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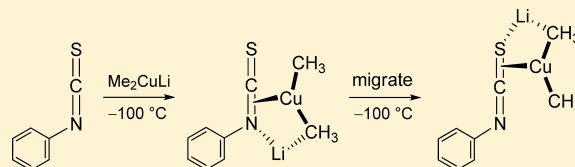
# Complexes of the Gilman Reagent with Double Bonds across the $\pi$ – $\sigma$ Continuum

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## S Supporting Information

**ABSTRACT:** By using rapid injection NMR at low temperatures, a variety of  $\pi$ -complexes of lithium dimethylcuprate(I) with C–C, C–N, and C–S double bonds have been prepared and characterized. Complexation is generally accompanied by large upfield changes in chemical shift for the substrate carbon atoms bonded to copper. In the case of  $\alpha,\beta$ -unsaturated carbonyl compounds, the changes for the carbonyl carbons are much smaller in magnitude, which is consistent with the usual  $\eta^2$  representation of these structures. It is possible for one ligand to displace another, and in this way an order of stability can be elucidated. Treatment of selected  $\pi$ -complexes with chlorosilanes or cyanosilanes gives  $\text{Cu}^{\text{III}}$  intermediates.



## INTRODUCTION

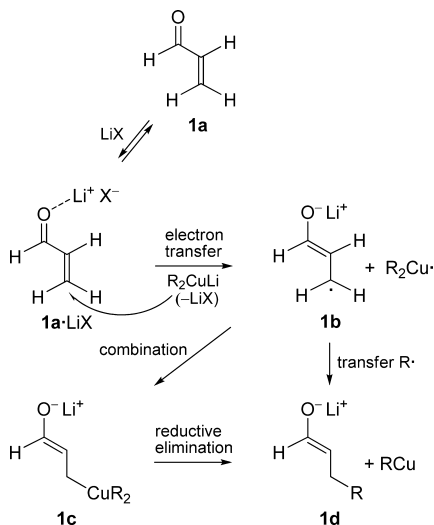
The history of organocopper chemistry has been replete with controversies, as the questions that arose were important and difficult. One of the earliest concerned the mechanism of the conjugate addition (1,4-addition) reaction of organocuprate(I) compounds (“Gilman reagents”). House championed a single-electron transfer (SET) mechanism wherein an electron is shuttled from the cuprate,  $\text{R}_2\text{CuLi}$ , to the  $\alpha,\beta$ -unsaturated carbonyl compound (e.g., **1a**, Scheme 1a), which is activated by  $\text{Li}^+$  complexation.<sup>1</sup> The resultant radical anion **1b** then combines with the oxidized copper species to form  $\text{Cu}^{\text{III}}$  intermediate **1c**, which undergoes reductive elimination to enolate **1d**. Alternatively, transfer of the R-radical to the

$\beta$ -carbon of **1b** affords **1d** directly. While he established the role of lithium–carbonyl complexes in the conjugate addition mechanism, House dismissed the idea of cuprate–olefin complexes on the basis of Occam’s razor.

The prospect of intermediate  $\pi$ -complexes rose like the phoenix when a group at Chalmers University of Technology prepared and characterized cinnamate–dimethylcuprate complexes in a seminal study.<sup>2</sup> Several years later, a Bell Laboratories group studied lithium–carbonyl and copper–olefin complexes in the reaction of  $\text{Me}_2\text{CuLi}$  with 10-methyl- $\Delta^{1,9}$ -2-octalone, a highly hindered 2-cyclohexenone derivative.<sup>3</sup> They proposed that aggregation might be responsible for multiple  $\pi$ -complexes, which was confirmed by more detailed NMR studies.<sup>4</sup> German chemists extended the Swedish work on cinnamate esters by replacing the phenyl with an alkynyl group.<sup>5</sup> A breakthrough was achieved by using rapid injection NMR techniques:<sup>6</sup> it was possible to prepare the  $\text{Me}_2\text{CuLi}$  complex of the highly reactive parent compound, 2-cyclohexenone (vide supra).<sup>7</sup> A number of  $\pi$ -complexes of activated olefins with homocuprates,<sup>3,5,7</sup> as well as mixed cuprates,<sup>8</sup> have now been reported.

Mechanisms involving  $\pi$ -complexes in the conjugate addition of organocuprates to  $\alpha,\beta$ -unsaturated carbonyl compounds are shown in Scheme 1b. Cuprate–olefin  $\pi$ -complex **1** (e.g.,  $\text{R} = \text{Me}$ , Chart 1) can undergo oxidative addition to give  $\text{Cu}^{\text{III}}$  intermediate **1c**, which advances via reductive elimination to enolate **1d**. Alternatively, the Berlan mechanism features a simple olefin insertion reaction to afford  $\alpha$ -cupriocarbonyl intermediate **1e**, which progresses via transmetallative rearrangement to enolate **1d**.<sup>9</sup> Both  $\eta^1$  ( $\sigma$ -allyl<sup>10–12</sup>) and  $\eta^3$  ( $\pi$ -allyl<sup>11,12</sup>)  $\text{d}^8 \text{Cu}^{\text{III}}$  intermediates have been prepared,

**Scheme 1a. Electron Transfer Mechanisms for Organocuprate Conjugate Addition**



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### Scheme 1b. $\pi$ -Complex Mechanisms for Organocuprate Conjugate Addition

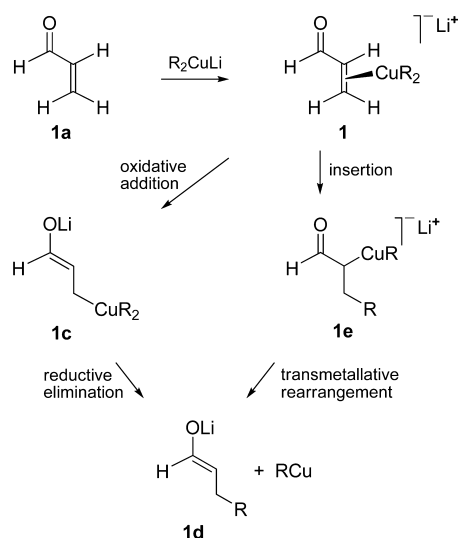
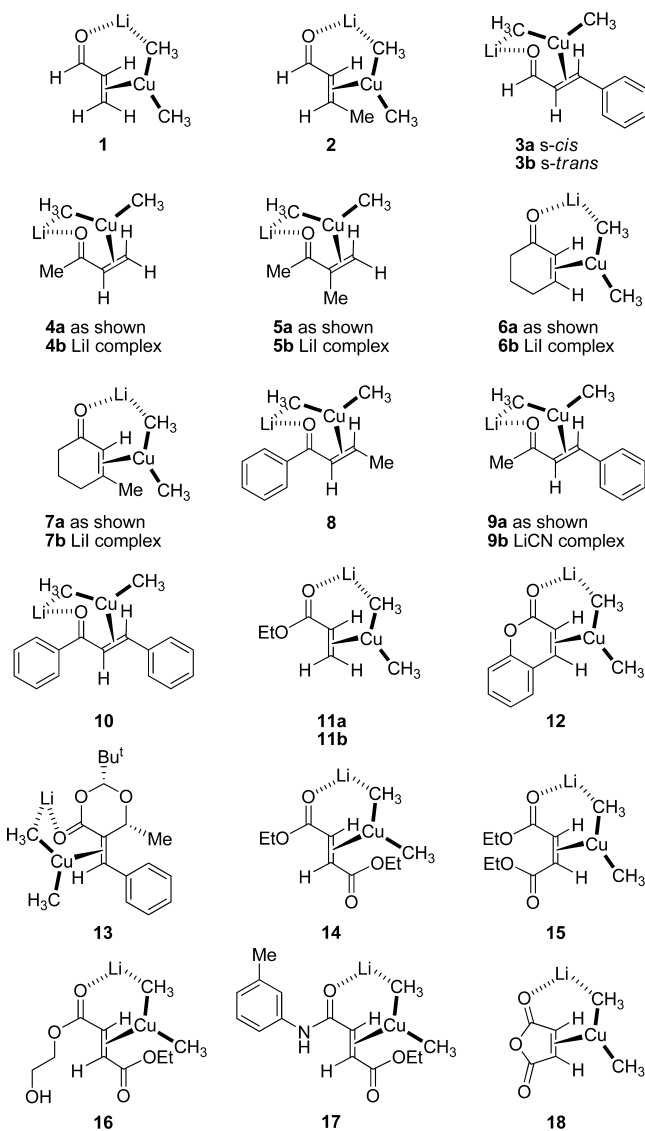


