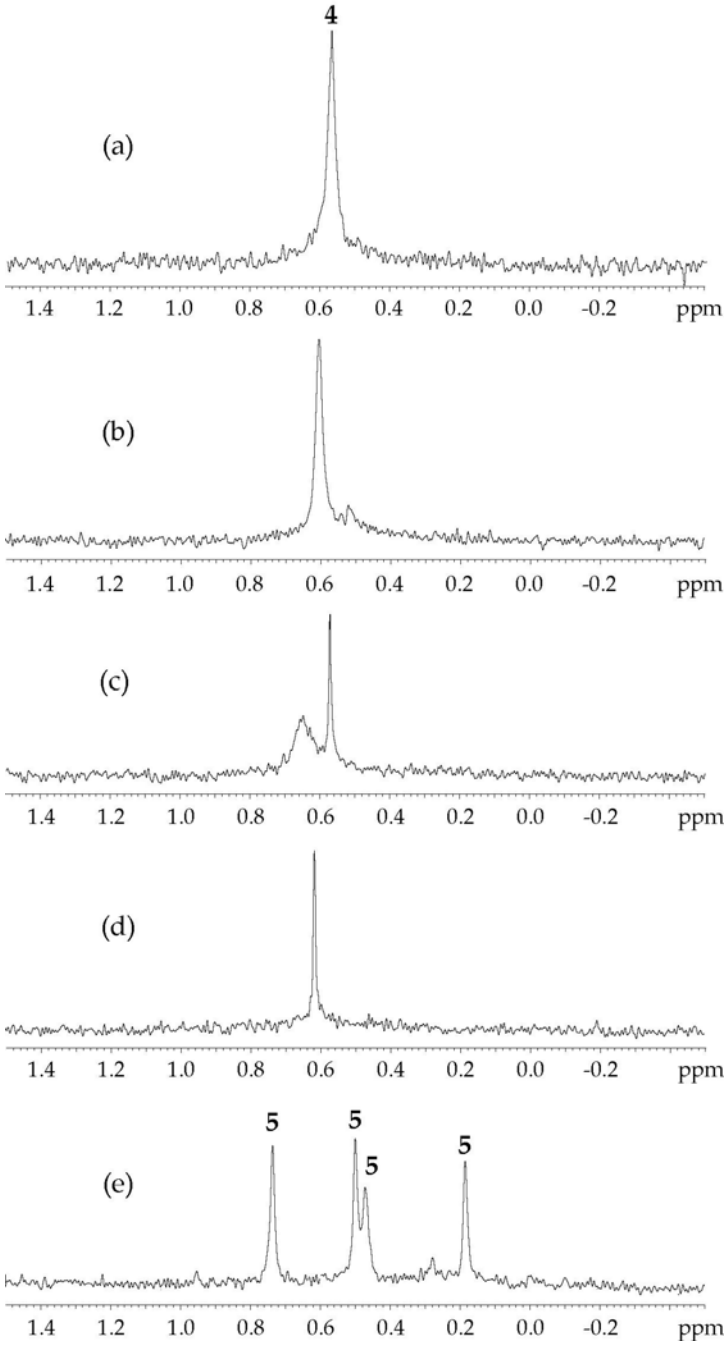
Mechanism of Acylation of Lithium Phenylacetylide with a Weinreb Amide

Bo Qu and David B. Collum*
Department of Chemistry and Chemical Biology
Baker Laboratory, Cornell University
Ithaca, New York 14853-1301

