

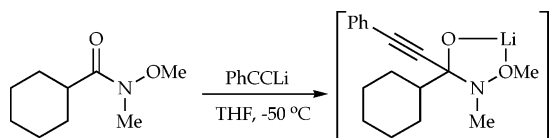
Mechanism of Acylation of Lithium Phenylacetylide with a Weinreb Amide

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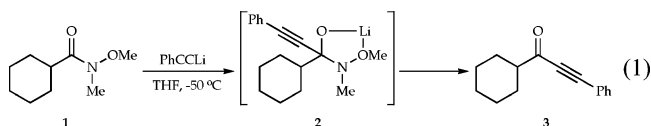
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Additions of lithium phenylacetylide to a Weinreb amide are described. Dimeric lithium acetylide reacts via a monosolvated monomer-based transition structure. The robust tetrahedral intermediate forms sequentially a C₁ 2:2 mixed tetramer with the excess lithium acetylide and a 1:3 (alkoxide-rich) mixed tetramer. The stabilities of the mixed tetramers are consistent with a pronounced autoinhibition.

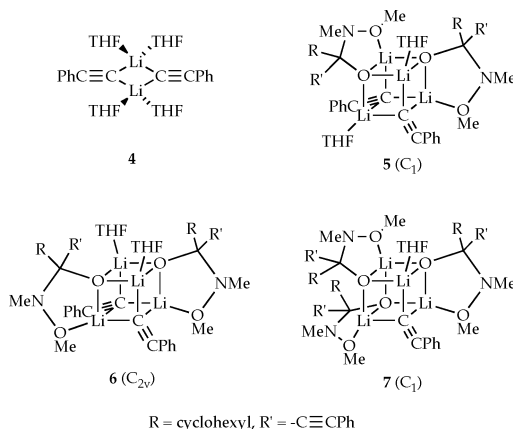
Acylation of organolithiums and organomagnesium reagents to form ketones is of central importance in organic synthesis.¹ Among the many acylating reagents, the so-called Weinreb amides (**1**) have moved to center stage.² Although it seems likely that the methoxy moiety facilitates the nucleophilic attack both inductively and through chelation, the mechanism of acylation is largely unknown. Suggestions that putative tetrahedral intermediate (**2**) are supported by limited indirect evidence.^{1,3} 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).⁴



Monitoring the addition of PhCCLi to Weinreb amide **1** using in situ IR spectroscopy⁵ provides qualitative insights. Amide **1**⁶ 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, ≥ 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⁻¹) 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 ⁶Li and ¹³C NMR spectroscopy. Broadband-decoupled ⁶Li NMR spectra recorded on mixtures of **1** and excess [⁶Li,¹³C]-PhCCLi⁷ reveal the resonances corresponding to dimeric [⁶Li,¹³C]PhCCLi^{7,8} (**4**) along with four new resonances in a 1:1:1:1 ratio (Figure 1). ¹³C NMR spectra reveal the resonance of **4** along with two new complex multiplets (1:1) corresponding to the labeled C₁ of the PhCCLi fragments. Deconvolution of the complex ⁶Li-¹³C coupling using ¹J(⁶Li,¹³C)-resolved NMR spectroscopy⁸ (Figure 1) aided by single-frequency decouplings revealed Li–C connectivities consistent with the 2:2 mixed tetramer **5** with C₁ symmetry (Supporting Information).



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

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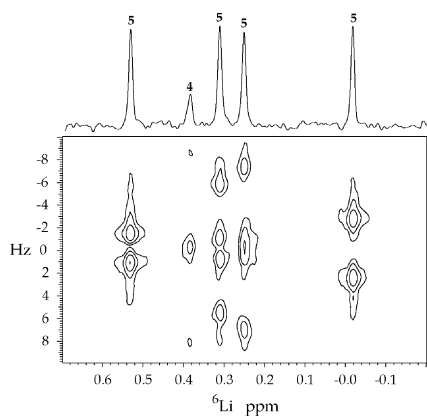


FIGURE 1. $J(^6\text{Li}, ^{13}\text{C})$ -resolved NMR spectrum recorded on 0.05 M $[^6\text{Li}, ^{13}\text{C}]\text{PhCClLi}$ and 0.05 M **1** in 9.60 M THF/pentane at -110°C after warming to -40°C .