Chart 1. Complexes from Unsaturated Carbonyl Compounds



and their structures are based on a square-planar geometry, rather than the trigonal one envisioned by earlier authors (cf. Schemes 1a and 1b).

Herein we report the details of our investigations into complexes of the Gilman reagent with C–C, C–N, and C–S double bonds, which reveal their structures and stabilities and inter alia help refine the mechanistic schemes. We describe the preparation of these complexes using rapid injection methodology, their structural characterization using 1D and 2D NMR, and the exploration of their reactivity patterns.

## RESULTS AND DISCUSSION

While it is possible to prepare relatively stable cuprate–olefin complexes by injecting the substrate from a gastight syringe into a solution of organocuprate in an NMR tube, cooled in a dry ice/acetone bath, and then transferring the tube to the precooled probe of an NMR spectrometer,<sup>3</sup> a much more elegant and effective method is now available. Rapid injection NMR makes it possible to prepare air-sensitive and thermally unstable species in an NMR tube as it spins in a spectrometer probe at a controlled temperature under a flow of dry nitrogen.<sup>6</sup> This technique minimizes side reactions that may occur during the preparation of delicate species such as cuprate–olefin  $\pi$ -complexes or  $\text{Cu}^{\text{III}}$  intermediates. Even when a species is very unstable, it is possible to put limits on the rate of reaction. For example, when we injected methyl vinyl ketone into a solution of lithium methyl(trimethylsilylmethyl)cuprate(I), no  $\pi$ -complex between the reactants was observed, and the product appeared during the first few seconds.<sup>8</sup>

Unless noted otherwise, all reactions reported here were run in freshly distilled deuterated tetrahydrofuran ( $\text{THF-}d_8$ ) by injecting a solution of substrate into a solution of cuprate at  $-100\text{ }^\circ\text{C}$ , as described above. Organocuprate reactions are very sensitive to experimental variables, which must be carefully controlled.<sup>13</sup> For example, virgin NMR tubes are sine qua non for experiments with cuprate–olefin  $\pi$ -complexes (see Experimental Section).

Tetrahydrofuran was chosen as the solvent in order to minimize the complexity of the systems under scrutiny, in terms of both the copper reagents and their complexes. A “side-by-side” comparison of the reactions of  $\text{Bu}^6\text{Li}$  with  $\text{Cu}^{15}\text{N}$  in (deuterated) ether versus THF was conducted by using  $^1\text{H}$ ,  $^6\text{Li}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR spectroscopy, and the spectra were in general much more complex in ether, owing to higher degrees of aggregation.<sup>14</sup> Spectra of cuprate–olefin complexes were also more complex in ether.<sup>4</sup> Finally, the fact that subsequent reactions of the  $\pi$ -complexes are much faster in ether limits the time available for characterization in this solvent, especially for 2D NMR methods. (N.B., Gschwind has written an exceptionally detailed review.<sup>4</sup>)

The carbon atoms,  $\text{C}_\alpha$  and  $\text{C}_\beta$ , and associated hydrogen atoms,  $\text{H}_\alpha$  and  $\text{H}_\beta$ , at the termini of a conjugated double bond (DB) are subsumed under  $\text{DB}_\alpha$  and  $\text{DB}_\beta$ , respectively, and methyl groups attached to copper,  $\text{Me}_{\text{Cu}}$ , are further specified as  $\text{Me}_\alpha$  and  $\text{Me}_\beta$ , where the former is closer to  $\text{DB}_\alpha$  and the latter to  $\text{DB}_\beta$ . Calculations support an approximately square-planar arrangement of  $\text{C}_\alpha$ ,  $\text{C}_\beta$ ,  $\text{Me}_\alpha$ , and  $\text{Me}_\beta$ .<sup>15</sup>

**Unsaturated Carbonyl Complexes.** Early studies of organocuprate  $\pi$ -complexes involved substrates with electronic or steric stabilization (cf. Introduction). With our rapid injection technology, we have been able to explore much more structural diversity, for example,  $\pi$ -complexes formed rapidly at  $-100\text{ }^\circ\text{C}$  between  $\text{Me}_2\text{CuLi}$  and  $\alpha,\beta$ -unsaturated aldehydes (1–3), ketones (4–10), and esters (11–17), as

Table 1.  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data for Complexes from Unsaturated Carbonyl Compounds<sup>a,b</sup>

