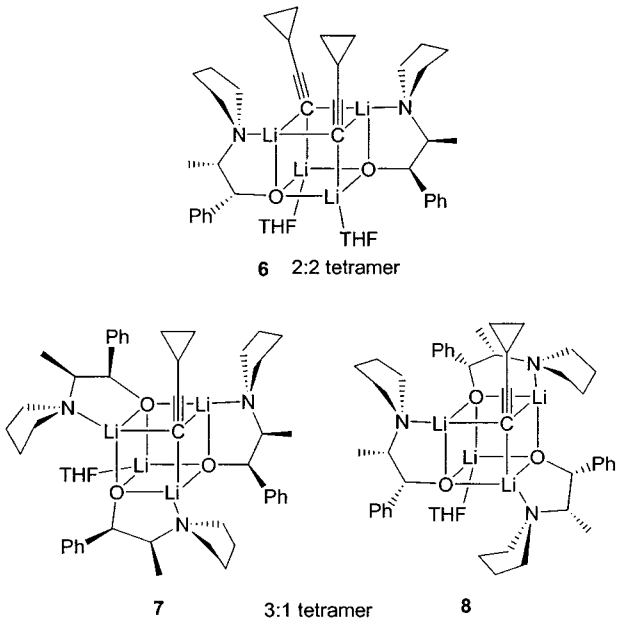

Figure 1. Tetramer structures.

the use of 2.0 equiv of **5** and 2.0 equiv of alkoxide **4**, which must be allowed to equilibrate at temperatures > −40 °C prior to reaction with keto aniline **2** at < −50 °C. Using 1.0 equiv each of equilibrated **4** and **5** provided only 50% conversion (98% ee) below −50 °C; subsequent warming of the reaction mixture to 0 °C provided 90% conversion at the expense of selectivity (82% ee). Generation of the alkoxide-acetylide mixture at low temperature without aggregate equilibration and subsequent reaction with keto-aniline **2** provided **3** in only 85% ee.[8]

Initial mechanistic studies on this reaction employing ^{6}Li, ^{13}C, and ^{15}N NMR spectroscopy and MNDO calculations have shed much light on these experimental observations.[8] ^{6}Li NMR spectroscopic studies on THF solutions containing lithium ephedrate **4** and lithium acetylide **5** in various proportions confirmed a slow aggregate equilibration at low temperature, which was rapid above −40 °C. It was determined that a 1:1 mixture of **4** and **5** equilibrates to a single C2-symmetrical 2:2 cubic tetramer **6** (Figure 1), which was fully characterized by ^{6}Li NMR spectroscopy. It was also shown that a 3:1 mixture of **4** and **5** equilibrates to a single cubic tetramer, assigned as **7** or **8** based on ^{6}Li−^{13}C and ^{6}Li−^{15}N couplings. The structure of **7** was supported by MNDO model calculations (Figure 1).

It was concluded that reaction of the ketoaniline **2** with the equilibrated 2:2 mixture of alkoxide and acetylide proceeds via the 2:2 tetramer **6**. A mechanism accounting for the observed stereochemical outcome was proposed on the basis of MNDO calculations (Scheme 2)[8,9] and was supported by several key observations: (1) the 2:2 tetramer **6** is the only detectable species present after equilibration of the equimolar mixture of alkoxide **4** and acetylide **5** and prior to addition of ketone **2**; (2) the 1,2-addition is fast at low temperature, as compared to the slow aggregate equilibration; (3) the reaction displays asymmetric amplification [50% ee *N*-pyrollidinylnorephedrine (**4a**) provides 77%ee product].

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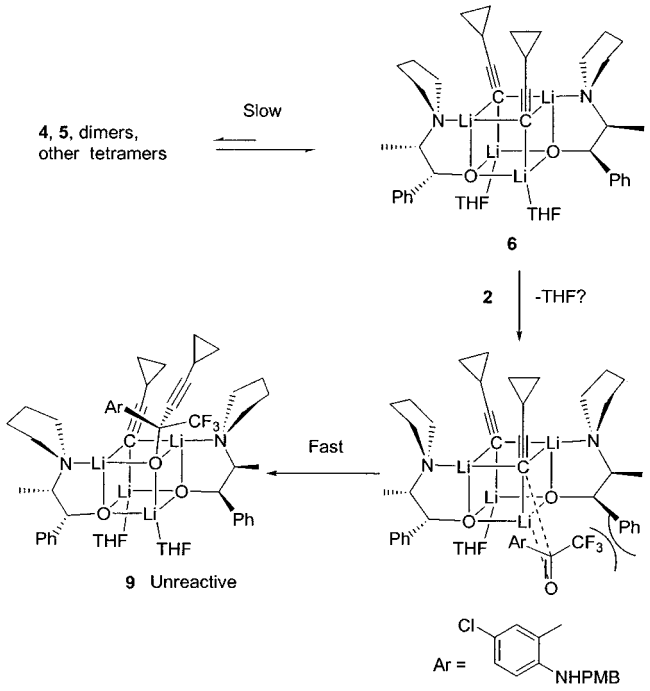
(9) Reaction of the ketoaniline **2** with the tetramer **6** possibly occurs via formation of a precomplex (replacement of THF in **6** with the carbonyl of **2**). The sense of facial selectivity in this reaction as predicted by MNDO calculations is readily explained in terms of steric effects. In the preferred transition state, the bulky aryl portion of **2** points away from the norephedrine substituents, as indicated in Scheme 3.