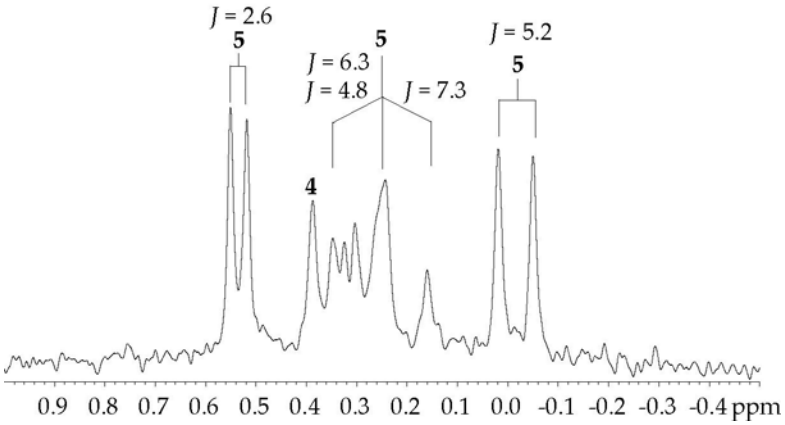
Supporting Information

^{6}Li NMR Spectra and IR Kinetics Studies

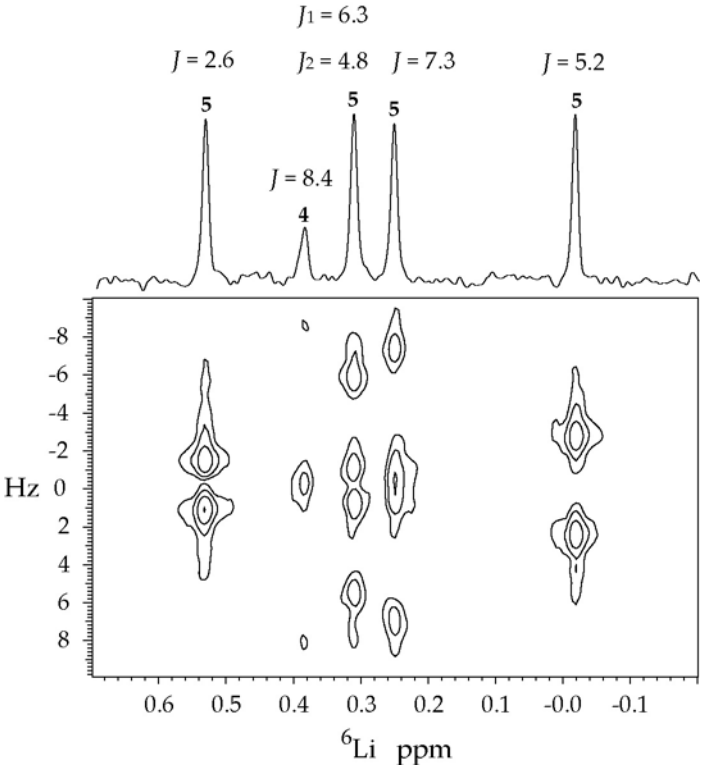


I. ^{6}Li NMR spectra* of a mixture of 0.05 M [^{6}Li]PhCCLi **4** and 0.06 M **1** in 6.0 M THF/pentane at: (a) -90 °C; (b) -75 °C; (c) -55 °C; (d) -40 °C; (e) back to -90 °C after warming to -40 °C, showing resonance of mixed aggregate **5**.

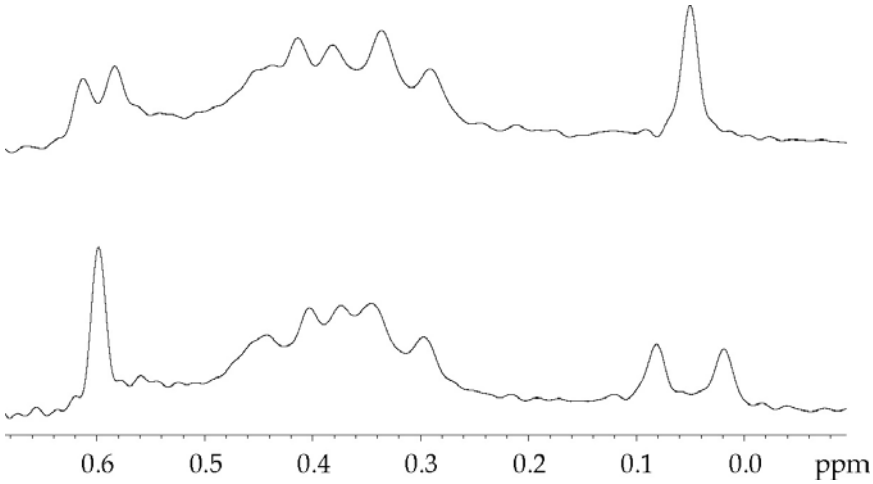
* ^{6}Li NMR spectra were recorded at 58.8 MHz. All other spectra in this Supporting Infomation were recorded at 73.7 MHz.



II. ^{6}Li NMR spectrum of a mixture of 0.05 M [^{6}Li,^{13}C]PhCCLi and 0.05 M **1** in 9.60 M THF/pentane at -110 °C, showing resonance of mixed aggregate **5** with unreacted PhCCLi **4**. *J* is in Hz.



III. *J*(^{6}Li,^{13}C)-resolved spectrum of a mixture of 0.05 M [^{6}Li,^{13}C] PhCCLi and 0.05 M **1** in 9.60 M THF/pentane at -110 °C. ^{6}Li spectrum is ^{13}C broad-band decoupled. *J* is in Hz.

