Solution Structures of the Mixed Aggregates Derived from Lithium Acetylides and a Camphor-Derived Amino Alkoxide

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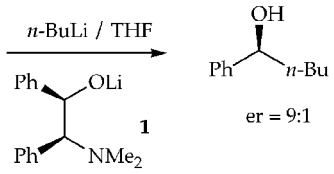
Low-temperature ^{6}Li, ^{13}C, and ^{15}N NMR spectroscopies reveal that mixtures of lithium cyclopropylacetylide or lithium phenylacetylide (RCCLi) and a vicinal amino alkoxide derived from camphor (R*OLi) in THF/pentane afford an asymmetric $(RCCLi)_3(R*OLi)$ mixed tetramer and a C_2-symmetric $(RCCLi)_2(R*OLi)_2$ mixed tetramer depending on the stoichiometries. The corresponding $(RCCLi)(R*OLi)_3$ mixed tetramer is not observed. R*OLi-mediated additions of PhCCLi to benzaldehyde proceed with up to an 8:1 enantiomeric ratio that depend on both the choice of R*OLi and the PhCCLi/R*OLi stoichiometries. The results are considered in light of a previously proposed mechanism for the 1,2-addition to a trifluoromethyl ketone.

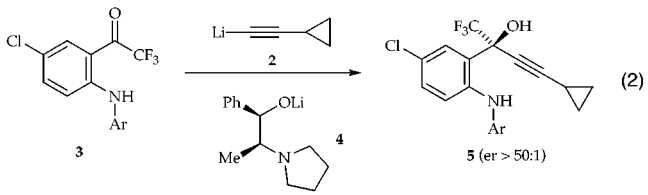
Introduction

In 1994 Jackman and co-workers reported that 1,2-additions of organolithiums to aldehydes could be effected with moderate enantioselectivity by adding vicinal amino alkoxides as chiral additives (eq 1).[1,2] Limited empirical



(1)

tuning afforded the highest selectivities with diphenyl-substituted amino alkoxide **1**.[1,2] The modest enantioselectivities imparted by the stoichiometric additives appeared to render the amino alkoxide-mediated asymmetric additions of only academic interest. Soon thereafter, however, the process groups at Merck Research Laboratories and DuPont Pharmaceuticals began applying this methodology with considerable success to syntheses of nonnucleoside reverse transcriptase inhibitors used to combat HIV-1 infection.[3−5] The enantioselective 1,2-addition of lithium cyclopropylacetylide (LiCPA; **2**) to ketone **3** in the presence of lithium ephedrate **4** (eq 2) has been used in plant-scale syntheses of Efavirenz,[1,6] an important HIV-1 therapeutic agent marketed under the names Stocrin and Sustiva.



(2)

Further studies reinforced the observation that each substrate required a judiciously chosen alkoxide additive (denoted generically as R*OLi) to maximize the enantioselectivity. For example, the Merck group found that the 1,2-addition of pyridyl-substituted lithium acetylide **6** to quinazolinone **7** (eq 3) is substantially more enantioselective using the lithium salt of quinine (**8**) compared to using lithium ephedrate **4**. The DuPont group's extensive efforts to prepare second-generation nonnucleoside reverse transcriptase inhibitors focused on 1,2-additions to quinazolinones such as **10**, in which the unprotected NH group is lithiated under the reaction conditions (eq 4). An extensive survey of more than 50 chiral additives revealed that (+)-carene-derived amino alkoxide **11** is singularly effective at mediating the enantioselective 1,2-addition. None of the alkoxide additives appear to be particularly effective at mediating the enantioselective additions of lithium acetylides to benzaldehyde (see below).

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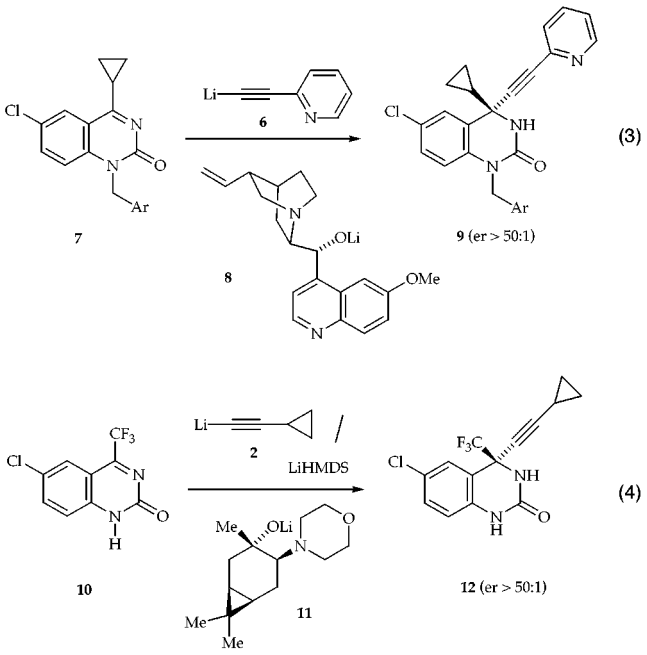
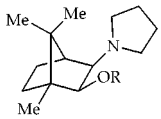


Chemists at Merck, DuPont, and Cornell collaborated to study the structural and mechanistic origins of the high stereocontrol in the amino alkoxide-mediated 1,2-additions.[7,8] We initially focused on a number of idiosyncracies underlying the 1,2-addition in eq 1, including pronounced aggregate aging effects, modest asymmetric amplification, and a high sensitivity to the structures and proportions of the organolithium reagents.[7a] Spectroscopic studies revealed a distribution of stereoisomerically pure 3:1, 2:2, and 1:3 mixed cubic tetramers (analogous to those shown in Scheme 1) in relative concentrations that could be controlled by adjusting the LiCPA/**4** ratios. Subsequent studies of *n*-BuLi/**4** and LiCPA/**11** mixtures examined how the choice of RLi−R*OLi influenced the stoichiometries, stereochemistries, and reactivities of the mixed aggregates.[7b]