Scheme 2. Proposed Reaction Pathways



The requirement for 2.0 equiv of **4** and **5** for full conversion (or 1.0 equiv of tetramer) was explained in terms of the formation of an unreactive 2:1:1 complex **9** containing product alkoxide, acetylide **5**, and 2 equiv of ephedrate **4**. This rationalization was consistent with the known low reactivity of the closely related 3:1 alkoxide:acetylide complex (**7** or **8**).

Although these studies have enormously increased our understanding of lithium acetylide−alkoxide complexes, some aspects of this interesting puzzle warranted further investigation. First, although there was ample evidence for generation of cubic tetrameric alkoxide−acetylide complexes in THF, there was no reported evidence for the formation of these species in other solvents or in the solid state. Second, although equimolar amounts of pyrrolidinylnorephedrine lithium alkoxide **4** and acetylide **5** rapidly equilibrate to a single tetrameric complex **6** above −40 °C, this behavior had not been confirmed for other *N*-substituted 1,2-aminoalkoxide−acetylide mixtures. These points are particularly pertinent, given the observed solvent and aminoalkoxide structural effects on the enantioselectivity of the 1,2-addition.[5] Finally, there was no direct spectroscopic evidence supporting the proposed tetramer-based mechanism for the 1,2-addition reaction.

The studies described herein were carried out to further explore the structures of acetylide−alkoxide complexes, to account for the experimental observations in the 1,2-addition, and to further substantiate the reaction mechanism proposed in the initial work.

Results and Discussions

Lithium Acetylide−Alkoxide Complexes: Solvent Effects. In the initial work on the asymmetric addition reaction, THF was found to give the best enantioselectivity (98%).[5] Comparable selectivity was observed in ethylene glycol dimethyl ether (DME) (92% ee), but lower ee's were obtained in diethyl ether (68% ee) or *tert*-butyl methyl ether (MTBE) (26% ee), and close to zero selectivity was observed in toluene. For reactions in THF, the maximum ee was obtained using solutions that had fully equilibrated to give a single 2:2 cubic tetramer **6** containing

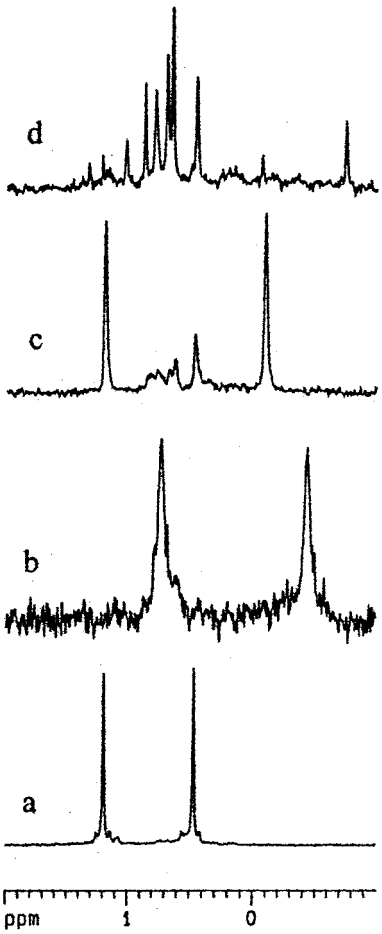
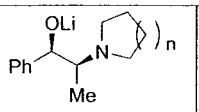


Figure 2. ^{6}Li NMR spectra of equilibrated samples containing **4** and **5** (1:1) (a) in THF/hexane/toluene (5:5:1) at −40 °C, (b) in DME/hexane/toluene (5:5:1) at −60 °C, (c) in Et_2O/hexane/toluene (5:5:1) at −40 °C, and (d) in *t*-BuOMe/hexane/toluene (5:5:1) at −40 °C.

2 mol of THF. This was the first piece of (circumstantial) evidence implicating the cubic tetramer itself in the addition reaction. It was suspected that it might be possible to correlate the observed solvent effects with the presence or absence of a single tetrameric structure (related to **6**), as determined from ^{6}Li NMR spectra of the alkoxide−acetylide mixtures. Thus, the ^{6}Li NMR spectra shown in Figure 2 were obtained for solutions containing equimolar amounts of acetylide **5** and alkoxide **4**, which had been allowed to equilibrate at 22 °C. In DME, a spectrum similar to that in THF was observed, which supports formation of a tetrameric complex similar to **6** (possibly with an η^1-bound DME in place of the THF). In diethyl ether, the ^{6}Li NMR spectrum showed two singlets, as in THF and DME, but there were other species formed. In MTBE, a complex mixture of species was formed. The high enantioselectivity is observed only in solvents which allow for formation of a single tetrameric complex at equilibrium prior to reaction with ketoaniline **2**.