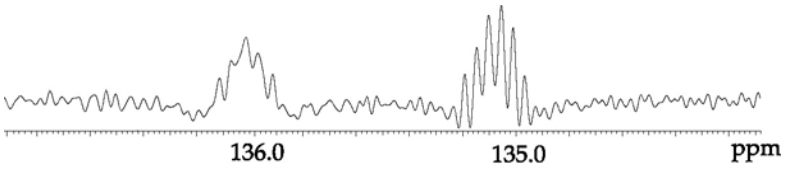


IV. ^{6}Li NMR ^{13}C single frequency decoupled spectra of **5** recorded on 0.05 M [^{6}Li,^{13}C]PhCCLi and 0.05 M **1** in 9.60 M THF/pentane at -110 °C.

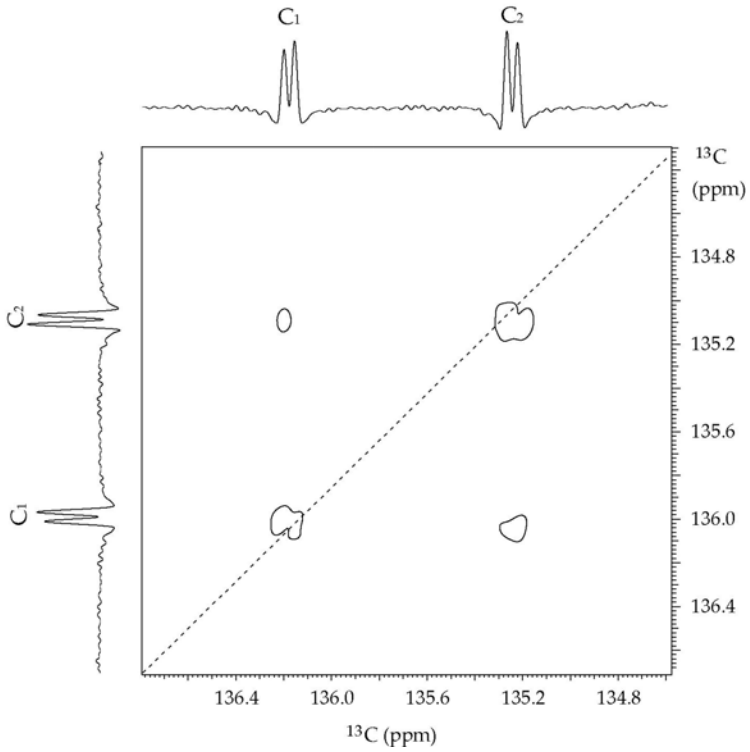
V. Table of ^{13}C NMR resonances for different aggregates upon warming.

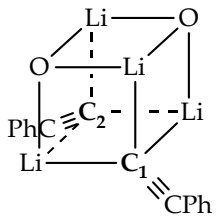
	^{13}C spectra		
	R-^{13}C≡C-Ph	Li-^{13}C≡C-Ph	Li-^{13}C≡C-Ph ^{13}C {^{6}Li}
4	na	139.1	139.1 (pentet) J = 8.4 Hz
5	95.1, 97.2	135.1 (d), 136.0 (d) J = 5.5 Hz	135.1 (sextet) J = 5.7 Hz* 136.0 (m)
7	93.3, 95.7, 96.5	136.6	136.6 (m)
uncharacterized aggregate after warming to RT	91.9	na	na

* The peak shows incomplete multiple couplings. Theretically it should be triplet of heptet.



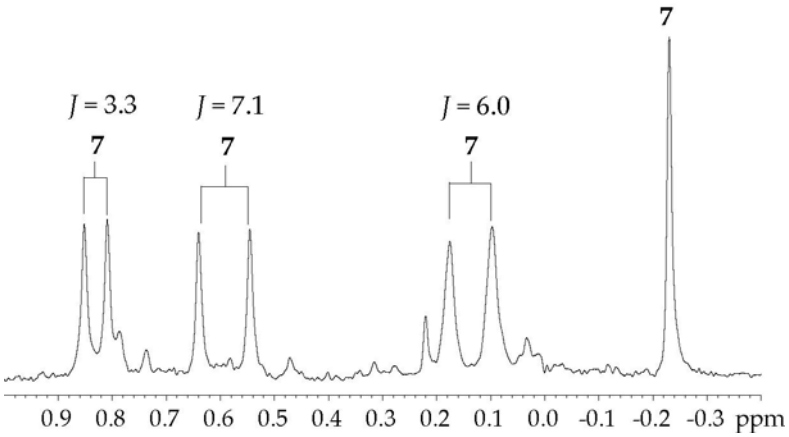
VI. ^{13}C NMR spectrum of **5** recorded on 0.05 M [^{6}Li,^{13}C]PhCCLi and 0.05 M **1** in 9.60 M THF/pentane at -110 °C with sine bell resolution enhancement applied to show multiplet couplings.