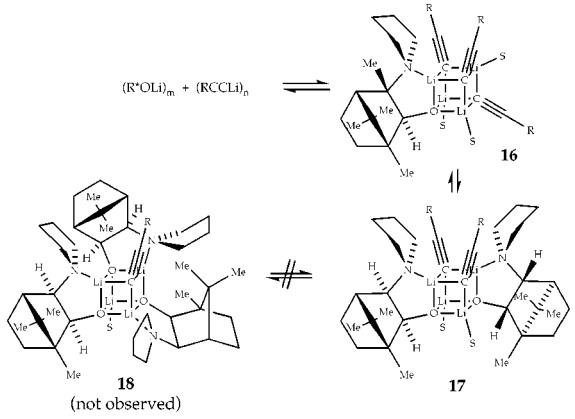


13; R = H
14; R = Li

2; R = cyclopropyl (LiCPA)
15; R = Ph

Camphor-derived amino alkoxide **14** appears to possess the favorable attributes anticipated for highly selective 1,2-additions, especially given the extensive history of camphor's use as an asymmetric scaffold.[9] Nevertheless, we will show that although mixtures of lithium acetylides and alkoxide **14** form mixed aggregates with credible control of stoichiometry and structure, **14** is particularly poor at mediating enantioselective 1,2-additions. The influence of both solvent (THF, Et_2O, and Me_2NEt) and substitution on the acetylide (**2** and **15**) on aggregate structure and reactivity are briefly discussed. The results add to the mounting evidence that control of aggregate structure is necessary, but not sufficient, to control the enantioselectivity of 1,2-additions.[10,11]

Scheme 1



Results

General. Spectroscopic data are summarized in Table 1. Selected spectra are shown in Figures 1−5. Additional spectra are included in Supporting Information. Previous ^{6}Li and ^{13}C NMR spectroscopic studies had shown LiCPA and PhCCLi to be dimer−tetramer mixtures in THF/hydrocarbon solutions (Figure 1A).[7a] Lithium alkoxides [^{6}Li]**14** and [^{6}Li,^{15}N]**14** were prepared in situ by lithiation of alcohols **13** and [^{15}N]**13**[12] using recrystallized lithium hexamethyldisilazide ([^{6}Li]LiHMDS).[13] ^{6}Li and ^{15}N NMR spectra recorded on THF/pentane solutions of **14** revealed a single, highly symmetric structural form (Figure 1B). The structural homogeneity is uncharacteristic of vicinal amino alkoxides.[7a,8,14] Although ^{6}Li−^{15}N coupling confirms coordination by the pyrrolidino group,[15,16] the high symmetry is consistent with a number of possible aggregates.[7a]

THF solutions containing the lithium acetylides and alkoxide **14** were prepared from concentrated stock solutions of [^{6}Li]RCCLi, alcohol **13**, and [^{6}Li]LiHMDS. The combined concentration of RCCLi and **14** was kept constant at 0.10 M unless noted otherwise. The ^{6}Li resonances of the LiHMDS dimer and monomer[17] con-

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

compound	RCCLi	solvent[b]	δ ^{6}Li (mult, J_{Li-C}; mult, J_{Li-N})[c]	δ ^{13}C (mult, J_{C-Li})	δ ^{15}N (mult, J_{N-Li})[d]
2	LiCPA	THF	0.05 (t, 9.2; dimer)	119.8 (q, 9.2)	−
			0.04 (qt, -; tetramer)	114.7 (br m)	−
2	LiCPA	Me_2NEt	0.59 (qt, 6.1; tetramer)	113.7 (br m)	−
15	PhCCLi	THF	0.92 (qt, 6.1; tetramer)	134.5 (br m)	−
			0.41 (t, 8.3; dimer)	140.7 (q, 8.3)	
15	PhCCLi	Me_2NEt	1.24 (qt, 6.1)	130.7 (br m)	−
14	−	THF	1.24 (−; d, 2.8)	−	58.2 (t, 3.0)
14	−	Me_2NEt	1.67 (−; d, 2.8)	−	59.4 (t, 2.8)
16	LiCPA	THF	1.10 (t, 6.0; d, 2.8)	114.9 (br m)	52.1 (t,2.8)
			0.07 (qt, 5.8; s)	115.3 (br m)	
			0.02 (t, 6.0; s)	115.3 (br m)	
			−0.54 (t, 6.3; s)		
16	PhCCLi	THF	1.70 (t, 6.4; d, 3.1)	133.2 (br m)	50.9 (t, 3.1)
			0.74 (qt, 6.0; s)	133.9 (br m)	
			0.66 (t, 5.2; s)	134.2 (br m)	
			0.16 (t, 5.4; s)		
17	LiCPA	THF	1.14 (t, 6.2; d, 3.0)	116.2 (br m)	52.0 (t, 3.0)
			−0.41 (d, 5.0; s)		
17	PhCCLi	THF	1.55 (t, 6.1; d, 3.0)	134.9 (br m)	50.8 (t, 3.0)
			−0.15(d, 4.7; s)		
19	−	Me_2NEt	2.23 (−; d, 3.3; d, 3.7[e])	−	57.5 (t, 3.2)
			0.91 (−; s; d, 3.5[e])		41.0 (m)[f]
20	LiCPA	Me_2NEt	1.60 (d,10.5; d, 3.1[e])	112.5 (qn, 10.5)	43.6 (qn, 3.1)[f]
20	PhCCLi	Me_2NEt	1.78 (d,9.9; d, 3.7[e])	130.8 (qn, 9.9)	44.0 (qn, 3.7)[f]
21	LiCPA	Me_2NEt	2.00 (d,5.9; d, 4.0[e])	112.9 (br m)	45.6 (−[g])[f]
			1.29 (d,7.2; t, 3.4[e])		