ID	Me <sub><math>\alpha</math></sub> H	Me <sub><math>\alpha</math></sub> C	Me <sub><math>\beta</math></sub> H	Me <sub><math>\beta</math></sub> C	DB <sub><math>\alpha</math></sub> H	DB <sub><math>\alpha</math></sub> C	DB <sub><math>\beta</math></sub> H	DB <sub><math>\beta</math></sub> C	C=O	$\Delta_\alpha$	$\Delta_\beta$	$\Delta_{\text{CO}}$
1	−0.90	0.00	−0.03	−5.81	3.76	85.52	2.09, 2.74	47.18	171.90	−50.94	−88.86	−21.40
2	−0.98	−1.60	−0.21	1.30	3.76	87.67	2.59, —	60.77	167.90	−45.67	−91.71	−24.08
3a <sup>c,d</sup>	−0.62	−11.68	−0.41	4.52	4.36	75.90	4.22, —	62.95	170.45	−53.42	−91.44	−24.25
3b <sup>c,d</sup>	−0.73	−1.06	−0.37	5.20	4.49	81.19	3.71, —	65.99	175.08	−48.13	−88.40	−19.62
4a	−1.07	−4.67	−0.33	−7.88	3.56	74.08	2.41, 2.12	43.78	185.74	−64.41	−86.89	−13.31
4b	−0.98	−3.05	−0.13	−6.42	3.60	78.27	2.29, 2.24	44.22	181.73	−60.22	−86.45	−17.32
5a	−1.20	−2.44	−0.31	−10.02	—	83.42	2.55, 2.29	51.89	185.59	−61.61	−75.19	−13.92
5b	−1.11	−4.12	−0.42	−9.93	—	81.54	2.74, 2.22	51.45	183.02	−63.49	−75.63	−16.49
6a	−1.12	−5.02	−0.10	−0.57	3.77	77.45	—, 3.26	61.50	194.75	−52.67	−90.15	−3.90
6b	−1.16	−5.56	−0.24	−1.85	3.68	75.82	—, 3.19	61.50	193.34	−54.30	−90.15	−5.31
6c <sup>e</sup>	−1.12	−7.08	−0.22	1.56	3.76	75.87	—, 3.11	61.65	193.85	−54.25	−90.00	−4.80
7a	−1.11	−5.30	−0.22	5.22	3.70	82.06	—, —	70.73	191.70	−40.60	−93.37	−7.46
7b	−1.15	−6.04	−0.38	2.99	3.63	80.42	—, —	70.59	191.44	−42.24	−93.51	−7.72
8 <sup>c</sup>	−1.26	−4.47	−0.26	0.47	4.30	78.70	3.29, —	58.80	177.13	−47.72	−86.78	−11.08
9a <sup>c</sup>	−0.87	−5.32	−0.59	1.89	4.36	71.54	4.14, —	63.10	184.53	−56.39	−81.54	−14.27
9b <sup>c</sup>	−0.79	−3.55	−0.41	4.11	4.53	75.26	4.09, —	63.85	181.54	−52.67	−80.79	−17.26
10 <sup>c</sup>	−1.05	−3.62	−0.45	3.99	5.13	69.38	4.40, —	64.20	178.99	−51.62	−80.86	−9.41
11a	−1.12	−8.55	−0.54	−8.22	3.02	52.94	2.16, 2.01	42.20	175.32	−75.79	−87.71	10.80
11b	−1.16	−7.90	−0.48	−6.71	2.67	54.19	2.26, 2.06	42.76	174.50	−74.54	−87.15	9.98
12	−0.93	−7.53	−0.54	2.06	3.33	50.47	—, 4.10	58.65	169.38	−65.26	−84.09	9.74
13	−0.83	−3.38	−0.57	1.83	—	67.75	4.04, —	63.59	168.22	−63.18	−75.26	2.41
14	−0.51	−5.30	−0.51	−5.30	3.35	50.94	3.35, —	50.94	174.73	−82.77	−82.80	9.67
15	−0.29	−3.61	−0.29	−3.61	2.88	50.12	— 2.88	50.12	175.42	−80.82	−80.82	9.38
16 <sup>f</sup>	−0.54	−5.26	−0.49	−5.04	3.49	51.04	3.49, —	51.04	174.92	−83.28	−83.28	9.69
17 <sup>g</sup>	−0.53	−5.83	−0.48	−3.93	3.88	56.43	3.50, —	50.87	172.40	−82.00	−79.57	10.90
18	−0.19	−2.31	−0.19	−2.31	3.67	52.26	— 3.67	52.26	171.57	−85.41	−85.41	4.75

<sup>a</sup>All shifts are in ppm, measured at  $-100\text{ }^\circ\text{C}$  unless otherwise noted. <sup>b</sup>Cuprates prepared from CuI unless otherwise noted. <sup>c</sup>Cuprate from CuCN.

<sup>d</sup>Measured at  $-70\text{ }^\circ\text{C}$  (too broad at  $-100\text{ }^\circ\text{C}$ ). <sup>e</sup>Cuprate ( $\text{Me}_2\text{CuMgCl}\cdot\text{MgCl}_2$ ) from CuCl. <sup>f</sup>Second CO peak at 172.32 ppm ( $\Delta_{\text{CO}} = 7.09\text{ ppm}$ ).

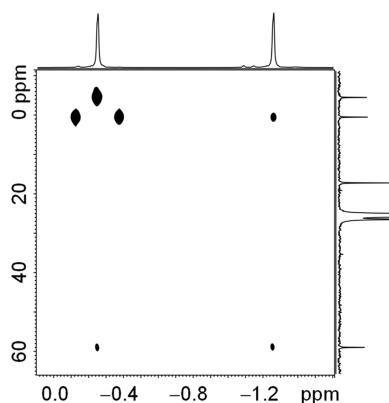
<sup>g</sup>Second CO peak at 173.39 ppm ( $\Delta_{\text{CO}} = 7.61\text{ ppm}$ ).

illustrated in Chart 1. Parent compounds and substituted derivatives were prepared, and both cyclic and acyclic ketones and esters were investigated. The preparations of complexes 16–18 that contained potentially reactive functional groups were carried out via direct and indirect routes, as described in detail in a later section. Important NMR shifts are listed in Table 1.

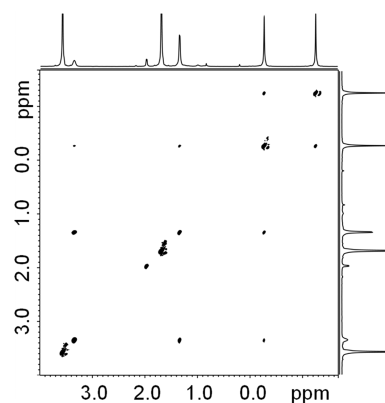
A  $\pi$ -complex of a cyclic ketone (6, 7), ester (12), or anhydride (18), where the double bond is endocyclic, is constrained in the *s-trans* conformation. On the other hand, a complex of a cyclic substrate such as 13, where the double bond is exocyclic, is fixed in the *s-cis* conformation. In cases such as these, the presence of multiple  $\pi$ -complexes is assumed to be

the result of aggregation, as with 6a/6b.<sup>7</sup> Addition of LiI to the mixture increased the proportion of minor species 6b; therefore, we considered it to be an aggregate with LiI and assumed 6a to be LiI-free.

2-Cyclohexenone gave two  $\pi$ -complexes with lithiocuprate  $\text{Me}_2\text{CuLi}\cdot\text{LiI}$  or  $\text{Me}_2\text{CuLi}\cdot\text{LiCN}$ ,<sup>7</sup> but only one  $\pi$ -complex, 6c, with a magnesiocuprate,  $\text{Me}_2\text{CuMgCl}\cdot\text{MgCl}_2$ . The NMR data for 6c do not indicate an aggregation state. It is not a stretch to propose that magnesiocuprate  $\pi$ -complexes such as 6c are intermediates in the Kharasch reaction of  $\alpha$ -enones with Grignard reagents, where a catalytic amount of copper salt suffices to change the regioselectivity from 1,2- to 1,4-addition.<sup>16</sup>



**Figure 1.** HMBC plot for crotonophenone  $\pi$ -complex 8, correlating H's of cuprate Me <sub>$\alpha$</sub>  (−1.26) and Me <sub>$\beta$</sub>  (−0.26) with substrate C <sub>$\beta$</sub>  (58.80 ppm). The H's of Me <sub>$\alpha$</sub>  also correlate with the C of Me <sub>$\beta$</sub> .