Lithium Acetylide−Alkoxide Complexes: Ephedrine Substituents. In the initial studies, *N*-pyrrolidinylnorephedrine lithium alkoxide **4** was identified as the optimal chiral mediator on the basis of studying a variety of different chiral aminoalkoxides in the addition reaction.[5] Much of these data were generated before the realization of slow aggregate equilibration and under conditions which did not guarantee complete equilibration of complexes (−40 °C). Thus, a study of the aggregate equilibrations of various acetylide **5**-alkoxide mixtures using ^{6}Li NMR was carried out. Three closely related aminoalkoxides (**4**, **10**, and **11**) were selected for this study to probe the effects of *N*-cycloalkyl ring size.[10] Thus, the complexes were prepared using equimolar quantities of lithium acetylide **5** and norephedrine alkoxides **4**, **10**, and **11**. In each case, the formation of fully equilibrated tetrameric complexes was found to be complete at −40 °C to give two-line spectra as expected (Table 1). The 1,2-addition reactions were then performed at −70 °C to determine ee% (Table 1). These data clearly show that the size of the *N*-cycloalkyl substituent is critical in this process and confirms the initial observation that (*1R*,*2S*)-*N*-pyrrolidinylnorephedrine (**4a**) is optimal.[9]

Table 1. Ring Size Effects on Reaction Enantioselectivity

	^{6}Li NMR (ppm)	ee%
10 (n = 0)	1.39, 0.41[a]	88
4 (n = 1)	1.19, 0.47[b]	99
11 (n = 2)	1.21, 0.47[a]	91

[a] ^{6}Li NMR was recorded in THF/hexane (1:1) at −60 °C. [b] ^{6}Li NMR was recorded in THF/hexane (1:1) at −40 °C.

Lithium Acetylide−Alkoxide Complexes: X-ray Crystallography. The tendency of lithium acetylides to form dimers, tetramers, and higher oligomers in the solid state is well-known. Lithium acetylides have been crystallized and characterized as tetramers by X-ray analysis,[11] but structural studies on mixed lithium acetylide−lithium alkoxide complexes have not been carried out.[12] Accordingly, we were quite interested in preparing X-ray quality crystals of these complexes to obtain structural information in the solid state.

X-ray quality crystals were readily obtained from a 3:1 mixture of alkoxide **4** and acetylide **5**. A solution of 3.0 equiv (*1R*,*2S*)-*N*-pyrrolidinylnorephedrine (**4a**) and 1.0 equiv cyclopropylacetylene (**5a**) was treated with 4 equiv *n*-BuLi in THF/

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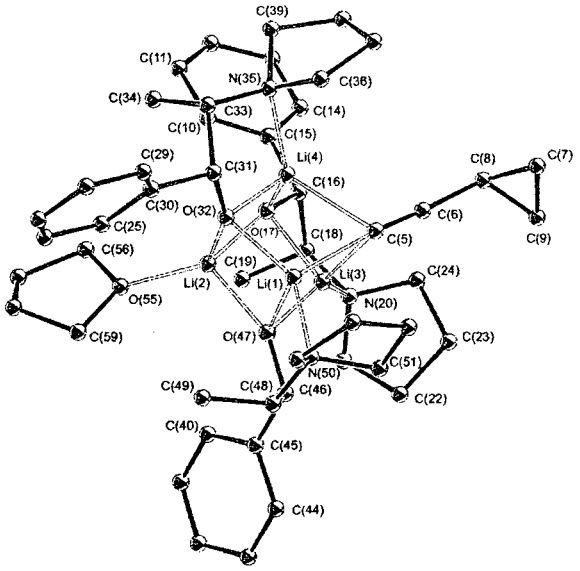


Figure 3. Perspective ORTEP drawings of 3:1 tetramer **8**. Hydrogen atoms have been omitted for clarity.

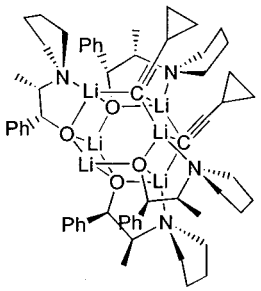
Table 2. Selected Bond Lengths (Å) and Angles (deg) for 3:1 Tetramer **8**