[a] The J_{C-Li} coupling constants were routinely measured from the *J*-resolved spectrum. The multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, qt = quartet, q = quintet, br = 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] THF refers to 50% THF/pentane at −115 °C for the LiCPA and 3:1:1 toluene:THF:pentane at −115 °C for PhCCLi. All Me_2NEt solutions are neat at −100 °C. [c] Li−N coupling is do to coupling of the ^{15}N-labeled pyrrolidino group unless marked otherwise. [d] Refers to ^{15}N resonance of pyrrolidino group unless marked otherwise. [e] Coupling from [^{6}Li,^{15}N]LiHMDS. [f] Resonance from [^{6}Li,^{15}N]LiHMDS. [g] Partially obscured by LiHMDS monomer resonance.

firmed that adequate base was added. Samples prepared using [^{6}Li,^{15}N]LiHMDS showed no ^{6}Li−^{15}N coupling diagnostic of N−Li bonds,[15] confirming that the excess LiHMDS does not form mixed aggregates with the other lithium salts in THF.[15a]

Related investigations[7,8] showed that the mixed aggregates derived from vicinal amino alkoxides and lithium acetylides in THF do not readily equilibrate on laboratory time scales at low temperatures. Thus, samples prepared at −78 °C without warming afford primarily the RCCLi and R*OLi homoaggregates (Figure 2A). Warming the samples for several minutes at room temperature prior to low-temperature spectroscopic analysis causes marked changes; additional warming causes no further changes. Accordingly, all samples were aged at room temperature for ≥10 min prior to low temperature spectroscopic analysis. (Samples in the less strongly coordinating[17,18] Me_2NEt and Et_2O required longer aging times; see below). The spectroscopic investigations of RCCLi/R*OLi mixtures are described using LiCPA/**14** by example.

Structures of Mixed Aggregates. Incremental additions of R*OLi **14** to LiCPA reveal sequential formation of 3:1 mixed tetramer **16** and 2:2 mixed tetramer **17** to the exclusion of the 1:3 mixed tetramer **18** (Figure 1C−F).[19] A significant reluctance to form mixed aggregates was indicated by the coexistence of **14** and LiCPA. An appreciable softness of the **16**/**17** equilibrium also was evidenced by the presence of residual **16** at >1:0 equiv of R*OLi. Tetramers **16** and **17** were characterized as follows.

The ^{6}Li NMR spectra recorded on a 3:1 mixture of [^{6}Li]LiCPA/[^{6}Li]**14** in 50% THF/pentane display the pair of ^{6}Li resonances attributed to 2:2 mixed tetramer **17** (see below) along with the four additional ^{6}Li resonances (Figure 1D) anticipated for 3:1 mixed tetramer **16**. The ^{6}Li and ^{13}C NMR spectra recorded on analogous samples containing [^{6}Li,^{13}C]LiCPA[7a] and [^{6}Li]**14** are complex due to severely overlapping multiplets. Fortunately, several two-dimensional NMR spectroscopic methods provided the requisite resolution. ^{1}J(^{6}Li,^{13}C)-resolved spectra[20] (Figure 3) display ^{6}Li−^{13}C coupling (along the orthogonal *y*-axis) consistent with the 3:1 mixed aggregate **16**. The ^{6}Li,^{13}C-heteronuclear multiple quantum correlation (HMQC) spectra[21,22] (Figure 4) show the expected cross-peaks that are consistent with the ^{6}Li-^{13}C connectivities. Although we observed overlap in the ^{13}C resonances of **16**, we noted complete resolution of all resonances in the PhCCLi analogue. ^{6}Li and ^{15}N NMR spectra recorded on solutions of [^{6}Li,^{15}N]**14** and [^{6}Li]LiCPA show ^{6}Li−^{15}N

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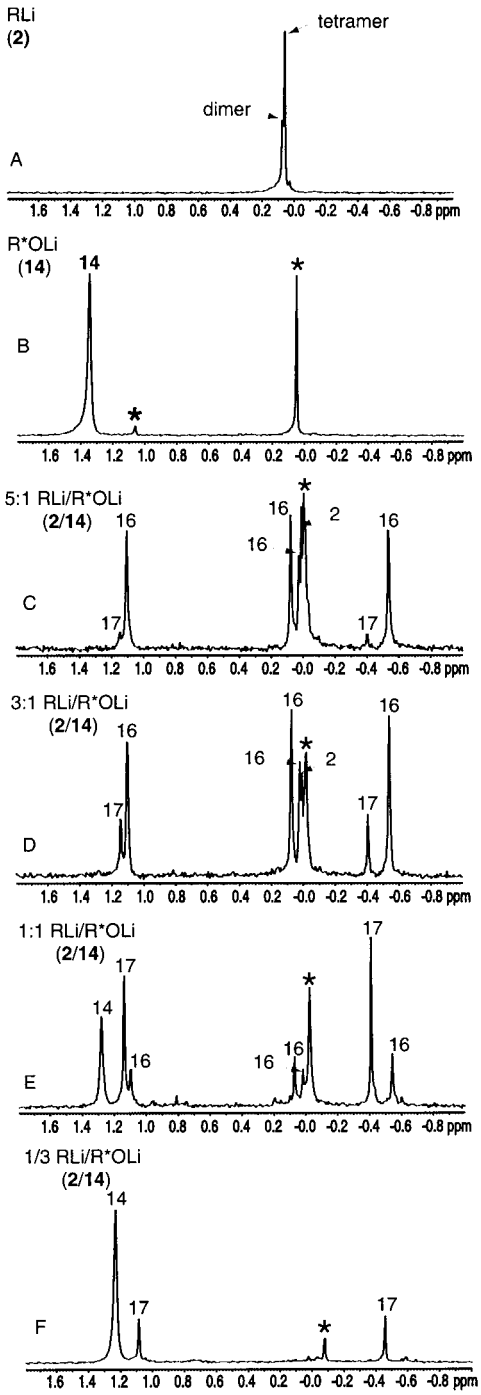

