

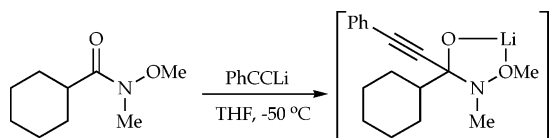
## Mechanism of Acylation of Lithium Phenylacetylide with a Weinreb Amide

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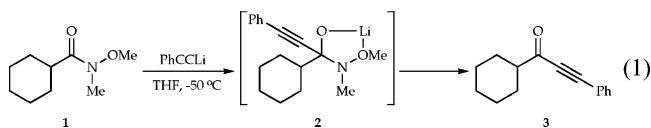
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Additions of lithium phenylacetylide to a Weinreb amide are described. Dimeric lithium acetylide reacts via a monosolvated monomer-based transition structure. The robust tetrahedral intermediate forms sequentially a C<sub>1</sub> 2:2 mixed tetramer with the excess lithium acetylide and a 1:3 (alkoxide-rich) mixed tetramer. The stabilities of the mixed tetramers are consistent with a pronounced autoinhibition.

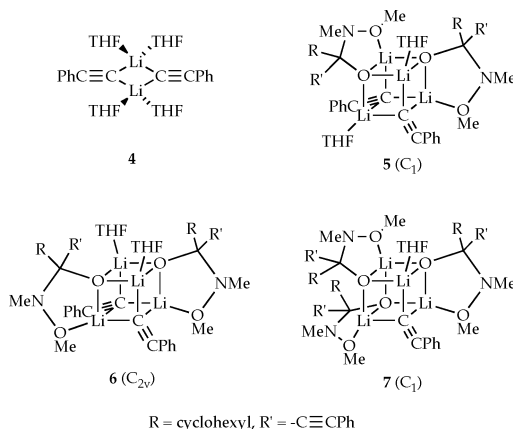
Acylation of organolithiums and organomagnesium reagents to form ketones is of central importance in organic synthesis.<sup>1</sup> Among the many acylating reagents, the so-called Weinreb amides (**1**) have moved to center stage.<sup>2</sup> Although it seems likely that the methoxy moiety facilitates the nucleophilic attack both inductively and through chelation, the mechanism of acylation is largely unknown. Suggestions that putative tetrahedral intermediate (**2**) are supported by limited indirect evidence.<sup>1,3</sup> We show herein that the acylation in eq 1 proceeds via a

monomer-based mechanism. A pronounced autoinhibition is traced to a mixed tetramer composed of intermediate **2** with lithium phenylacetylide (PhCCLi).<sup>4</sup>



Monitoring the addition of PhCCLi to Weinreb amide **1** using in situ IR spectroscopy<sup>5</sup> provides qualitative insights. Amide **1**<sup>6</sup> does not appreciably complex PhCCLi in all THF/pentane mixtures studied, as evidenced by the absence of a shift in the carbonyl absorbance. Reaction of 1.0 equiv of PhCCLi with **1** at -50 °C stalls at 50% conversion. The absence of a new carbonyl absorbance is consistent with a stable tetrahedral intermediate. Warming to 20 °C results in the slow consumption of the starting carboxamide. In contrast,  $\geq 2.0$  equiv of PhCCLi in 3.0 M THF/pentane causes complete consumption of **1** at -50 °C within 1.0 h, affording ketone **3** in 90–95% yield. Under no conditions is ketone **3** (1671 cm<sup>-1</sup>) detectable in the IR spectrum before quenching, nor is the tertiary alcohol resulting from double addition detected after quenching.

The source of the apparent autoinhibition was ascertained using <sup>6</sup>Li and <sup>13</sup>C NMR spectroscopy. Broadband-decoupled <sup>6</sup>Li NMR spectra recorded on mixtures of **1** and excess [<sup>6</sup>Li,<sup>13</sup>C]-PhCCLi<sup>7</sup> reveal the resonances corresponding to dimeric [<sup>6</sup>Li,<sup>13</sup>C]PhCCLi<sup>7,8</sup> (**4**) along with four new resonances in a 1:1:1:1 ratio (Figure 1). <sup>13</sup>C NMR spectra reveal the resonance of **4** along with two new complex multiplets (1:1) corresponding to the labeled C<sub>1</sub> of the PhCCLi fragments. Deconvolution of the complex <sup>6</sup>Li-<sup>13</sup>C coupling using <sup>1</sup>J(<sup>6</sup>Li,<sup>13</sup>C)-resolved NMR spectroscopy<sup>8</sup> (Figure 1) aided by single-frequency decouplings revealed Li–C connectivities consistent with the 2:2 mixed tetramer **5** with C<sub>1</sub> symmetry (Supporting Information).