Bond Distances			
C(5)−Li(1)	2.13(2)	O(17)−Li(4)	1.86(2)
C(5)−Li(3)	2.29(3)	O(55)−Li(2)	1.97(3)
C(5)−Li(4)	2.27(3)	N(20)−Li(3)	2.04(2)
O(17)−Li(2)	2.00(2)	N(35)−Li(4)	2.07(1)
O(17)−Li(3)	1.97(2)	N(50)−Li(1)	2.07(3)
Bond Angles			
O(32)−Li(1)−O(47)	95.5(12)	C(16)−O(17)−Li(3)	97.0(7)
O(32)−Li(1)−C(5)	104.8(10)	Li(2)−O(17)−Li(3)	78.9(8)
O(47)−Li(1)−N(50)	90.2(6)	Li(2)−O(17)−Li(4)	82.5(8)
O(47)−Li(1)−C(5)	101.6(6)	Li(3)−O(17)−Li(4)	87.1(9)
O(17)−Li(2)−O(32)	94.2(8)	Li(1)−C(5)−Li(3)	71.0(8)
O(17)−Li(2)−O(47)	96.6(7)	Li(1)−C(5)−Li(4)	70.3(9)
O(32)−Li(2)−O(47)	95.8(12)		

hexane at −10 to 0 °C under nitrogen. The mixture was concentrated in vacuo, and the solvent ratio was adjusted to approximately 40% THF in hexane at a concentration of about 0.15 M (for the 3:1 tetramer). X-ray quality single crystals were obtained from this mixture at room temperature under an atmosphere of N_2. The ^1H, ^6Li, and ^{13}C NMR spectra measured on a solution prepared by dissolving the crystals in THF-d_8 at room temperature were identical to the spectra previously obtained from an equilibrated solution of the 3:1 aggregate. Treatment of this solution with ketoaniline **2** at −40 °C provided the addition product **3** in 99% ee and 60% yield, as expected for a reaction involving the 3:1 tetramer.[8]

The structure of the crystalline material, as determined by X-ray diffraction analysis at −165 °C, was shown to be the 3:1 tetramer **8** (Figure 1). The ORTEP drawing is displayed in Figure 3, and the selected bond lengths and angles are summarized in Table 2. It is interesting that the three Li−C bonds in 3:1 tetramer **8** are slightly longer than the Li−O bonds, which distorts the cubic structure somewhat. Surprisingly, the THF O−Li bond [O(55)−Li(2)] is almost the same length as other O−Li bonds and shorter than the N−Li bonds, which indicates a strong binding of THF to lithium in the tetrameric structure. Interestingly, each of the three internal O−Li−N angles (inside the five membered ring) are right angles.

The structure of the 3:1 cubic tetramer **8** in the solid state is identical to one of the two solution structures that are assigned on the basis of the earlier NMR studies.[8] However, the alternative stereoisomer **7** (Figure 1) was predicted to be more stable on the basis of MNDO model calculations. If the solution and solid-state structures of the 3:1 tetramer are indeed different, the behavior of the 3:1 alkoxide:acetylide mixture, which was prepared by dissolving the crystalline material in THF, would require the facile conversion of **8** to **7** in solution.



4:2 hexamer **12**

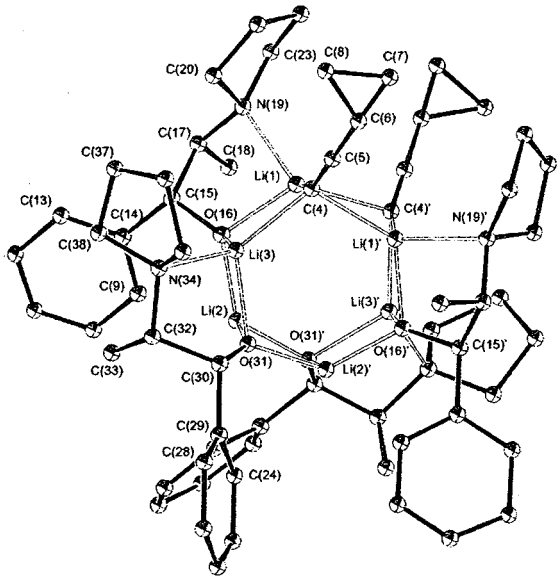


Figure 4. 4:2 hexamer **12** structure and its perspective ORTEP drawings. Hydrogen atoms have been omitted for clarity.

Encouraged by our success in obtaining X-ray quality crystals from the 3:1 complex, we attempted to prepare crystalline material from a solution of the 2:2 alkoxide **4**:acetylide **5** mixture. A crystalline solid was obtained from this mixture only with difficulty, and this required removal of most of the THF. Thus, a THF−hexane solution of a 1:1 mixture of cyclopropylacetylene (**5a**) and (*1R,2S*)-*N*-pyrrolidinylnorephedrine (**4a**) was treated with 2.0 equiv *n*-BuLi at −10 to 0 °C. The solution was concentrated in vacuo and more hexane was added to adjust the solvent ratio to 1−2% THF in hexane (concentration of 2:2 tetramer, approximately 0.2 M). X-ray quality single crystals were obtained from this mixture at room temperature under a nitrogen atmosphere. X-ray diffraction analysis carried out at −174 °C under an atmosphere of N_2 revealed hexamer **12** (Figure 4). The ORTEP drawing is displayed in Figure 4, and selected bond lengths and angles are summarized in Table 3.