Figure 1. ^{6}Li NMR spectra showing 3:1 RLi/R*OLi (**16**) and 2:2 RLi/R*OLi (**17**) mixed tetramers. Spectra were recorded on mixtures of [^{6}Li]LiCPA (**2**) and [^{6}Li]**14** in 50% THF/pentane at −115 °C. The total titer of **2** and **14** is 0.10 M in the proportions labeled on each spectrum. Residual [^{6}Li]LiHMDS is marked by an asterisk (*).

coupling (Figure 2B and 2C). The ^{6}Li−^{6}Li exchange (EXSY)[23] spectrum recorded at −110 °C (Figure 5) reveals cross-peaks between the three ^{6}Li resonances of **16** assigned as proximate to the oxygen; these peaks are consistent with a rapid 3-fold degenerate exchange of the chelate shown in eq 5. The fourth (remote) ^{6}Li site does not show appreciable exchange.

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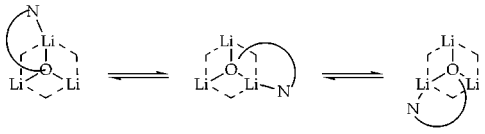
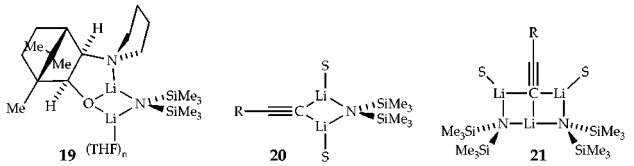


The ^{6}Li NMR spectrum recorded on an aged 1:1 mixture of LiCPA and R*OLi **14** in 50% THF/pentane shows predominantly a pair of resonances at 1.14 and −0.41 ppm in a 1:1 ratio (Figure 1E). Although the 1:1 ratio is consistent with a (LiCPA)(R*OLi) mixed dimer or any of three possible 2:2 $(LiCPA)_2(R^*OLi)_2$ mixed tetramers, further studies were only consistent with mixed tetramer **17** as follows. Spectra recorded on 1:1 mixtures of [^{6}Li,^{13}C]LiCPA/**14** display the ^{6}Li resonance at 1.14 ppm as a triplet (Figure 1D). The coupling to *two* LiCPA terminal carbons is inconsistent with a mixed dimer containing a single LiCPA fragment. The ^{6}Li resonance at −0.41 ppm appears as a doublet due to coupling with one LiCPA terminal carbon. The ^{13}C NMR spectrum displays predominantly a broad multiplet at 116.2 ppm, which is shown by single-frequency decoupling and ^{6}Li,^{13}C−HMQC spectroscopy to be coupled to both ^{6}Li resonances (Figure 4). ^{15}N NMR spectroscopy reveals a ^{15}N resonance coupled to the ^{6}Li resonance at 1.14 ppm previously shown to adjoin *two* LiCPA fragments (Figure 2E and 2F). Among the three possible 2:2 mixed tetramers, isomer **17** is the only isomer containing a pair of symmetry-equivalent ^{6}Li nuclei simultaneously connected to two carbons *and* a pyrrolidine nitrogen.

Substituent and Solvent Effects. We briefly explored how the lithium acetylide substituents and the solvent influence aggregate structure. Many of the results do not depart markedly from the structures described for LiCPA; therefore, the spectra are included as Supporting Information, and the key observations are simply summarized as follows:

(1) Et_2O presents solubility problems. The solution equilibria that can be observed in the heterogeneous systems are complex. Tetrahydropyran (THP) functions interchangeably with THF.

(2) Me_2NEt, a relatively poorly coordinating solvent,[17,18] completely precludes mixed aggregation of lithium alkoxide **14** and LiCPA. Although previous investigations of LiCPA/**11** mixtures have shown that aggregate aging can be remarkably slow in Me_2NEt (requiring up to 24 h at 25 °C), forcing conditions failed to produce any evidence of LiCPA/**14** mixed aggregates. In contrast to the results in THF solution, however, lithium alkoxide **14** and the residual LiHMDS in Me_2Et afford mixed dimer **19**,



readily characterized using [^{6}Li,^{15}N]**14** and [^{6}Li,^{15}N]-LiHMDS (Table 1).[15] Similarly, mixtures of LiCPA and LiHMDS in Me_2NEt afford mixed dimer **20** and ladder **21**. (The ladder rather than the cyclic trimer structure is confirmed by transannular ^{6}Li−^{13}C coupling; Table 1). PhCCLi/LiHMDS mixtures in Me_2NEt affords dimer **20** to the exclusion of ladder **21** (Table 1). The tendency of LiHMDS to form mixed aggregates only in poorly coordinating solvents has been noted previously.[15a]