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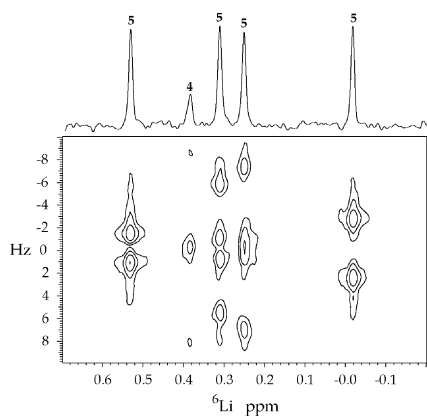
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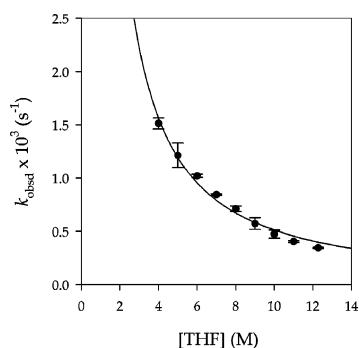
(6) The absorbance of **1** is solvent dependent in the absence of lithium salts, varying from 1681 cm<sup>-1</sup> in neat pentane to 1663 cm<sup>-1</sup> in neat THF.

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**FIGURE 1.**  $J(^6\text{Li},^{13}\text{C})$ -resolved NMR spectrum recorded on 0.05 M  $[^6\text{Li},^{13}\text{C}]\text{PhCClLi}$  and 0.05 M **1** in 9.60 M THF/pentane at  $-110^\circ\text{C}$  after warming to  $-40^\circ\text{C}$ .



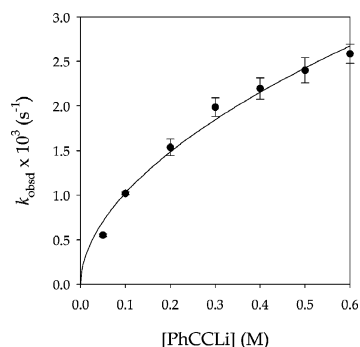
**FIGURE 2.** Plot of  $k_{\text{obsd}}$  vs  $[\text{THF}]$  for acylation of  $\text{PhCClLi}$  (0.10 M) with **1** (0.005 M) in pentane cosolvent at  $-50^\circ\text{C}$ . The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = a[\text{THF}]^n$  [ $a = (8.5 \pm 0.9) \times 10^{-3}$ ,  $n = -1.22 \pm 0.06$ ].

Although we were somewhat surprised that the  $C_{2v}$  isomer (**6**) was not formed, both the  $C_1$  and the  $C_{2v}$  isomers have been observed for structurally similar lithium acetylide-lithium amino alkoxide mixed aggregates.<sup>8,9</sup> Failure to resolve diastereomers resulting from the stereogenic centers within the chelates is not surprising. Further warming to  $0^\circ\text{C}$  converted 2:2 mixed tetramer **5** into a new species displaying three  $^6\text{Li}$  doublets and a singlet (1:1:1:1), consistent with mixed tetramer **7**.

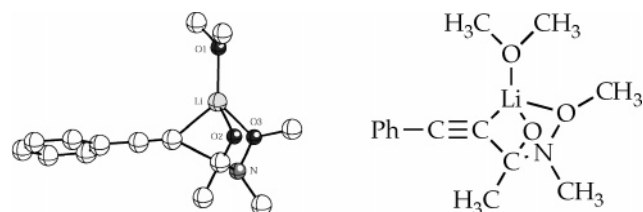
Rate studies were carried out under pseudo-first-order conditions using Weinreb amide **1** at low (0.005 M) concentrations. The  $\text{PhCClLi}$  and THF were maintained at high, yet adjustable, concentrations with pentane as the cosolvent.  $\text{PhCClLi}$  is dimeric under all conditions used.<sup>7,8</sup> The loss of **1** was monitored using in situ IR spectroscopy. An *inverse*-first-order THF dependence

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**FIGURE 3.** Plot of  $k_{\text{obsd}}$  vs  $[\text{PhCClLi}]$  for acylation of  $\text{PhCClLi}$  with **1** (0.005 M) in 6.0 M THF and pentane cosolvent at  $-50^\circ\text{C}$ . The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = a[\text{PhCClLi}]^b$  [ $a = (3.5 \pm 0.2) \times 10^{-3}$ ,  $b = 0.53 \pm 0.04$ ].