The preferential crystallization of the 4:2 hexamer **12** was an interesting, yet unexpected, result, and all subsequent attempts to obtain crystals of the 2:2 tetramer **6** have failed.[13] Some interesting features of this 4:2 complex were noted. The C2-symmetrical hexamer **12** consists of two stacked chairlike six-membered rings (displaced approximately 60° relative to each

Table 3. Selected Bond Lengths (Å) and Angles (deg) for 4:2 Hexamer **12**

Bond Distances			
O(16)−Li(1)	1.906(5)	N(19)−Li(1)	2.121(10)
O(16)−Li(2)	1.850(5)	C(4)−Li(1)	2.215(11)
O(31)−Li(3)	2.005(5)	C(4)−Li(1′)	2.262(11)
O(16)−Li(3′)	1.940(10)	C(4)−Li(3)	2.121(5)
Bond Angles			
Li(1)−O(16)−Li(2)	113.9(4)	O(16)−Li(1)−N(19)	87.8(4)
Li(1)−O(16)−Li(3)	84.1(3)	O(16)−Li(1)−C(4′)	125.6(3)
Li(1)−C(4)−Li(1′)	77.9(4)	O(16)−Li(1)−C(4)	99.7(4)
Li(1)−C(4)−Li(3)	103.4(3)	O(16)−Li(2)−O(31′)	99.7(4)

other) that contain two alkoxides and one acetylide. Two lithium atoms (those directly opposite to the acetylide carbon atoms) are three-coordinate and are not bonded to THF. Additionally, each of the four internal O−Li−N angles (within the five-membered ring) are close to right angles, which is similar to that observed in 3:1 tetramer **8**.

Dissolving the crystalline 4:2 hexamer **12** in THF at room temperature, followed by cooling to −70 °C and reaction with ketone **2**, provided the addition product **3** in 99% ee. Identical results were obtained by using an equilibrated solution of 4 equiv alkoxide **4** and 2 equiv acetylide **5**, which suggests the formation of solutions having similar composition in both cases. To better understand these results, ^{6}Li NMR spectra were recorded for both solutions in THF-d_8. It was immediately apparent that dissolving the hexamer **12** in THF and a 4:2 mixture of alkoxide **4** and acetylide **5** generated in situ provide mixtures containing predominantly the 2:2 tetramer **6** and 3:1 tetramer **7** or **8**. This is consistent with the highly enantioselective reactions that are observed in both cases with ketone **2** at −70 °C.[5,8] The conclusion is that hexamer **12** is less stable than either tetrameric structure in THF, that equilibration is fast at room temp, and that **12** is not important in the addition reaction pathway.

Acetylide-Transfer Mechanism: ^{6}Li NMR Studies. According to the proposed mechanism outlined in Scheme 2, reaction of cubic tetramer **6** with the ketone **2** at low temperature results in the rapid transfer of one acetylide to give a less-reactive product complex **9** containing two ephedrates, one product alkoxide, and one acetylide. Strong support for this mechanism was obtained by following the reaction using ^{6}Li NMR spectroscopy. A solution of 1.0 equiv mixed 2:2 tetramer **6** in THF and hexane, generated as usual, was cooled to −100 °C.[14] To this solution was added, slowly and with good mixing, a solution of approximately 0.5 equiv ketone **2** in THF. The ^{6}Li NMR spectrum at −100 °C showed the appearance of four new singlets, with equal intensities (1.13, 0.95, 0.77, and 0.60 ppm) (Figure 5). Further conversion of the 2:2 tetramer to this four-line intermediate was achieved upon further addition of keto aniline **2**.[15]

The four-line spectrum is fully consistent with the formation of a mixed cubic tetramer **9** containing the product alkoxide and provides the first strong evidence in favor of the 1,2-addition reaction proceeding via the 2:2 tetramer **6**. Employing [1-^{13}C]-labeled acetylene **5a** revealed that three of four ^{6}Li resonances were split into doublets due to spin−spin coupling to ^{13}C. This coupling was verified by a ^{6}Li NMR spectrum (spectrum B, Figure 6) with ^{13}C decoupling. A broad signal at 116.2 ppm in the ^{13}C NMR spectrum at −100 °C is consistent with an alkyne bound to several ^{6}Li nuclei, and a signal of equal intensity at 75.45 ppm is consistent with the alkyne carbon in the product alkoxide itself. Using ^{15}N-labeled ephedrine **4a**,[10,16] revealed that the ^{6}Li NMR spectrum showed splitting of signals at 1.13 and 0.95 ppm into doublets due to a coupling with ^{15}N (Table 4). Using [^{15}N]ketoaniline **2**,[6,17] the ^{6}Li NMR spectrum obtained at −100 °C showed no connection between the nitrogen atom

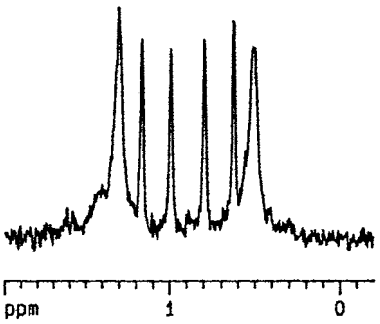


Figure 5. ^{6}Li NMR spectrum at −100 °C after treatment of the 2:2 tetramer **6** with 0.5 equiv of ketone **2** in THF/pentane (1:1) at −100 °C.