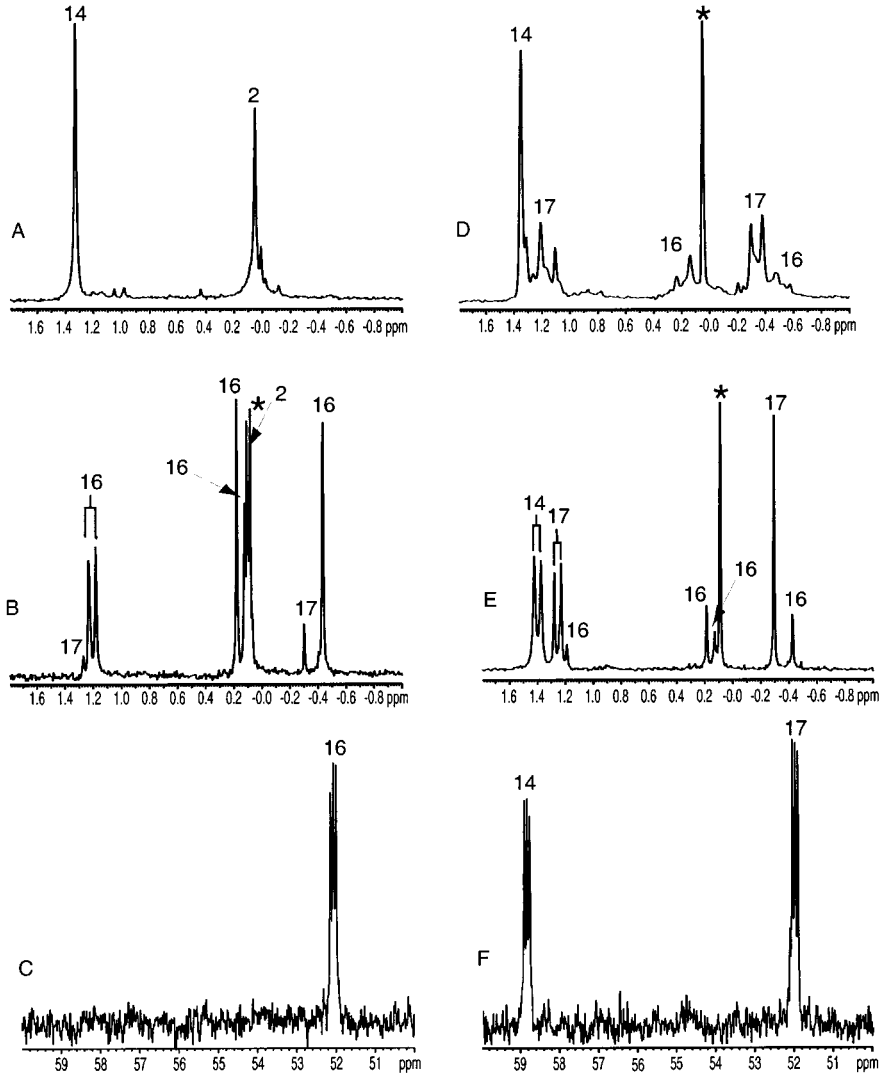


Figure 2. ^{6}Li and ^{15}N NMR spectra recorded at −115 °C of 50% THF/pentane solutions containing residual [^{6}Li]LiHMDS (marked by *) and the following: (A) ^{6}Li spectrum of a 1:1 mixture of [^{6}Li]LiCPA and [^{6}Li]**14** prior to aging; (B) ^{6}Li spectrum of a 5:1 mixture of [^{6}Li]LiCPA and [^{6}Li,^{15}N]**14**; (C) ^{15}N spectrum of a 5:1 mixture of [^{6}Li]LiCPA and [^{6}Li,^{15}N]**14**; (D) ^{6}Li spectrum of a1:1 mixture of [^{6}Li,^{13}C]LiCPA/[^{6}Li]**14**; (E) ^{6}Li spectrum of a 1:1 mixture of [^{6}Li]LiCPA and [^{6}Li,^{15}N]**14**; (F) ^{15}N spectrum of a 1:1 mixture of [^{6}Li]LiCPA and [^{6}Li,^{15}N]**14**.

(3) Mixtures of lithium *tert*-butylacetylide and **14** afford 3:1 and 2:2 mixed aggregates in complete analogy to LiCPA. Although this result may appear to have been a foregone conclusion given the remoteness of the substituent, significant differences in lithium acetylide reactivities were noted in the 1,2-addition to ketone **3**.[4]

(4) In the case of the PhCCLi/**14** mixed aggregates, we noticed a softness in the **16**/**17** equilibrium. In THF/pentane, 2:2 mixed tetramer **17** coexisted with considerable concentrations of free PhCCLi. In 3:1:1 toluene/THF/pentane, the 3:1 mixed tetramer **16** was measurably more prominent. The origin of this hydrocarbon effect is unclear.

Enantioselective 1,2-Additions. To understand how aggregate structure correlates with reactivity, we investigated the 1,2-addition of PhCCLi to PhCHO. Figure 6 depicts the enantioselectivities as a function of the R*OLi/PhCCLi ratio in THF at −78 °C. A 2-fold excess of PhCCLi relative to PhCHO was maintained at all R*OLi/PhCCLi stoichiometries. Results from analogous PhCCLi/**4** and PhCCLi/**11** mixtures are included for comparison. Reduced percent conversions were observed at the elevated R*OLi concentrations (chronically so for the PhCCLi/**14** mixtures). ReactIR spectroscopy revealed that this was due to reversible formation of the R*OCH(OLi)-Ph 1,2-adduct[24] rather than a lowered reactivity of the mixed aggregates.

Discussion

Mixtures of lithium acetylides (RCCLi; **2** or **15**) and a (+)-3-camphor-derived amino alkoxide (R*OLi; **14**) in THF afford 3:1 and 2:2 mixed aggregates **16** and **17** in relative concentrations that depend on the RCCLi/R*OLi proportions. At low R*OLi concentrations, 3:1 mixed tetramer **16** is the predominant mixed aggregate. At high R*OLi concentrations, the C_2-symmetric 2:2 mixed tetramer **17** is observed to the exclusion (<10%) of other possible stereoisomers. Although previous studies of organolithium alkoxide mixtures have revealed structural analogues of **16** and **17**,[7,8] this particular RCCLi/R*OLi combination differs somewhat. The corresponding

(24) Reynolds, K. A.; Finn, M. G. *J. Org. Chem.* **1997**, *62*, 2574.