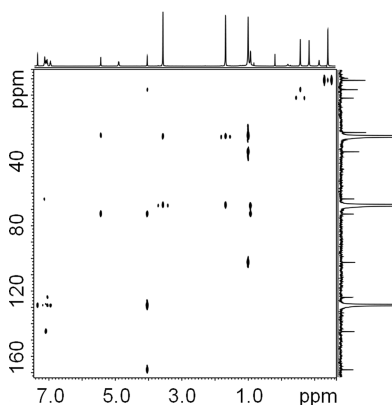
**Figure 2.** NOESY plot for crotonophenone  $\pi$ -complex 8, showing strong interactions of the H's of cuprate Me <sub>$\beta$</sub>  (−0.26) with substrate methyl H's (1.35) and H <sub>$\beta$</sub>  (3.29 ppm).

Acyclic substrates with more than one  $\pi$ -complex can in principle be the result of differences in conformation or aggregation (or both). In the case of **1**, NOESY established that the conformation of the acrolein moiety was *s-trans*, as there was a strong cross-peak between the aldehydic hydrogen and one of the  $\beta$ -hydrogens, but no interaction between the former and the  $\alpha$ -hydrogen. In the case of cinnamaldehyde, NOESY indicated a mixture (ca. 1:1) of *s-cis* and *s-trans* complexes **3a** and **3b**, respectively. In contrast, methyl vinyl ketone complexes **4a** and **4b** both had the *s-cis* conformation, as did both benzalacetone complexes **9a** and **9b**, which implied aggregation with the lithium halide or pseudohalide (LiI or LiCN, respectively). Exchange (ROESY) in the case of **11a** and **11b** precluded using NOE to assign stereochemistry.

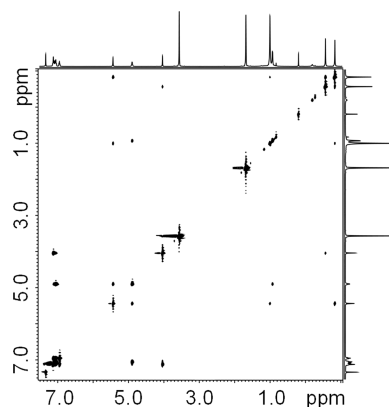
It must be emphasized that we do not have direct evidence for the structures of the aggregates, and in this regard we depend upon the experimental studies of the Gschwind group,<sup>4</sup> as well as theoretical work by the Nakamura group.<sup>17</sup> In the examples reported here, the aggregates were usually present to the extent of 10–30%. In the case of benzalacetone, as many as six complexes were observed at  $-100\text{ }^{\circ}\text{C}$ ; however, most of them could not be characterized completely, owing to low concentrations. Upon warming to  $-80\text{ }^{\circ}\text{C}$ , two significant species remained, and they persisted upon cooling back to  $-100\text{ }^{\circ}\text{C}$ , where they were characterized. In the two systems studied in detail, **6a/6b** and **9a/9b**, the results were very similar using  $\text{Me}_2\text{CuLi}$  prepared from either CuI or CuCN, and only minor differences in chemical shifts were noted.

Typical 2D NMR plots are shown in Figures 1–4. HMBC and NOESY were especially valuable because they proved that  $\text{Me}_{\text{Cu}}$  and certain substrate C or H atoms were integral parts of the same molecule. Furthermore, NOESY proved that the  $\text{Me}_a\text{CuMe}_b$  moiety was on the least hindered face of the substrate in **13** (cf. Figure 4) and **36** (vide infra). The  $\alpha$  and  $\beta$  positions of **17** were assigned with the aid of HMBC. They were not resolved in **14**–**16** and **18**.

A useful parameter for understanding the change in bonding upon complexation is the difference in chemical shift,  $\Delta_N = \delta_{\text{N,C}} - \delta_{\text{N,U}}$ , where  $\delta_{\text{N,C}}$  is the chemical shift of nucleus N in complex C, and  $\delta_{\text{N,U}}$  is the chemical shift of the corresponding nucleus in uncomplexed substrate U. We focus on the values of  $\Delta_N$  for the carbon atoms attached to copper, especially  $\Delta_\alpha$  and  $\Delta_\beta$  for the carbon atoms  $\text{C}_\alpha$  and  $\text{C}_\beta$  of the double bonds. It is also



**Figure 3.** HMBC plot for  $\pi$ -complex **13**, correlating substrate  $\text{H}_\beta$  (4.04) with cuprate  $\text{Me}_a\text{C}$  (−3.38), ring allylic C (72.87), Ph *ipso*-C (128.96), and carbonyl C (168.22 ppm).



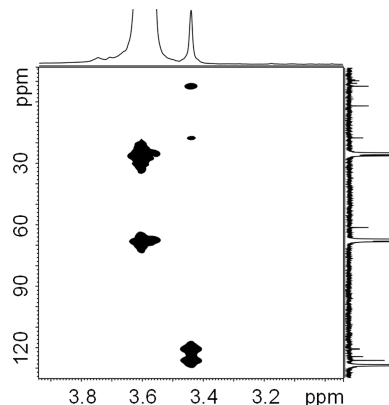
**Figure 4.** NOESY plot for  $\pi$ -complex **13**, showing strong H–H interactions between cuprate  $\text{Me}_a$  (−0.83) and ring  $\text{O}_2\text{CH}$  (5.44) and between cuprate  $\text{Me}_b$  (−0.57) and substrate  $\text{H}_\beta$  (4.04 ppm).

interesting to compare values of  $\Delta_{\text{CO}}$  for the carbonyl groups. The methyl groups on copper in the complexes can be compared directly, since the chemical shifts for the starting cuprates do not change significantly ( $^{13}\text{C}$  NMR ca.  $-10\text{ ppm}$ ,  $^1\text{H}$  NMR ca.  $-1.4\text{ ppm}$ ).

The chemical shifts of the olefinic carbon atoms,  $\text{C}_\alpha$  and  $\text{C}_\beta$ , are sent dramatically upfield upon coordination by copper, especially  $\text{C}_\beta$ . All of the upfield shift changes for  $\text{C}_\alpha$  fall in the range  $\Delta_\alpha \approx -60 \pm 30\text{ ppm}$  (ca. mean  $\pm$  twice the standard deviation), and those for  $\text{C}_\beta$  in the range  $\Delta_\beta \approx -85 \pm 10\text{ ppm}$ . The values of  $\Delta_{\text{CO}}$  populate the ranges  $-25$  to  $-19\text{ ppm}$  for aldehydes,  $-18$  to  $-3\text{ ppm}$  for ketones, and  $2$  to  $11\text{ ppm}$  for esters. The magnitudes (absolute values) of  $\Delta_\alpha$  and  $\Delta_\beta$  are much larger than those of  $\Delta_{\text{CO}}$  ( $|\Delta_\beta| > |\Delta_\alpha| \gg |\Delta_{\text{CO}}|$ ), which leads us to conclude that **1**–**18** are all  $\eta^2$ - and not  $\eta^3$ -complexes.<sup>18</sup>

**Unsaturated Nitriles and Sulfones.** Nitriles and sulfones with conjugated C–C double bonds also formed  $\pi$ -complexes. A mononitrile (**19**), a 1,2-dinitrile (**20**), and four 1,1-dinitriles (**21**–**24**) were examined, and all of them gave  $\pi$ -complexes that were stable enough to characterize. The HMBC plot for benzylidenemalononitrile  $\pi$ -complex **22** in Figure 5 helped locate  $\text{C}_\omega$  and it also proved that the dimethylcuprate and malononitrile moieties were part of the same molecule.