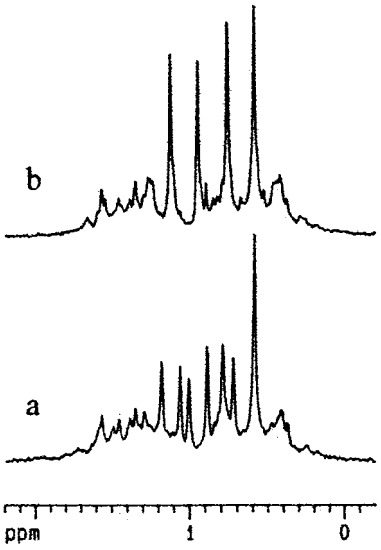
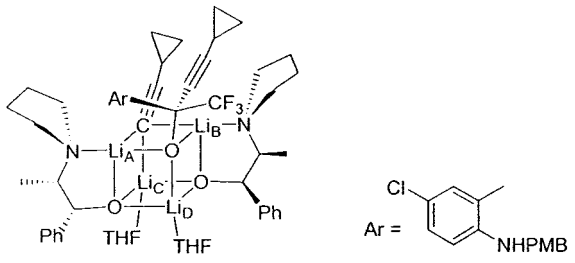


Figure 6. ^{6}Li NMR spectra at −100 °C after treatment the 2:2 tetramer **6** with ketone **2** in THF/pentane (1:1) at −100 °C (a) using [1-^{13}C]-labeled acetylene **5a** and (b) using [1-^{13}C]-labeled acetylene **5a** with waltz-16 ^{13}C decoupling.

Table 4. NMR Spectroscopic Data for 2:1:1 Tetramer **9**



2:1:1 tetramer **9**

Li atom	ppm	^{13}C−^{6}Li coupling	^{15}N−^{6}Li coupling
Li_A, Li_B	1.13	d (J = 6.8 Hz)	d (J = 2.9 Hz)
	0.95	d (J = 6.8 Hz)	d (J = 2.9 Hz)
Li_C	0.77	d (J = 4.0 Hz)	none
Li_D	0.60	none	none

(13) Preferential crystallization of the 4:2 hexamer from the 2:2 mixture was found to occur reproducibly, regardless of solvent composition or crystallization temperature.

(14) The best quality spectral data were obtained at −100 °C. Interestingly, subsequent warming to −70 °C did not afford any new species, but caused broadening of the signal assigned as Li_C (Figure 5), which sharpened upon re-cooling.

(15) Reaction of the sample in the NMR tube with ketoaniline **2** provided the product **3** in 99% ee.

in addition product **3** and any lithium atom in the product alkoxide complex. This is surprising because the 3:1 tetramer **8** features bonding of the nitrogen atom in each ephedrate to a lithium atom in the tetramer.[18] On the basis of these data, the product complex is assigned as the tetramer **9**,[19] the logical product of asymmetric 1,2-addition of the tetramer **6** to the ketoaniline **2**.

Summary

Continued studies of lithium 1,2-aminoalkoxide−lithium acetylide mixtures have substantially increased our understanding of these complexes in solution and in the solid state. In particular, it was confirmed that single tetrameric aggregates are formed at equilibrium in THF and DME, while complex mixtures are present in diethyl ether and MTBE. In addition, it was shown that equimolar mixtures of lithium acetylide **5** and *N*-cycloalkyl lithium aminoalkoxides equilibrate to single tetrameric species at approximately the same rate in THF and confirmed that there is a substantial ring-size effect on the enantioselectivity of the 1,2-addition reaction. X-ray crystallographic studies revealed a symmetrical cubic tetrameric structure **8** for the 3:1 aggregate which is in close agreement with a structure proposed on the basis of solution NMR data. A new hexameric complex **12** was prepared by crystallization from a 2:2 mixture of alkoxide:acetylide and was characterized by X-ray crystallography. This structure is not stable in the solution and provides mixtures containing predominantly the 2:1 and 3:1 tetramer aggregates.

Further studies on the mechanism of the 1,2-addition reaction have resulted in the spectroscopic characterization of the tetrameric reaction intermediate **9**, which leads us to conclude that the reaction proceeds via the cubic tetramer **6** and that pathways involving dimeric intermediates are not relevant in this process.[20]