**FIGURE 4.**  $[(\text{CH}_3\text{C}(=\text{O})\text{NMe}(\text{OMe})(\text{PhCClLi})(\text{Me}_2\text{O}))^\ddagger]$  calculated with density functional theory (B3LYP method and 6-31G\* basis set).  $\Delta G^\ddagger = 28$  kcal/mol from  $(\text{PhCClLi})_2(\text{Me}_2\text{O})_4$  as the reference state.

and half-order  $\text{PhCClLi}$  dependence (Figures 2 and 3) afford the idealized rate law in eq 2, consistent with a monosolvated monomer-based transition structure,  $[(\text{PhCClLi})(\text{THF})(\mathbf{1})]^\ddagger$ . Density functional theory computations (B3LYP method and 6-31G\* basis set)<sup>10</sup> using a simplified model system afforded a transition structure akin to that proposed by Weinreb with an  $\eta^3$ -coordinated substrate (Figure 4). The mechanism of additions deriving from the mixed-aggregates is unknown.

$$-d[\mathbf{1}]/dt = k[\text{PhCClLi}_{\text{total}}]^{1/2}[\text{THF}]^{-1}[\mathbf{1}]^1 \quad (2)$$

Autoinhibition due to highly stabilized mixed aggregates appears to be prevalent,<sup>4</sup> which explains why so many organolithium reactions require excess organolithium reagent. Conversely, mixed aggregation might also stabilize tetrahedral intermediate **2**, precluding formation of tertiary alcohol resulting from double addition. We close with a caveat: The results described above may be general—we suspect that they are—but they currently apply to a single substrate—organolithium—solvent combination: Structural and mechanistic diversity are the norm within organolithium chemistry.

## Experimental Section

**NMR Spectroscopic Analyses.**  $[^6\text{Li}]\text{PhCClLi}$  and  $[^6\text{Li},^{13}\text{C}]\text{PhCClLi}$  were prepared and recrystallized in pentane using recrystallized  $[^6\text{Li}]\text{LiHMDS}$ <sup>11</sup> and commercially available phenylacetylene and  $[^{13}\text{C}-1]$ phenylacetylene. All samples were prepared under helium using stock solutions, sealed under partial vacuum, and stored in a liquid nitrogen bath prior to analysis. Standard  $^6\text{Li}$  and  $^{13}\text{C}$  NMR spectra were recorded on a 500 MHz spectrometer at 73.7 and 125.0 Hz, respectively. The  $^6\text{Li}$  resonances were referenced to 0.3 M  $[^6\text{Li}]\text{LiCl}/\text{MeOH}$  at  $-90^\circ\text{C}$  (0.0 ppm). The spectra were

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recorded with a three-channel probe designed to accommodate lithium and carbon pulses. The tube was transferred from the liquid nitrogen bath to a  $-78\text{ }^{\circ}\text{C}$  bath to thaw the solution and then was quickly transferred into the spectrometer and shimmed off the proton spectrum.

**IR Spectroscopy.** IR spectra were recorded using an in situ IR spectrometer fitted with a 30-bounce silicon-tipped probe.<sup>5</sup> The IR probe was inserted through a nylon adapter and FETFE O-ring seal into a cylindrical flask fitted with a magnetic stir bar and T-joint. The T-joint was fitted with a nitrogen line and septum for injections. The flask was heated under full-vacuum and flushed twice with nitrogen. PhCCLi was weighted in a glovebox and dissolved in THF before syringe-transferred to the IR vessel. Pentane was added to the vessel to make the total volume 10 mL. The solution was cooled to  $-50\text{ }^{\circ}\text{C}$  in a thermostated bath for 25 min. A background spectrum was recorded, followed by addition of 0.05 mL of a 1.0 M stock solution of **1** while stirring. Spectra were recorded every

30 s for 5 half-lives. The rates of acylation of lithium phenylacetylide with Weinreb amide **1** were monitored by following the loss of **1**. The disappearance of the amide **1** was fit to the equation  $y = ae^{bx} + c$ . Term  $c$  is a measure of the absorbance remaining at  $t = \infty$ , which is typically a positive number at  $\leq 5\%$  of  $a$ .

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**Supporting Information Available:** NMR and IR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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