Phenyl vinyl sulfone formed a stable  $\pi$ -complex (**25**), as did its  $\beta$ -chloro and  $\beta$ -methyl derivatives. Injection of phenyl



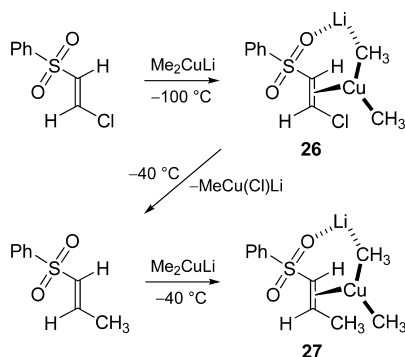
**Figure 5.** HMBC plot for  $\pi$ -complex **22**, correlating substrate  $\text{H}_\beta$  (3.44) with cuprate  $\text{Me}_a\text{C}$  (−7.63), substrate  $\text{C}_\alpha$  (17.58), both CN carbons (120.56, 120.77), and *o*-Ph C atoms (126.23 ppm).



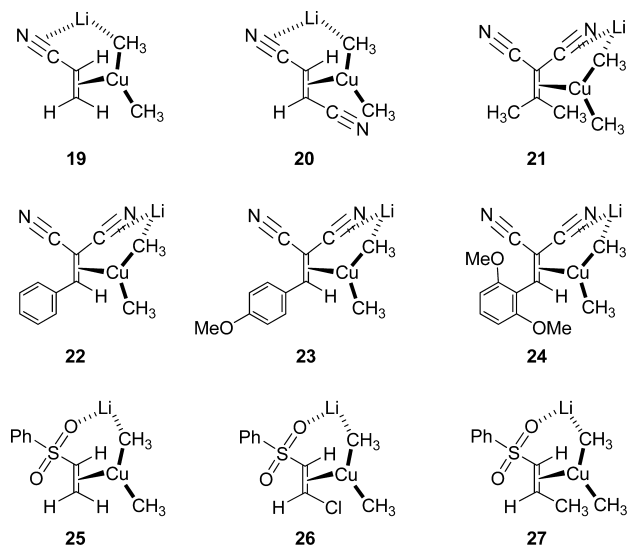
(*E*)-2-chlorovinyl sulfone (Scheme 2) into 1 equiv of  $\text{Me}_2\text{CuLi}\cdot\text{LiI}$  at  $-100^\circ\text{C}$  gave  $\pi$ -complex **26**, which went on to phenyl (*E*)-propenyl sulfone upon warming to  $-40^\circ\text{C}$ . In the presence of a second equivalent of  $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ , this product gave  $\pi$ -complex **27** at this temperature. Chart 2 summarizes the structures and Table 2 the NMR data for the unsaturated nitriles and sulfones.

The upfield chemical shift changes,  $\Delta_\alpha \approx -65 \pm 10$  ppm, for  $\alpha,\beta$ -unsaturated nitrile complexes are approximately the same as for  $\alpha,\beta$ -unsaturated carbonyl complexes, and the magnitudes of  $\Delta_\beta \approx -110 \pm 20$  ppm for the former are significantly larger than those for the latter. (Note that fumaronitrile complex **20** is

**Scheme 2.** Preparation of Substituted Sulfone Complexes



**Chart 2.** Complexes from Unsaturated Nitriles and Sulfones



**Table 2.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data for Complexes from Unsaturated Nitriles and Sulfones<sup>a,b</sup>

ID	$\text{Me}_{\alpha\text{H}}$	$\text{Me}_{\alpha\text{C}}$	$\text{Me}_{\beta\text{H}}$	$\text{Me}_{\beta\text{C}}$	$\text{DB}_{\alpha\text{H}}$	$\text{DB}_{\alpha\text{C}}$	$\text{DB}_{\beta\text{H}}$	$\text{DB}_{\beta\text{C}}$	$\text{C}\equiv\text{N}$	$\Delta_\alpha$	$\Delta_\beta$	$\Delta_{\text{CN}}$
19	-0.88	-8.37	-0.48	-7.86	2.08	42.31	1.89, 1.91	22.20	129.27	-65.97	-116.23	12.16
20	-0.34	-5.60	-0.34	-5.60	2.28	24.06	2.28, —	24.06	124.92, 124.92	-95.31	-95.31	10.57, 10.57
21	-0.96	-10.51	-0.31	3.71	—	22.90	—, —	64.09	119.92, 119.92	-62.01	-118.54	6.68, 6.68
22	-0.57	-7.63	-0.34	1.97	—	17.58	3.44, —	61.34	120.77, 120.56	-65.27	-99.87	5.60, 6.48
23	-0.67	-8.10	-0.37	1.51	—	17.61	3.42, —	61.43	120.86, 120.63	-60.31	-98.93	5.12, 5.87
24	-0.71	-8.75	-0.32	-3.24	—	16.51	3.64, —	50.54	121.92, 122.37	-69.45	-109.44	6.60, 8.15
25	-0.69	-8.18	-0.42	-6.26	3.12	62.25	1.75, 2.03	37.60	N/A	-77.22	-91.18	N/A, N/A
26	-0.58	-9.32	-0.17	-0.19	3.40	63.73	4.34, —	60.63	N/A	-71.32	-76.85	N/A, N/A
27	-0.69	-9.59	-0.40	-1.66	3.13	66.56	2.71, —	51.38	N/A	-66.11	-91.91	N/A, N/A

<sup>a</sup>All shifts are in ppm, measured at  $-100^\circ\text{C}$ . <sup>b</sup>Cuprates prepared from  $\text{CuI}$ .

a special case, owing to symmetry in the substrate.) The values of  $\Delta_{\text{CN}} \approx 5\text{--}12$  ppm for the nitriles are relatively small and positive, similar to  $\Delta_{\text{CO}} \approx 2\text{--}11$  ppm for esters (Table 1), which suggests they have similar bonding patterns.

The values of  $\Delta_\alpha$  and  $\Delta_\beta$  for  $\alpha,\beta$ -unsaturated sulfones are very similar to those for  $\alpha,\beta$ -unsaturated ketones. This observation supports  $\eta^2$ -structures for both kinds of complexes.

**Compounds with C–N Double Bonds.** In 1979, it was discovered that  $\text{Cu}^{\text{I}}$  activates the C–N double bond for the addition of an alkyl lithium to the carbon atom.<sup>19</sup> One possible explanation is coordination of  $\text{Cu}^+$  to the lone pair on the imine nitrogen in analogy with the activation of a C–O double bond by coordination of  $\text{Li}^+$  to a lone pair on oxygen. A second possibility is initial formation of an organocupper(I) reagent, which then adds to the C–N double bond. Attempts to observe complexes between cuprates and simple imines were not successful; therefore, we looked for special cases, which would hold synthetic as well as theoretical interest.