Experimental Section

General Considerations. Unless otherwise noted, all of the reactions and manipulations were carried out using dry glassware under a nitrogen atmosphere. All solvents were dried over 4-Å molecular sieves and checked for water content by Karl-Fisher titration. ^{6}Li (95%, enriched), $^{15}NH_3$ (98%, enriched), and $^{15}NH_2OH{\cdot}HCl$ (99%, enriched) were purchased from Aldrich. $^{13}CBr_4$ (99%, enriched) was purchased from Icon Services Inc. *n*-Bu^{6}Li was prepared[21] in pentane from commercial ^{6}Li and *n*-butyl chloride and was filtered to remove solids before use. ^{15}N-labeled (*1R,2S*)-*N*-pyrrolidineylnorephedrine **4a** was prepared from ^{15}N-labeled (*1R,2S*)-norephedrine, which was synthesized from propiophenone via a literature procedure using $^{15}NH_2OH{\cdot}HCl$.[10,16] ^{15}N-labeled ketoaniline **2** was prepared from [^{15}N]-4-chloroaniline using the existing procedures.[6] [^{15}N]-4-Chloroaniline was prepared from 4-chlorobenzoic acid via Hofmann rearrangement using $^{15}NH_3$ as the source of the label.[17]

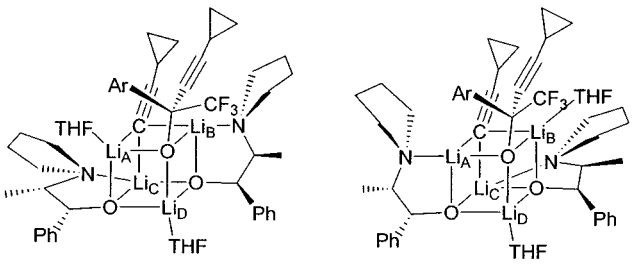
Instrument Descriptions. NMR Spectroscopic Analyses: For ^{1}H, spectra were obtained on a Bruker AMX-400 operating at 399.87 MHz. ^{6}Li and ^{13}C spectra were recorded at 58.85 and 100.55 MHz, respectively. In the ^{6}Li spectrum of tetramer **6** at −40 °C, the low-field signal was referenced to $\delta = 1.19$ ppm.[8] Subsequent ^{6}Li spectra were referenced to the ^{2}H lock frequency. ^{13}C spectra were referenced to the high-field signal from THF-d_8 ($\delta = 25.4$ ppm). Low-temperature calibration was determined using 4% CH_3OH in CD_3OD and the Bruker variable temperature calibration curve. ^{13}C-decoupled ^{6}Li spectra were obtained using standard Waltz-16 decoupling on an "X" tuneable ^{13}C/^{1}H triple-resonance probe.

X-ray Crystallography: All crystallographic studies were performed on a Picker four-circle goniostat using a locally designed interface and nitrogen gas flow cooling system of local design. In both studies, crystals were affixed to the end of glass fibers using silicone grease and transferred to the system where they were cooled for characterization and data collection. Details of the diffractometer, low-temperature facilities, and computational procedures employed by the Molecular Structure Center are available elsewhere.[22] The structures were solved by direct methods (SHELXTL) and Fourier methods and refined on F2 using full-matrix least-squares techniques.

[1-^{13}C]Cyclopropylacetylene (5a).[8,23] To a solution of PPh_3 (15.8 g, 60.3 mmol) in 40 mL of dry methylene chloride at −40 °C was added a solution of $^{13}CBr_4$ (10.0 g, 30.1 mmol) in 40 mL of dry THF at such a rate as to keep the temperature below −20 °C. After aging 15 min at −20 °C, the mixture was cooled to −70 °C, and Et_3N (5.0 mL, 36.2 mmol) was added dropwise. A solution of cyclopropane carboxaldehyde (4.23 g, 60.3 mmol) in 5 mL of dichloromethane was added at such a rate as to keep the temperature below −55 °C. The reaction mixture was aged at −40 °C for 1.5 h (reaction completion determined by GC analysis) and was then quenched in 50 mL of water. The organic layer was separated, and the aqueous layer was extracted using 15 mL of dichloromethane. The combined organic solution was dried over Na_2SO_4 and concentrated under reduced pressure to give a white slurry. 100 mL of hexane was added, and the solid was removed by filtration through a thin pad of Celite. Concentration of the filtrate provided 5.5 g of [1-^{13}C]-1,1-dibromocyclopropylethylene as a colorless liquid (81% yield). The spectral data for this material exactly matched those reported in the literature.[23d]

To a solution of 5.1 g (22.6 mol) of [1-^{13}C]-1,1-dibromocyclopropylethylene in 8 mL of dry toluene and 11 mL of dry THF was slowly added 5.0 mL of *n*-BuLi (50 mmol, 10 N in hexane) while keeping the temperature below −10 °C. The reaction mixture was aged between −10 and 25 °C for 1 h (reaction completion determined GC analysis), and then 10 mL of 10% NH_4Cl was added while keeping the temperature below −15 °C. The organic phase was separated at 0 to −5 °C and was dried over Na_2SO_4 at 0 °C. Short-path distillation of the resulting solution under an atmosphere of nitrogen gave 14.0 g of a solution of ^{13}C-labeled cyclopropylacetylene solution in THF−hexane (7.2 wt % solution, 68% yield) and 55% overall yield.

General Procedure for the Preparation of 2:2 Tetramer 6. To a solution of (*1R,2S*)-*N*-pyrrolidinylnorephedrine (**4a**) (10.0 g, 45.79 mmol) and Ph_3CH (10 mg) in 80 mL of dry THF was charged *n*-BuLi (1.6 M in hexane) while maintaining the temperature below −10 °C.