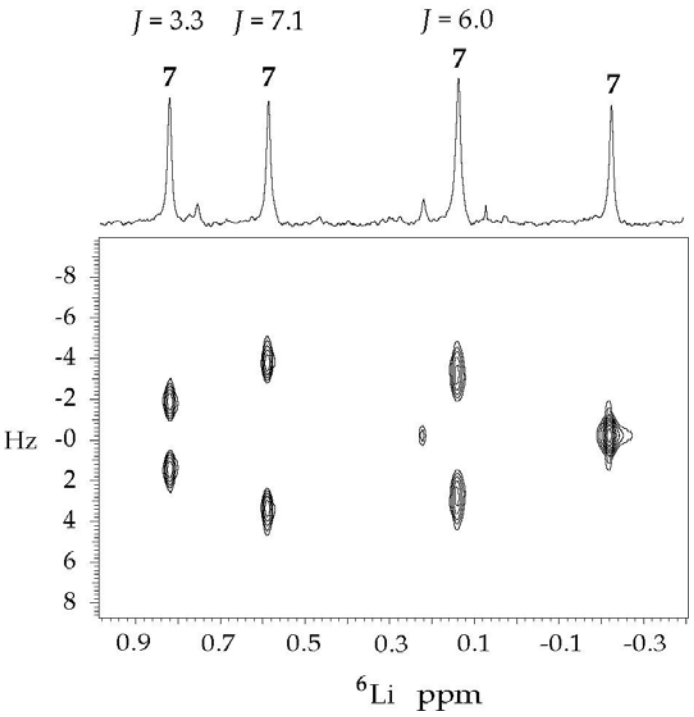


5 (shows only the core of tetramer)

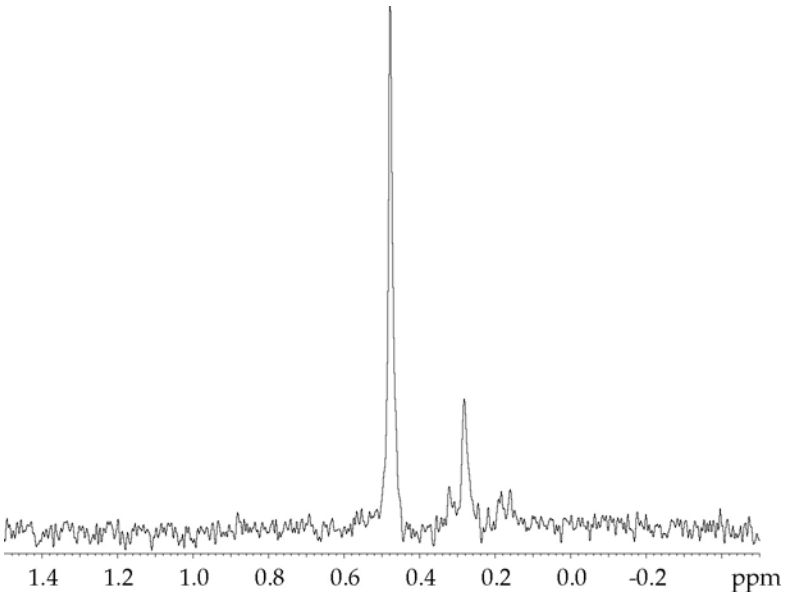
VII. ^{13}C,^{13}C-COSY spectrum of **5** recorded on 0.05 M [^{6}Li,^{13}C]PhCCLi and 0.05 M **1** in 9.60 M THF/pentane at -110 °C, showing the coupling of C_1 and C_2. ^{13}C spectrum is ^{6}Li broad-band decoupled with sine bell resolution enhancement applied to show the couplings.



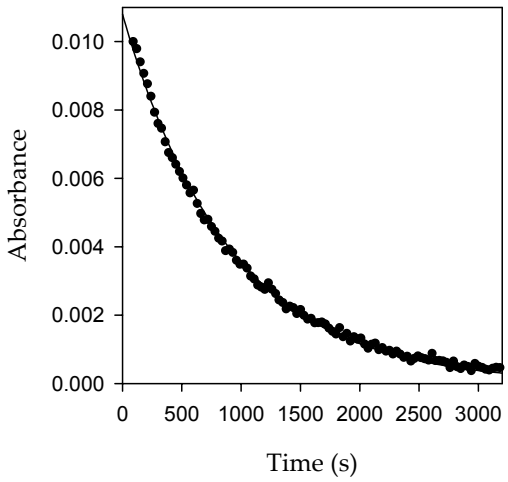
VIII. ^{6}Li NMR spectrum of **7** recorded on 0.05 M [^{6}Li, ^{13}C]PhCCLi and 0.05 M **1** in 9.60 M THF/pentane at -110 °C. *J* is in Hz.