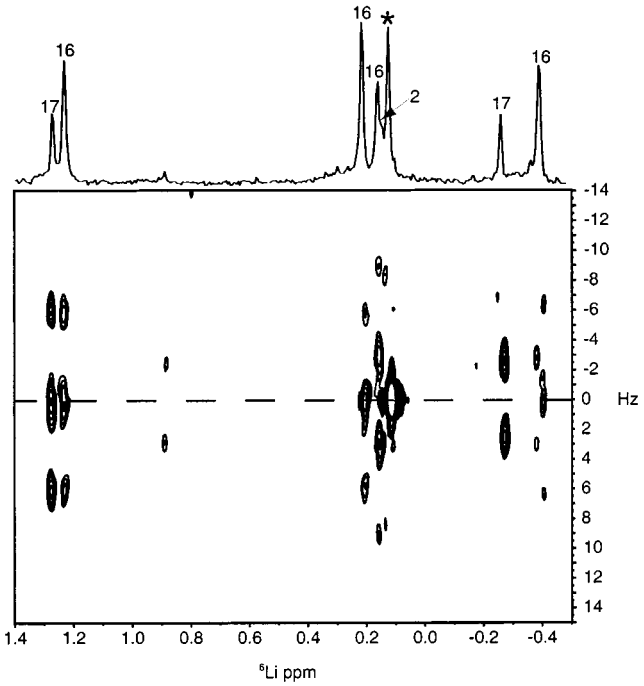


Figure 3. $^1J(^6\text{Li},^{13}\text{C})$-resolved spectrum of a 3:1 mixture of [^{6}Li,^{13}C]LiCPA (0.2 M) and [^{6}Li]**14** (0.2 M) in 50% THF/pentane at −115 °C showing mixed tetramers **16** and **17**. LiHMDS is indicated by an asterisk (*).

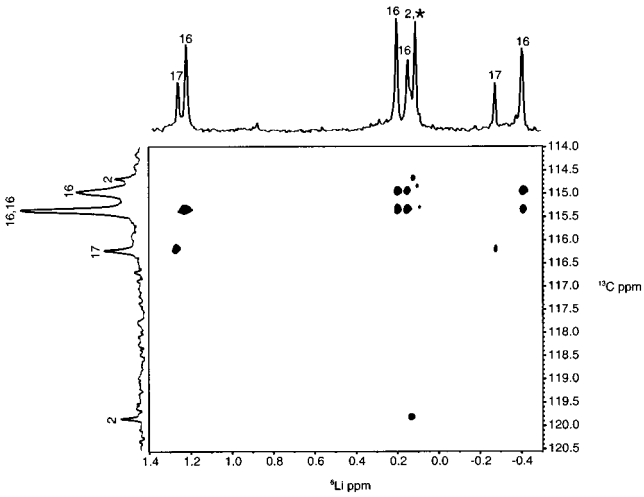


Figure 4. ^{6}Li,^{13}C-HMQC spectrum recorded on a 3:1 mixture of [^{6}Li,^{13}C]LiCPA (0.2 M) and [^{6}Li]**14** (0.2 M) in 50% THF/pentane at −115 °C showing mixed tetramers **16** and **17**. LiHMDS is indicated by an asterisk (*).

1:3 mixed tetramer **18** is conspicuously absent. A similar lack of 1:3 mixed aggregate was noted for *n*-BuLi/**15** mixtures, and simple (nonchelating) alkyllithiums and lithium alkoxides resist forming the $(RLi)(ROLi)_3$ mixed tetramers.[25] Other RCCLi−R*OLi combinations, however, display a strong tendency to form C_3-symmetric tetramers analogous to **18**.[7,8] We also noted a "softness" in the mixed aggregation. Equimolar solutions of RCCLi and R*OLi contain low concentrations of both homo-

(25) For leading references to structural studies of RLi/R′OLi mixed aggregates, see: Thomas, R. D.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 1, 11239. Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, 1115. Sorger, K.; Schleyer, P. v. R.; Fleischer, R.; Stalke, D. *J. Am. Chem. Soc.* **1996**, *118*, 6924.

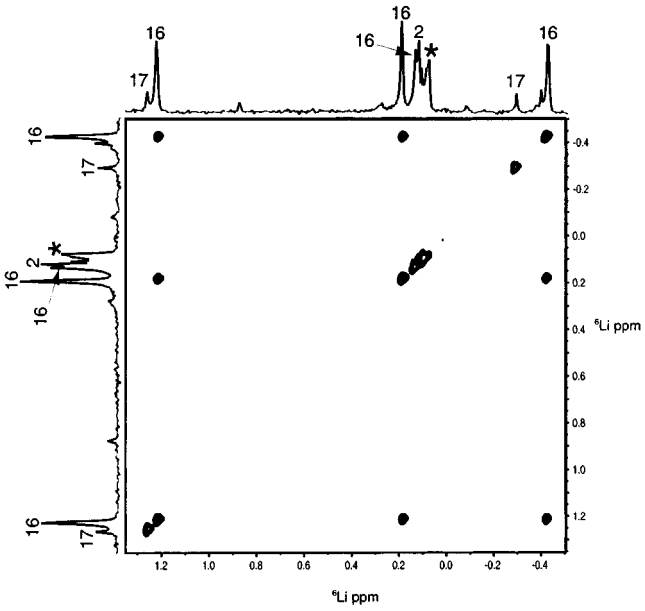


Figure 5. ^{6}Li,^{6}Li-exchange (EXSY) spectrum (τ = 3.0 s) recorded on a 3:1 mixture of [^{6}Li]LiCPA (0.5 M) and [^{6}Li]**14** (0.5 M) in 50% THF/pentane at −110 °C showing mixed tetramers **16** and **17**. LiHMDS is indicated by an asterisk (*).