The choice of examples with C–N double bonds was largely dictated by the stability of the substrates. The preparation of 2-azachalcone  $\pi$ -complex **28** was routine under the usual conditions. The isomeric 3-azachalcone was not stable, and it was necessary to use the 4-fluoro derivative, which gave complex **29**. The azachalcone complexes slowly decomposed at  $-100^\circ\text{C}$  with the liberation of ethane, presumably from reductive elimination of the two methyl groups on copper. In contrast, chalcone complex **10** was stable at this temperature, and warming to  $-10^\circ\text{C}$  yielded only 1,4-addition product and no ethane.<sup>12</sup>

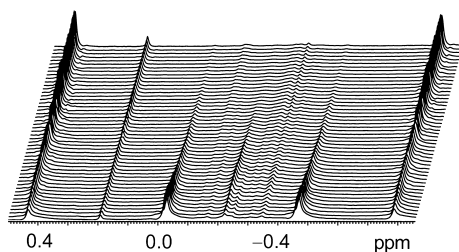
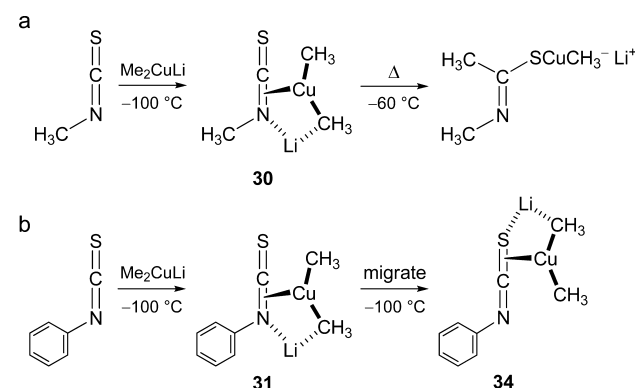
Isothiocyanates are a fascinating class of compounds with both C–N and C–S double bonds. The C–S double-bond complexes are discussed in the next section. Methyl isothiocyanate gave C–N complex **30**, which was stable at  $-100^\circ\text{C}$ . Warming the sample to  $-60^\circ\text{C}$  resulted in addition (Scheme 3). No C–S complex (vide infra **33**) was observed in this case. In contrast, phenyl isothiocyanate gave transient C–N complex **31**, which rearranged to a stable C–S complex (vide infra **34**).<sup>20</sup> Stacked  $^1\text{H}$  NMR plots for this transformation are shown in Figure 6. Chart 3 summarizes the structures and Table 3 the NMR data for the complexes with C–N double bonds.

Values of  $\Delta_\alpha = -65$  ppm for **29** and  $\Delta_\beta = -100$  ppm for **28** are larger in magnitude than the corresponding values,  $\Delta_\alpha = -52$  ppm and  $\Delta_\beta = -81$  ppm, for chalcone complex **10**. The magnitudes of  $\Delta_{\text{CO}}$  for complexes **28** ( $-8$  ppm), **29** ( $-17$  ppm), and **10** ( $-9$  ppm) are relatively small, which suggests they involve dihapto-coordination.

The large, positive value of  $\Delta_{\text{CN}} = 83$  ppm for complex **30** is similar to  $\Delta_{\text{CS}} = 85$  ppm for complex **32** from carbon disulfide (next section).

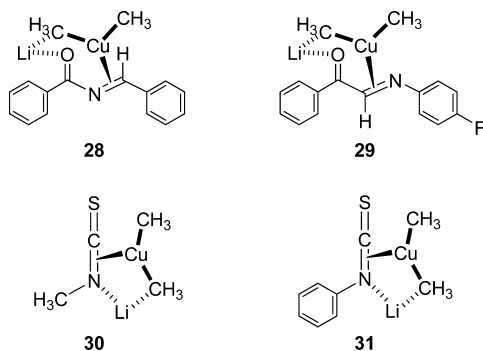
**Compounds with C–S Double Bonds.** We discovered that carbon disulfide formed a complex, **32**, with lithium dimethylcuprate(I) during our investigation into reactions of lithium tetramethylcuprate(III),<sup>21</sup> the Cu<sup>III</sup> analogue of the

**Scheme 3. Reactions of Isothiocyanates with Lithium Dimethylcuprate(I)**



**Figure 6.** Stacked  $^1\text{H}$  NMR plots for the conversion of C–N complex **31** (−0.03, −0.47 ppm) to C–S complex **34** (0.43, −0.79 ppm). (The total time was 40 min.)

**Chart 3. Complexes of Compounds with C–N Double Bonds**



**Table 3.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data for Complexes of Compounds with C–N Double Bonds<sup>a,b</sup>

ID	Me <sub>α</sub> H	Me <sub>α</sub> C	Me <sub>β</sub> H	Me <sub>β</sub> C	DB <sub>α</sub> H	DB <sub>α</sub> C	DB <sub>β</sub> H	DB <sub>β</sub> C	C=O, C=N <sup>c</sup>	$\Delta_\alpha$	$\Delta_\beta$	$\Delta_{\text{CO}}, \Delta_{\text{CN}}$
<b>28</b>	−1.07	−1.05	−0.26	5.02	—	—	4.73	66.36	173.33, —	—	−100.30	−7.66, N/A
<b>29</b>	−0.43	10.86	−0.09	5.96	5.25	93.52	—	—	174.09, —	−65.15	—	−17.04, N/A
<b>30</b>	−0.48	−1.48	0.52	−1.25	N/A	N/A	N/A	N/A	N/A, 207.85	N/A	N/A	N/A, 82.85
<b>31<sup>d</sup></b>	−0.47	−2.76	−0.03	2.15	N/A	N/A	N/A	N/A	N/A, — <sup>d</sup>	N/A	N/A	N/A, — <sup>d</sup>

<sup>a</sup>All shifts are in ppm, measured at −100 °C. <sup>b</sup>Cuprates prepared from CuI. <sup>c</sup>For **30** and **31**; for **28** and **29** see DB entries. <sup>d</sup>Transient intermediate;  $^{13}\text{C}$  NMR not measured.

Gilman reagent. While  $\text{Me}_4\text{CuLi}$  did not react with  $\text{CS}_2$ , we noticed that a small amount of residual starting material,  $\text{Me}_2\text{CuLi}$ , was rapidly replaced by a new species, identified as **32** (Scheme 4a). Therefore, we investigated the reactions of  $\text{Me}_2\text{CuLi}$  with diverse thiocarbonyl compounds, as summarized in Chart 4 and Table 4. (Scheme 4b, methanol reactions, will be discussed in the next section.)

Carbon disulfide and isothiocyanates are the only substrates that exhibit large downfield changes in chemical shift upon complexation (cf. **30**, **32**, and **34**). Dithioester complexes **37**–**40** exhibit large upfield changes,  $\Delta_{\text{CS}} \approx -148 \pm 6$  ppm, and thioketone complexes even larger ones,  $\Delta_{\text{CS}} = -157$  ppm for **35** and  $\Delta_{\text{CS}} = -182$  ppm for **36**. The latter has the largest absolute value we have measured to date, and all the values of  $\Delta_{\text{CS}}$  for thioketone and dithioester complexes are significantly greater in magnitude than any value of  $\Delta_\alpha$  or  $\Delta_\beta$  for C–C or C–N double-bond complexes.