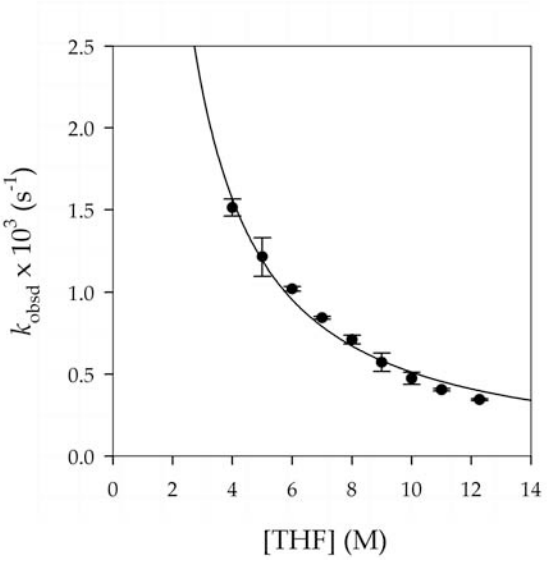
IX. *J*(^{6}Li,^{13}C)-resolved spectrum of **7** recorded on 0.05 M [^{6}Li,^{13}C] PhCCLi and 0.05 M **1** in 9.60 M THF/pentane at -110 °C. ^{6}Li spectrum is ^{13}C broad-band decoupled. *J* is in Hz.



X. ^{6}Li NMR spectrum recorded on a mixture 0.05 M [^{6}Li,^{13}C]PhCCLi and 0.05 M **1** in 9.60 M THF/pentane at -110 °C, showing resonance of the uncharacterized aggregates upon further warming to RT.



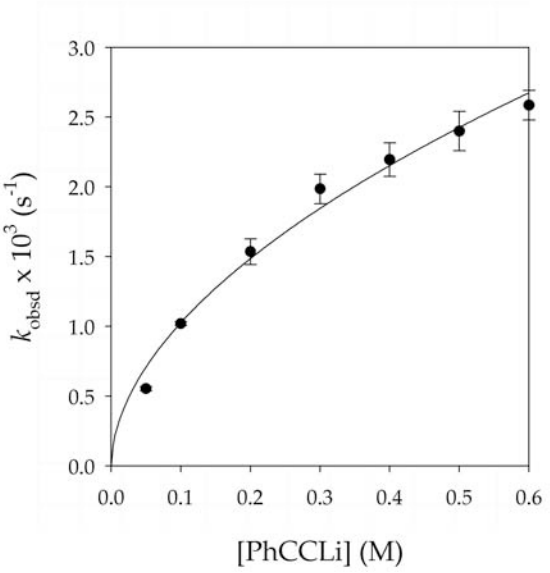
XI. ReactIR plot showing loss of carboxamide **1** (1673 cm^{-1}) upon reaction with 0.10 M PhCCLi in 4.0 M THF/pentane at -50 °C.



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

XIII. Table of data for plot in Section XII.

[THF] (M)	k_{obsd} 1 (s^{-1})	k_{obsd} 2 (s^{-1})	k_{obsd} 3 (s^{-1})	k_{obsd} (av) (s^{-1})
4.0	0.00150 ± 4E-5	0.00157 ± 1E-5	0.00147 ± 1E-5	0.00151 ± 5E-5
5.0	0.00133 ± 3E-5	0.00110 ± 1E-5	0.00121 ± 1E-5	0.0012 ± 1E-4
6.0	0.00103 ± 5E-5	0.00101 ± 2E-5		0.00102 ± 1E-5
7.0	0.000850 ± 7E-6	0.000838 ± 4E-6		0.00084 ± 1E-5
8.0	0.00073 ± 3E-5	0.000692 ± 4E-6		0.00071 ± 3E-5
9.0	0.000533 ± 4E-6	0.000612 ± 4E-6		0.00057 ± 5E-5
10.0	0.00050 ± 1E-5	0.000448 ± 3E-6		0.00047 ± 4E-5
11.0	0.000400 ± 2E-6	0.000411 ± 2E-6		0.000406 ± 8E-6
12.27	0.000340 ± 5E-6	0.000349 ± 2E-6		0.000345 ± 6E-6



XIV. Plot of k_{obsd} vs [PhCCLi] for acylation of PhCCLi 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 $k_{obsd} = a[\text{PhCCLi}]^b$ ($a = 3.5 \pm 0.2 \times 10^{-3}$, $b = 0.53 \pm 0.04$).