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14

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(18) It was pointed out correctly by a referee that the 3:1 tetramer **8** may not predict reactivity of the intermediate **9** due to differences in Li−N bonding in these structures.

(19) The NMR data are also consistent with the diastereoisomers **13** and **14**. The structure **9** is proposed because it derived immediately from the 1,2-addition reaction, and it is plausibe that internal reorganization is slow at low temperature.

(20) Dissociation of the tetramer **6** to its corresponding dimer followed by reaction with ketone **2** and recombination to a single product **9** is considered unlikely.

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The amount of *n*-BuLi added at the red end point was noted. The same amount of *n*-BuLi was then added (total amount of *n*-BuLi, 91.58 mmol), and then a solution of cyclopropylacetylene (**5a**) in THF−heptane (45.8 mmol) was added below 0 °C until the red color disappeared. The mixture was aged at 0−5 °C for 30 min to complete the formation of tetramer **6**.

Generation of ^{6}Li-Labeled Tetramer 6 and Observation of the Addition Reaction by ^{6}Li NMR Spectroscopy. The 2:2 tetramer **6** was prepared as described in the general procedure, except that the deprotonation of both ephedrine **4a** and acetylene **5a** was carried out using *n*-Bu^{6}Li (1.4 M in pentane) below −70 °C. Immediately after the addition of acetylene **5a**, the solution was transferred into a 5-mm NMR tube while taking care to maintain low temperature. Low-temperature ^{6}Li NMR spectra were recorded on this solution as described in the general considerations section. The ^{6}Li NMR spectrum at −70 °C was quite complicated (see spectrum in Supporting Information). Upon gradual warming of the solution, growth of 2:2 tetramer peaks at 1.19 and 0.47 ppm was observed in the ^{6}Li NMR spectrum. As soon as the temperature reached to −40 °C, the formation of 2:2 tetramer **6** was complete (concentration, approximately 0.13 M).

Solutions of the 2:2 tetramer **6** solution in THF−hexane were generated according to the general procedure using *n*-Bu^{6}Li in pentane and labeled or nonlabeled norephedrine **4a** and acetylene **5a**. A portion (0.4 mL) of the 2:2 tetramer solution (0.13 M, 0.052 mmol) was transferred into a 5-mm NMR tube and cooled to −100 to −105 °C. A solution of labeled or nonlabeled ketone **2** (0.17 mL, 0.233 M, 0.040 mmol) in THF-d_8 was slowly added with good mixing. NMR spectra were recorded starting at −100 °C (Table 4), as described in the text. Spectra are also included as Supporting Information.

Crystallization of 3:1 Tetramer. To a solution of (*1R,2S*)-*N*-pyrrolydinylnorephedrine (**4a**) (5.0 g, 27.47 mmol) and Ph_3CH (5 mg) in 40 mL of dry THF at −10 °C was added *n*-BuLi (1.6 M, 25.2 mL, 40.18 mmol). The color of the reaction solution became red after the addition of three-fourths of the theoretical amount of *n*-BuLi. Cyclopropylacetylene (a solution either in THF−heptane or neat) was added at −10 to 0 °C until the reaction solution became colorless. The solution was aged at room temperature for 30 min and then concentrated in vacuo to a volume of approximately 10 mL. A portion (15mL) of THF and 70 mL of pentane were added. The concentration of 3:1 tetramer was approximately 0.15 M in approximately 30% THF:70% hydrocarbon. The solution was allowed to stand at room temperature under a nitrogen atmosphere for 6 h, which resulted in the slow growth of the 3:1 tetramer crystals **8**.

Crystallization of 4:2 Hexamer. A solution of the 2:2 tetramer **6** in THF−hexane was generated as in the general procedure starting from 5.0 g (27.47 mmol) norephedrine **4a**. The solution was concentrated in vacuo to a volume of approximately 7 mL, and 60 mL of pentane was added. The concentration of 2:2 tetramer **6** was approximately 0.2 M in approximately 2% THF−hydrocarbon. The solution was allowed to stand at room temperature under a nitrogen atmosphere for several days, which resulted in the slow growth of the 4:2 hexamer crystals **12**.

Supporting Information Available: ^{6}Li NMR spectra for the tetramers in Table 1 and the 3:1 tetramer. ^{6}Li NMR spectra after treatment of the 2:2 tetramer **6** with ketone **2** at −100 °C using ^{15}N-labeled ketone **2** and using ^{15}N-labeled ephedrine **4a**. ^{6}Li NMR spectra at −40 °C (2:1 ratio of **4** and **5** generated in situ and equilibrated at room temperature, hexamer **12** crystals dissolved in THF-d_8, and lithium ephedrate **4**). X-ray structural data for **8** and **12**, including complete atomic coordinates and thermal parameters, bond distances, and angles. This material is available free of charge via the Internet at http:/pubs.acs.org.

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