**Ligand Exchange Reactions.** The relative stabilities of representative complexes were determined by adding a second substrate to a preformed complex. For example, addition of methyl dithio-4-trifluoromethylbenzoate to the methyl dithiobenzoate–cuprate complex **38** resulted in a smooth conversion to complex **40** and free methyl dithiobenzoate. In this way, the order of stability for C–S double-bond complexes was determined to be **40** > **38** > **39** > **37** > **32**. We note that the electron-withdrawing trifluoromethyl group has a stabilizing effect, whereas the electron-donating methoxy group is destabilizing relative to H.

A similar study with C–C double bonds in  $\alpha$ -enones resulted in the order **4** > **10** > **9** > **6**. Methyl dithioacetate displaced methyl vinyl ketone from  $\pi$ -complex **4** to give thiocarbonyl complex **37**; therefore, the weakest dithioester complex was more stable than the strongest  $\alpha$ -enone complex.

The  $\alpha,\beta$ -unsaturated nitriles constitute an especially interesting series. Acrylonitrile gave a very weak complex, **19**. The acrylonitrile ligand was even displaced by 2-cyclohexenone, which formed the weakest  $\alpha$ -enone complex, **6**. On the other hand, fumaronitrile complex **20** was one of the strongest, and fumaronitrile displaced benzylidenemalononitrile from **22**, the most stable malononitrile complex. The complete order of stability was **20** > **22** > **23** > **24** > **21** > **19**. Fumaronitrile also displaced diethyl fumarate from complex **14** to give **20** quantitatively.

It must be emphasized that when we discuss “stability” in this section, it applies only to competition between ligands, and it is entirely distinct from other kinds of reactivity such as thermal stability. For example, the weakest  $\pi$ -complex studied here was **19**; nevertheless, it was thermally stable up to 25 °C, while most of the other complexes went on to products at lower temperatures.

Treatment of C–S double-bond complex **32** or **40** with methanol (4 equiv) at −100 °C did not lead to decomposition. The same result was obtained for  $\text{Me}_4\text{CuLi}$  at this temperature (Scheme 4b).

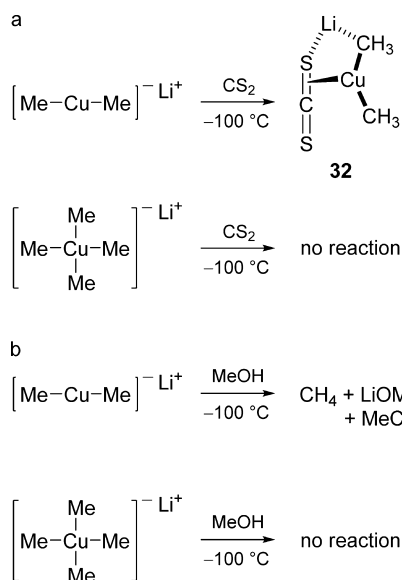
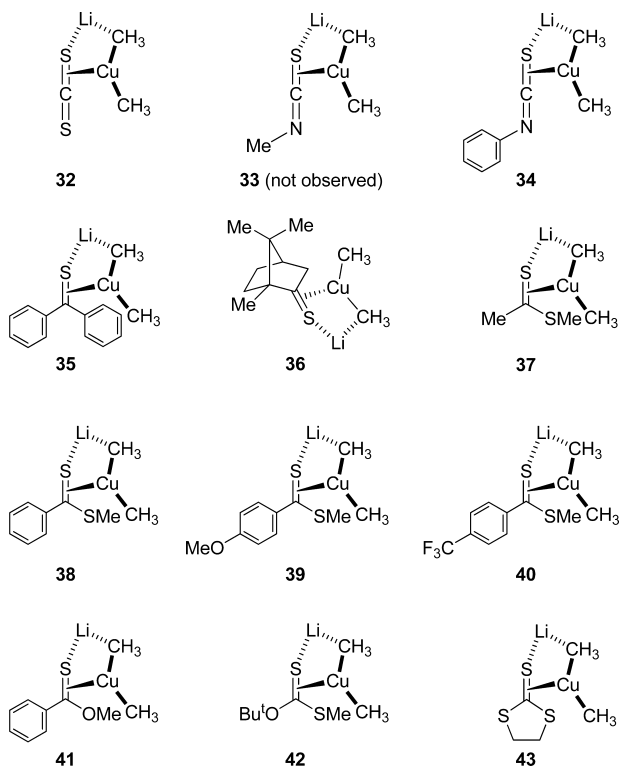
Scheme 4. Treatment of  $\text{Me}_2\text{CuLi}$  and  $\text{Me}_4\text{CuLi}$  with (a) Carbon Disulfide and (b) Methanol

Chart 4. Complexes of Compounds with C–S Double Bonds



In contrast,  $\text{Me}_2\text{CuLi}$  reacted rapidly with methanol (4 equiv) to produce methane under the same conditions. During the first few seconds, the homocuprate was converted to an Ashby cuprate,  $\text{Me}_3\text{Cu}_2\text{Li}$  ( $\text{MeCu} + \text{Me}_2\text{CuLi}$ ),<sup>22</sup> which also reacted with methanol at  $-100\text{ }^\circ\text{C}$ .

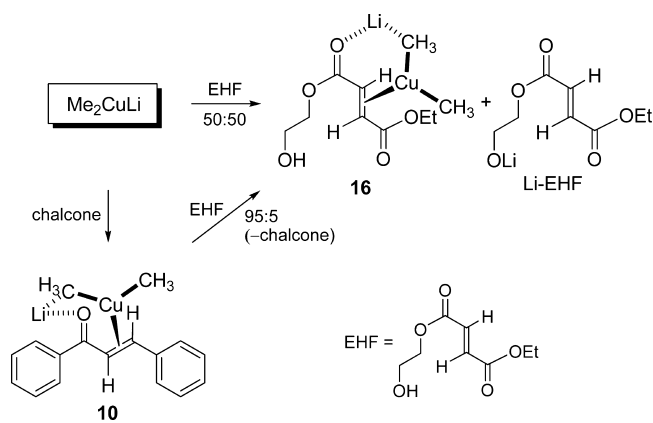
When carbon disulfide complex 32 was treated with methyl dithio-4-trifluoromethylbenzoate in the presence of methanol (4 equiv) at  $-100\text{ }^\circ\text{C}$ , the ligand exchange proceeded to complex 40 and carbon disulfide as usual, without the appearance of methane. We believe that a dissociative mechanism involving free  $\text{Me}_2\text{CuLi}$  would have resulted in

Table 4.  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data for Complexes of Compounds with C–S Double Bonds<sup>a,b</sup>

ID	$\text{Me}_{\alpha\text{H}}$	$\text{Me}_{\alpha\text{C}}$	$\text{Me}_{\beta\text{H}}$	$\text{Me}_{\beta\text{C}}$	C=S	$\Delta_{\text{CS}}$
32	−0.76	−10.54	0.37	20.10	279.19	85.29
33 <sup>c</sup>	—	—	—	—	—	—
34	−0.79	−9.09	0.43	10.81	193.88	61.43
35	−0.55	−9.02	−0.33	9.13	81.89	−157.49
36	−0.83	−6.76	−0.15	3.26	91.22	−181.93
37	−0.96	−8.58	−0.16	7.17	84.44	−152.08
38	−0.68	−9.31	−0.29	9.35	81.91	−148.27
39	−0.74	−9.46	−0.29	9.19	82.08	−144.90
40	−0.52	−9.18	−0.27	9.18	79.71	−149.33
41	−0.91	−9.23	−0.59	6.50	116.79	−95.42
42	−1.00	−9.34	−0.03	4.06	111.57	−103.40
43	−0.76	−9.51	0.12	8.84	84.69	−143.92

<sup>a</sup>All shifts are in ppm, measured at  $-100\text{ }^\circ\text{C}$ . <sup>b</sup>Cuprates prepared from  $\text{CuI}$ . <sup>c</sup>Not observed.