XV. Table of data for plot in Section XIV.

[PhCCLi] (M)	k_{obsd} 1 (s^{-1})	k_{obsd} 2 (s^{-1})	k_{obsd} (av) (s^{-1})
0.05	0.000542 ± 4E-6	0.000563 ± 5E-6	0.00055 ± 1E-5
0.10	0.00103 ± 5E-5	0.00101 ± 2E-5	0.00102 ± 1E-5
0.20	0.00147 ± 2E-5	0.00160 ± 2E-5	0.00154 ± 9E-5
0.30	0.00191 ± 3E-5	0.00206 ± 3E-5	0.0020 ± 1E-4
0.40	0.00211 ± 4E-5	0.00228 ± 5E-5	0.0022 ± 1E-4
0.50	0.00230 ± 3E-5	0.00248 ± 4E-5	0.0024 ± 1E-4
0.60	0.00251 ± 4E-5	0.00266 ± 6E-5	0.0026 ± 1E-4

XVI. The Cartesian coordinates and energies for the reaction of Weinreb Amide **1** with Lithium Phenylacetylide calculated at the B3LYP/6-31G(d) level (Energy values and coordinates are in Hartrees and Angstroms, respectively).

Dimethyl ether

SCF Done: E(RB+HF-LYP) =	-155.025044225
Zero-point correction=	0.080306 (Hartree/Particle)
Thermal correction to Energy=	0.084599
Thermal correction to Enthalpy=	0.085544
Thermal correction to Gibbs Free Energy=	0.054941
Sum of electronic and zero-point Energies=	-154.944738
Sum of electronic and thermal Energies=	-154.940445
Sum of electronic and thermal Enthalpies=	-154.939501
Sum of electronic and thermal Free Energies=	-154.970103

Center Number	Atomic Number	Atomic Type	Coordinates X	Y	Z
1	6	0	-1.170929	0.195252	-0.000006
2	8	0	-0.000014	-0.589896	0.000002
3	6	0	1.170935	0.195242	0.000003
4	1	0	-1.232061	0.839934	-0.892752
5	1	0	-2.021904	-0.491258	-0.000344
6	1	0	-1.232447	0.839444	0.893087
7	1	0	1.232215	0.839800	0.892842
8	1	0	2.021897	-0.491289	0.000160
9	1	0	1.232371	0.839569	-0.892992

	1	2	3
Frequencies --	223.7415	250.0383	415.2796

Weinreb amide 1

SCF Done: E(RB+HF-LYP) = -362.985543527

Zero-point correction= 0.134747 (Hartree/Particle)

Thermal correction to Energy= 0.143392

Thermal correction to Enthalpy= 0.144337

Thermal correction to Gibbs Free Energy= 0.101792

Sum of electronic and zero-point Energies= -362.850797

Sum of electronic and thermal Energies= -362.842151

Sum of electronic and thermal Enthalpies= -362.841207

Sum of electronic and thermal Free Energies= -362.883752

Center Number	Atomic Number	Atomic Type	Coordinates X	Y	Z
1	6	0	2.269916	-0.099961	0.283493
2	6	0	0.845791	-0.525003	-0.052876
3	8	0	0.558622	-1.677713	-0.328811
4	7	0	-0.122940	0.465609	0.060615
5	6	0	0.113906	1.892456	-0.086016
6	8	0	-1.367898	0.133757	-0.510453
7	6	0	-2.195480	-0.531670	0.446628
8	1	0	2.874543	-1.006180	0.338166
9	1	0	2.684284	0.554174	-0.492731
10	1	0	2.329036	0.431183	1.239522
11	1	0	0.133687	2.193272	-1.142381
12	1	0	-0.689849	2.435834	0.417893
13	1	0	1.061403	2.160334	0.383545
14	1	0	-3.152692	-0.673902	-0.062009
15	1	0	-1.770412	-1.502081	0.717299
16	1	0	-2.340011	0.084820	1.343120

	1	2	3
Frequencies --	96.3286	110.9917	142.1267

Lithium phenylacetylide dimer $(PhCCLi)_2 \cdot (Me_2O)_4$

SCF Done: E(RB+HF-LYP) =	-1250.93775564
Zero-point correction=	0.530908 (Hartree/Particle)
Thermal correction to Energy=	0.571599
Thermal correction to Enthalpy=	0.572544
Thermal correction to Gibbs Free Energy=	0.442905
Sum of electronic and zero-point Energies=	-1250.406847
Sum of electronic and thermal Energies=	-1250.366156
Sum of electronic and thermal Enthalpies=	-1250.365212
Sum of electronic and thermal Free Energies=	-1250.494851