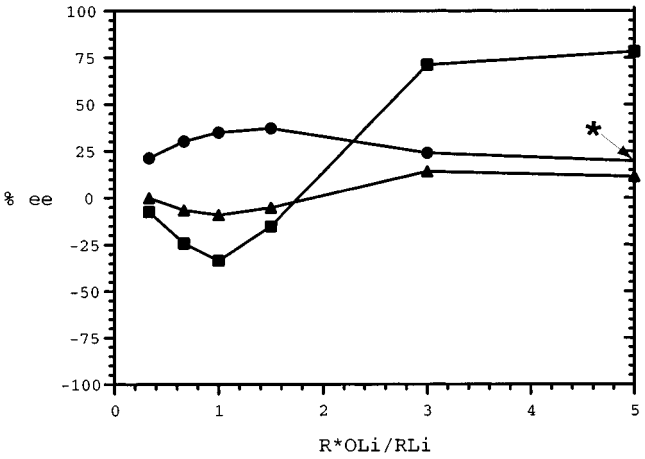


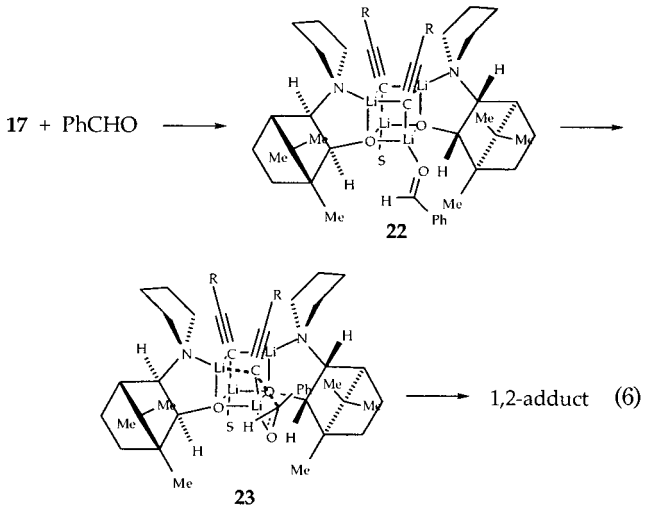
Figure 6. Enantioselectivities for the 1,2-addition of PhCCLi to PhCHO (eq 7) as a function of R*OLi equiv at −78 °C in THF. (R*OLi: ● = **14**; ▲ = **11**; ■ = **4**). *Measured at −40 °C.

aggregates, suggesting a incomplete mixed aggregation. Moreover, measurable concentrations of 3:1 mixed aggregate **16** persist unless a significant R*OLi excess is present. The reluctance of this amino alkoxide to form mixed tetramers was underscored by investigations of RCCLi/R*OLi mixtures in Me_2NEt that showed no mixed aggregation.

We believe that the spectroscopic studies point to severe steric demands of amino alkoxide **14**. The ^{1}H NMR spectra of amino alcohol **13** show temperature-dependent broadening near ambient temperatures, consistent with restricted rotation about the pyrrolidino moiety. The ^{6}Li NMR spectrum of **14** shows a single aggregate in solution. Although the structure of the R*OLi homoaggregate cannot be determined (beyond the existence of an internal chelate), the structural homogeneity is unique among a number of seemingly related amino alkoxides.[7,8,14] We suspect that the putative steric congestion in **14** might force the formation of a dimer rather than allow a range

of higher oligomers to coexist. The steric effects of this camphor-derived fragment within the mixed aggregates would be interesting to probe using semiempirical computational methods given the successes obtained with the mixed aggregates derived from lithium ephedrate **4**.[7a] However, the RLi−R*OLi mixed aggregates derived from **14** proved to be beyond the limits of the sterically sensitive[26] computational methods.

It may be instructive to evaluate how these steric demands influence reactivity. We had previously posited a mechanism for the highly enantioselective addition of LiCPA to ketone **3**.[7a] The C_2-symmetric cleft of the 2:2 mixed tetramer seemed especially rational and was surprisingly well supported by computations and a number of key experimental observations. The mechanism is reiterated using the camphor-derived mixed tetramer **17** and PhCHO as shown in eq 6. Let us suppose



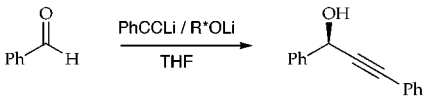
(6)

for the sake of discussion that the camphor-derived fragments in mixed tetramer **17** and precomplex **22** are indeed very sterically demanding. Because **17** is essentially the only observable mixed tetramer at elevated R*OLi concentrations, it stands to reason that the 1,2-addition to the coordinated PhCHO would be especially selective when compared to sterically less demanding R*OLi derivatives. A quick inspection of the enantioselectivities obtained for the addition of PhCCLi to PhCHO reveals a gap in our reasoning, however.

The results may have failed expectations for three reasons:

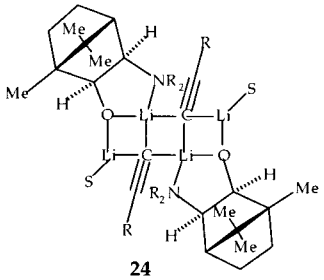
(1) The model depicted in eq 6 may be fundamentally incorrect. This is obviously an important possibility. The self-consistency of such a mechanism with previously reported experimental and theoretical data[7a] combined with the logic backing the notion that high selectivities emanate from the C_2 symmetry of the 2:2 mixed tetramers seems compelling. Nonetheless, detailed rate studies have not yet been used to eliminate mixed dimer-based models. We hope to pursue these studies shortly.

(2) The model depicted in eq 6 may be correct, but the selectivity could, at least in principle, be eroded by significant changes in aggregate structure as the RCCLi is consumed and the 1,2-adduct is formed. Interestingly, we found that the 1,2-addition in eq 2 proceeds faster than the aggregates exchange, precluding dependencies on percent conversion. In the case of *n*-BuLi additions to PhCHO in eq 1, aggregate equilibrations appeared to be much faster, yet the equilibration of the mixed aggregates regenerated the C_2-symmetric mixed tetramers. Again, no dependence on percent conversion was noted. Most important, the **14**-mediated 1,2-addition of PhCCLi to PhCHO with varying equiv of RCCLi reveals that the selectivities in eq 7 do not change significantly with percent conversion.