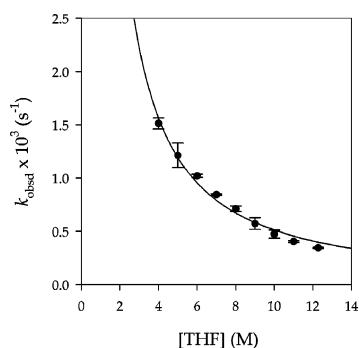


FIGURE 2. Plot of k_{obsd} vs $[\text{THF}]$ for acylation of PhCClLi (0.10 M) with **1** (0.005 M) in pentane cosolvent at -50°C . The curve depicts an unweighted least-squares fit to $k_{\text{obsd}} = a[\text{THF}]^n$ [$a = (8.5 \pm 0.9) \times 10^{-3}$, $n = -1.22 \pm 0.06$].

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.^{8,9} Failure to resolve diastereomers resulting from the stereogenic centers within the chelates is not surprising. Further warming to 0°C converted 2:2 mixed tetramer **5** into a new species displaying three ^6Li 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 PhCClLi and THF were maintained at high, yet adjustable, concentrations with pentane as the cosolvent. PhCClLi is dimeric under all conditions used.^{7,8} The loss of **1** was monitored using in situ IR spectroscopy. An *inverse*-first-order THF dependence

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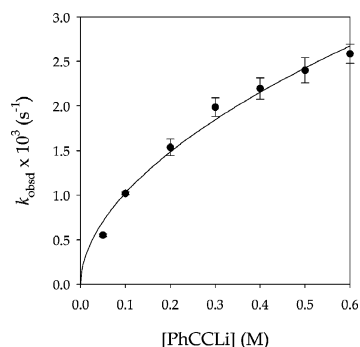


FIGURE 3. Plot of k_{obsd} vs $[\text{PhCClLi}]$ for acylation of PhCClLi with **1** (0.005 M) in 6.0 M THF and pentane cosolvent at -50°C . The curve depicts an unweighted least-squares fit to $k_{\text{obsd}} = a[\text{PhCClLi}]^b$ [$a = (3.5 \pm 0.2) \times 10^{-3}$, $b = 0.53 \pm 0.04$].

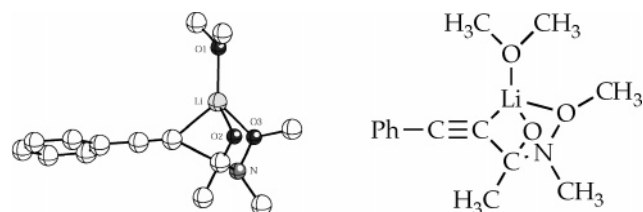


FIGURE 4. $[(\text{CH}_3\text{C}(=\text{O})\text{NMe}(\text{OMe})(\text{PhCClLi})(\text{Me}_2\text{O}))^\ddagger]$ calculated with density functional theory (B3LYP method and 6-31G* basis set). $\Delta G^\ddagger = 28$ kcal/mol from $(\text{PhCClLi})_2(\text{Me}_2\text{O})_4$ as the reference state.

and half-order 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)¹⁰ using a simplified model system afforded a transition structure akin to that proposed by Weinreb with an η^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,⁴ 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 $[^6\text{Li}]\text{LiHMDS}$ ¹¹ 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 ^6Li and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer at 73.7 and 125.0 Hz, respectively. The ^6Li resonances were referenced to 0.3 M $[^6\text{Li}]\text{LiCl}/\text{MeOH}$ at -90°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.⁵ 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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