Center Number	Atomic Number	Atomic Type	Coordinates X	Y	Z
1	6	0	-3.010047	0.028976	0.005445
2	6	0	-1.771641	0.061733	0.008779
3	3	0	0.000052	1.316565	-0.000008
4	3	0	-0.000329	-1.148892	0.000049
5	6	0	1.771416	0.061093	-0.007811
6	6	0	3.009831	0.028585	-0.005433
7	6	0	4.441514	-0.004349	-0.006372
8	6	0	5.169247	0.009676	-1.215494
9	6	0	6.561670	-0.025251	-1.214130
10	6	0	7.266575	-0.074551	-0.008857
11	6	0	6.562339	-0.088359	1.197693
12	6	0	5.169936	-0.053903	1.201335
13	8	0	-0.000674	-2.313389	-1.625844
14	6	0	-1.186465	-2.890680	-2.153073

15	6	0	1.187289	-2.755444	-2.268157
16	8	0	-0.000343	-2.316204	1.624172
17	6	0	-1.187494	-2.750102	2.273547
18	6	0	1.186334	-2.884482	2.159210
19	8	0	0.107312	2.603466	1.520654
20	6	0	-1.059178	3.367049	1.805885
21	6	0	0.789993	2.169200	2.693291
22	8	0	-0.106571	2.602375	-1.521470
23	6	0	-0.789161	2.167422	-2.693931
24	6	0	1.060124	3.365507	-1.807054
25	6	0	-4.441730	-0.004011	0.005365
26	6	0	-5.169257	-0.054673	-1.202835
27	6	0	-6.561661	-0.089123	-1.200184
28	6	0	-7.266787	-0.074219	0.005834
29	6	0	-6.562773	-0.023826	1.211583
30	6	0	-5.170351	0.011106	1.213939
31	1	0	-1.342820	-3.829809	2.131788
32	1	0	-2.009511	-2.188013	1.826778
33	1	0	-1.138576	-2.536222	3.350971
34	1	0	-2.021890	-2.408467	-1.642278
35	1	0	-1.261195	-2.702534	-3.233817
36	1	0	-1.209186	-3.976500	-1.978541
37	1	0	1.785440	2.771591	-2.378959
38	1	0	0.799749	4.271151	-2.373264
39	1	0	1.499286	3.645156	-0.847944
40	1	0	1.617561	1.543171	2.356041
41	1	0	1.169146	3.032519	3.258641
42	1	0	0.120913	1.581704	3.338022
43	1	0	-7.100088	-0.127440	-2.144166
44	1	0	-4.622598	-0.065451	-2.141539
45	1	0	-4.624168	0.052183	2.152018
46	1	0	-7.102215	-0.010954	2.155682

47	1	0	-8.353278	-0.101021	0.006021
48	1	0	7.100418	-0.013239	-2.158636
49	1	0	4.622376	0.049896	-2.153211
50	1	0	4.623974	-0.063824	2.140454
51	1	0	7.101456	-0.125823	2.141315
52	1	0	8.353065	-0.101358	-0.009828
53	1	0	1.260358	-2.682260	3.237450
54	1	0	1.210978	-3.972411	1.998692
55	1	0	-1.617019	1.541951	-2.356364
56	1	0	-1.167884	3.030448	-3.260014
57	1	0	-0.120165	1.579160	-3.338036
58	1	0	-1.784579	2.773641	2.378213
59	1	0	-0.798536	4.272973	2.371522
60	1	0	-1.498365	3.646220	0.846649
61	1	0	2.021141	-2.407333	1.642715
62	1	0	1.342727	-3.833197	-2.112251
63	1	0	1.139549	-2.555579	-3.348320
64	1	0	2.008639	-2.187588	-1.827470

	1	2	3
Frequencies --	7.1050	8.2535	12.6860

Transition Structure

SCF Done: E(RB+HF-LYP) =	-833.378121098
Zero-point correction=	0.318725 (Hartree/Particle)
Thermal correction to Energy=	0.341000
Thermal correction to Enthalpy=	0.341945
Thermal correction to Gibbs Free Energy=	0.262301
Sum of electronic and zero-point Energies=	-833.059396
Sum of electronic and thermal Energies=	-833.037121
Sum of electronic and thermal Enthalpies=	-833.036176