(6)

(3) The putative 2:2 mixed tetramer may be ladder **24**[27] rather than cubic tetramer **17**. The spectroscopically opaque Li−O linkages make **17** and **24** indistinguishable (at least by our spectroscopic methods). In previous investigations we considered this possibility and largely dismissed such a structural model because the 1:3 and 3:1 mixed tetramers (analogous to **16** and **18**) are readily shown to be cubic. However, the differences displayed by **14** when compared with other amino alkoxides (especially the reluctance to form the 1:3 mixed tetramer) leave us less convinced that 2:2 mixed ladder **24** is necessarily unlikely. Nonetheless, it is unclear how ladder **24** offers significant relief from the steric demands of the camphor fragment.



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In summary, we observed reasonable control of stoichiometry and stereochemistry of mixed aggregates derived from lithium acetylides with (+)-3-camphor-derived amino alkoxide **15**. Nonetheless, the 1,2-additions of the lithium acetylides to PhCHO are poorly selective. If one considers the selectivities described by eqs 1−4 and 7 in total, one finds a compellingly complex picture in which each substrate appears to demand a particular chiral additive to attain optimum selectivity. We still do not see a clear pattern emerging, although work is in progress.

Experimental Section

Reagents and Solvents. THF, Et_2O, Me_2NEt, and all hydrocarbons used for the spectroscopic studies were vacuum-transferred from degassed blue or purple stills containing sodium benzophenone ketyl. The hydrocarbon stills contained 1% tetraglyme to dissolve the ketyl. Air- and moisture-sensitive materials were manipulated using vacuum line and syringe techniques. Amino alcohols **13** and [^{15}N]**13** were prepared using a literature procedure.[12] [^{6}Li]LiCPA and

(26) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166 and references therein.

(27) Leading reference to organolithium ladders: Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47. Mulvey, R. E. *Chem. Soc. Rev.* **1991,** *20*, 167. Beswick, M. A.; Wright, D. S. In *Comprehensive Organometallic Chemistry II*; Abels, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 1, Chapter 1. Mulvey, R. E. *Chem. Soc. Rev.* **1998**, *27*, 339.

[^{6}Li,^{13}C]LiCPA were prepared by lithiation of cyclopropylacetylene and [^{13}C-2]cyclopropylacetylene[28] using [^{6}Li]*n*-BuLi (unrecrystallized)[29] and isolated as a white solid as described previously.[7a] Lithium alkoxide **14** was generated in situ from **14** and LiHMDS. [^{6}Li]LiHMDS and [^{6}Li,^{15}N]LiHMDS were isolated as crystalline solids.[13]

NMR Spectroscopic Analyses. All NMR tubes were prepared using stock solutions and sealed under vacuum. [^{6}Li]LiHMDS and [^{6}Li,^{15}N]LiHMDS were kept in slight excess at all times to scavenge the cyclopropylacetylene and amino alcohol **14**. Spectra were recorded using methods described previously.[30] ^{6}Li,^{6}Li-EXSY[23] and Li,^{13}C-HMQC spectroscopy[21] are well-established methods. The ^1J(^{6}Li,^{13}C)-resolved spectroscopy has also been reported, but is relatively untested.[20a] The ^1J(^{6}Li,^{13}C)-resolved spectra were recorded using existing protocols with some modification.[20b] The ^{6}Li was observed, and the ^{13}C pulses employed a separate Rf-channel. The first decoupling[20b] was replaced by a 180° pulse on ^{6}Li. The phases of the two 180° pulses were the same. Due to this specific implementation, the splittings in the ^1J(^{6}Li,^{13}C)-resolved spectra are identical to those in the standard ^{6}Li spectra instead of $^1/_2J$ as described. The pulse sequence for the ^{6}Li,^{6}Li-EXSY was implemented in states mode to obtain pure absorption spectra. To determine the exchange rates quantitatively, exchange spectra were taken at several different mixing times (τ_m) ranging from 0.5 to 4.0 s, consecutively. The EXSY cross-peak volumes were measured as the intensity by using the NMRPipe software.

1,2-Additions to Benzaldehyde. General Procedure. To a series of 10 mL vessels containing 0.1 M solution of PhCCLi in THF (0.5 mL) was added varying quantities of a 0.5 M R*OLi solution in THF. Additional THF was added to bring the final lithium acetylide concentration to 0.05 M and a total volume of 1.0 mL. Reactions were stirred for ≥30 min at 25 °C to allow complete aggregate equilibration. The vessels were cooled to −78 °C and charged with 0.5 M solutions of benzaldehyde in THF (50 μL). After 15 min the reactions were quenched with 3 mL of a 5% H_2O in THF and further diluted to 10 mL with 50% MeOH/CH_3CN. The enantioselectivities were determined by HPLC analysis on a Chiralpak AD-RH (Daicel) with UV detection at 245 nm. The absolute configurations were determined by comparing the optical rotations of isolated samples with literature values.[31] The enantioselectivities for the PhCCLi/**14** mixtures were measured at a 3-fold relative dilution due to decreased solubilities at high **14** concentrations. The data are displayed in Figure 6.

Acknowledgment. We wish to thank the National Institutes of Health and DuPont Pharmaceuticals for direct support of this work as well as DuPont Pharmaceuticals, Merck Research Laboratories, 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: NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) [2-^{13}C]cyclopropylacetylene used to prepare lithium acetylide [2-^{13}C]**2** was synthesized from cyclopropane carboxaldehyde and [^{13}C]CBr_4 by a literature procedure: Baldwin, J. E.; Villarica, K. A. *J. Org. Chem.* **1995**, *60*, 186. Also, see ref 7.

(29) Kottke, T.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 580. Rennels, R. A.; Maliakal, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 421.

(30) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575.

(31) Ramos Tombo, G. M.; Didier, E.; Loubinoux, B. *Synlett.* **1990**, 547.