Sum of electronic and thermal Free Energies= -833.115820

Center Number	Atomic Number	Atomic Type	Coordinates X	Y	Z
1	3	0	1.643978	0.833698	-0.061057
2	8	0	2.271320	-0.253138	1.333890
3	6	0	1.570915	-1.185012	0.827877
4	7	0	1.981381	-1.741733	-0.451160
5	8	0	2.635132	-0.715884	-1.215893
6	6	0	4.053838	-0.578870	-0.986252
7	6	0	2.667139	-3.022335	-0.502212
8	6	0	0.891909	-2.198418	1.734890
9	6	0	-0.125155	-0.253238	0.133776
10	6	0	-1.356054	-0.214549	0.068264
11	6	0	-2.780150	-0.156270	-0.036804
12	6	0	-3.568235	0.294934	1.042587
13	6	0	-4.956084	0.346362	0.938878
14	6	0	-5.590319	-0.048238	-0.241953
15	6	0	-4.823266	-0.497081	-1.320289
16	6	0	-3.435256	-0.552387	-1.221696
17	8	0	1.938266	2.730509	-0.172432
18	6	0	2.291634	3.363193	1.058859
19	6	0	1.154891	3.562914	-1.025594
20	1	0	0.217203	3.850861	-0.533036
21	1	0	0.929741	2.983920	-1.923387
22	1	0	1.717574	4.464527	-1.301414
23	1	0	2.833552	2.624454	1.651961
24	1	0	2.931636	4.234955	0.869445
25	1	0	1.391915	3.680660	1.602156
26	1	0	4.336385	0.313628	-1.551869
27	1	0	4.270156	-0.442206	0.075058

28	1	0	4.601849	-1.437711	-1.389115
29	1	0	3.620012	-3.065017	0.050018
30	1	0	1.995325	-3.777860	-0.089180
31	1	0	2.847822	-3.272631	-1.551644
32	1	0	1.664813	-2.809897	2.220538
33	1	0	0.351832	-1.652721	2.508642
34	1	0	0.195066	-2.842064	1.194665
35	1	0	-5.309864	-0.806723	-2.241938
36	1	0	-2.836506	-0.902670	-2.057203
37	1	0	-3.072943	0.600825	1.959497
38	1	0	-5.546213	0.695683	1.782588
39	1	0	-6.673540	-0.006892	-0.321000

	1	2	3
Frequencies--	-276.2004	10.2634	14.276

Experimental Section

Reagents and Solvents. THF and pentane were vacuum-transferred from degassed blue or purple stills containing sodium benzophenone ketyl. The pentane still contained 1% tetraglyme to dissolve the ketyl. Air- and moisture-sensitive materials were manipulated using vacuum line and syringe techniques. Weinreb amide **1** was prepared from cyclohexanecarboxaldehyde and N-methyl-N-methoxylhydroxylamine hydrochloride using literature procedures. [^{6}Li]PhCCLi and [^{6}Li,^{13}C]PhCCLi were prepared and recrystallized in pentane using recrystallized [^{6}Li]LiHMDS and commercially available phenylacetylene and [^{13}C-1]phenylacetylene. The phenylacetylenes were vacuum-transferred from 4 Å molecular sieves.

NMR Spectroscopic Analyses. All tubes were prepared under helium and stored in a liquid nitrogen bath prior to analysis. Tubes were prepared using stock solutions and sealed under partial vacuum. Standard ^{6}Li and ^{13}C NMR spectra were recorded on a 500 MHz

spectrometer at 73.7 and 125.0 Hz respectively. The ^{6}Li and resonances were referenced to 0.3 M [^{6}Li]LiCl/MeOH at -90 °C (0.0 ppm). The spectra were 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 °C bath to thaw the solution, then quickly transferred into the spectrometer and shimmed off the proton spectrum.

Rate Studies by In Situ ReactIR Spectroscopy. IR spectra were recorded using an in situ IR spectrometer fitted with a 30-bounce silicon-tipped probe. 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 glove box 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 mixture was cooled to -50 ºC in a thermostatted bath for 25 minutes. 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 seconds for 5 half-lives. The rates of acylation of lithium penylacetylide with Weinreb amide **1** were monitored by following the loss of **1** (1673 cm^{-1}).

The disappearance of the amide **1** was fit to the equation $[A]/[A_0] = a*e^{-k_{obsd}t} + c$. Where [A] is the concentration of **1** at time "t" and $[A_0]$ is the concentration of **1** at t = 0. Term "c" is a measure of the amount of amide remaining at $t = \infty$, which is typically a positive number at ≤ 5% of $[A_0]$.