Scheme 5. Preparation of Hydroxy Complex 16 by Direct and Indirect Routes



significant methane generation. These experiments support our proposal that an associative mechanism is involved.<sup>20</sup> Theoretical studies also support this conjecture.<sup>23</sup>

Ligand exchange has proven to be a useful synthetic technique. For example, injection of ethyl 2-hydroxyethyl fumarate (EHF) into the usual  $\text{Me}_2\text{CuLi}$  solution at  $-100\text{ }^\circ\text{C}$  resulted in a mixture (ca. 1:1) of hydroxy complex 16 and lithiated substrate (Li-EHF, Scheme 5). In contrast, when chalcone complex 10 was prepared first and then treated with EHF, the product was predominately 16 (95%), which was stable enough for the usual spectral characterization. If there were significant equilibrium concentrations of  $\text{Me}_2\text{CuLi}$  in solutions of 16, we would expect this product to be transient at best.

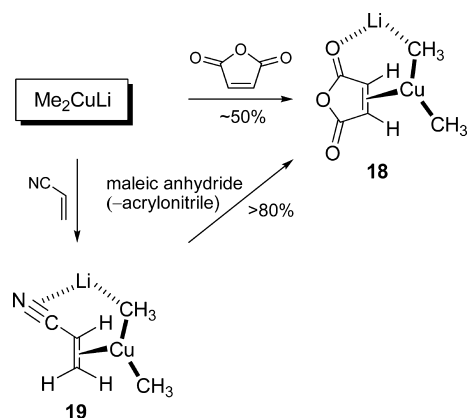
Amide complex 17 was prepared in reasonably good yield (75%) using our standard methodology and in very good yield (92%) via the displacement of chalcone from its  $\pi$ -complex 10. Two N–H peaks (ca. 3:1) were present in the  $^1\text{H}$  NMR spectrum of 17, which indicated at least two conformers were present.

Monoethyl fumarate quenched the cuprate solution immediately upon injection. It was not possible to make a monoethyl fumarate complex by indirect means, either.

Injection of solutions of maleic anhydride into solutions of  $\text{Me}_2\text{CuLi}\cdot\text{LiI}$  at  $-100\text{ }^\circ\text{C}$  gave  $\pi$ -complex 18 in variable yields, which depended upon how long the injector was cooled in the probe before injection. In contrast, injection of maleic

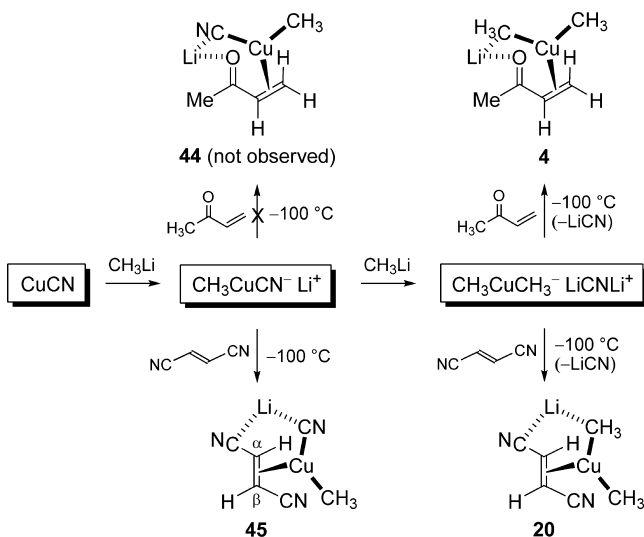


Scheme 6. Preparation of Maleic Anhydride Complex 18 by Direct and Indirect Routes



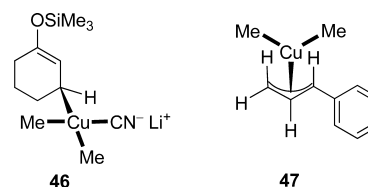
anhydride into a solution of 19 resulted in the rapid displacement of acrylonitrile and formation of complex 18 (Scheme 6).

**Coupling Constants.** Whereas methyl vinyl ketone (MVK) failed to yield a stable  $\pi$ -complex (cf. 44, Scheme 7) with  $\text{MeCuCNLi}$ ,<sup>8</sup> fumaronitrile afforded complex 45, which was stable at  $-100^\circ\text{C}$ , provided excess substrate (2 equiv) was used. With a stoichiometric amount of substrate, mixed cuprate complex 45 metathesized to homocuprate complex 20. This process is discussed in detail in an accompanying communication.<sup>24</sup>

Scheme 7. Reactions of MVK and Fumaronitrile with  $\text{MeCuCNLi}$  and  $\text{Me}_2\text{CuLi}\cdot\text{LiCN}$ 

Two-bond  $J$ -coupling across copper was introduced as a structure probe for organocopper compounds in 1991; for example,  $^{13}\text{CH}_3\text{Cu}^{13}\text{CNLi}$  was shown to have one methyl and one cyano group bonded to the same copper atom ( $^2J_{\text{CC}} = 21.6\text{ Hz}$ ).<sup>25</sup> Both  $^2J_{\text{CC}}$  and  $^2J_{\text{CP}}$  have been applied to structure problems.<sup>26</sup> When  $\eta^1\text{Cu}^{\text{III}}$  complex 46 (Chart 5) was prepared using  $^{13}\text{CH}_3\text{Li}$  and  $\text{Cu}^{13}\text{CN}$ , both small *cis* ( $^2J_{\text{CC}} = 5.4\text{ Hz}$ ) and large *trans* ( $^2J_{\text{CC}} = 35.4\text{ Hz}$ ) coupling constants were measured between the  $^{13}\text{C}$ -labeled methyl groups on copper and  $^{13}\text{CN}$ ; the methyl–methyl *cis* coupling was also small ( $^2J_{\text{CC}} = 2.9\text{ Hz}$ ).<sup>10</sup>

When  $\text{Cu}^{13}\text{CN}$  was used as the precursor for 45, *cis* ( $^2J_{\text{CC}} = 4.4\text{ Hz}$ ) and *trans* ( $^2J_{\text{CC}} = 11.5\text{ Hz}$ ) couplings to  $\text{C}_\alpha$  and  $\text{C}_\beta$ ,

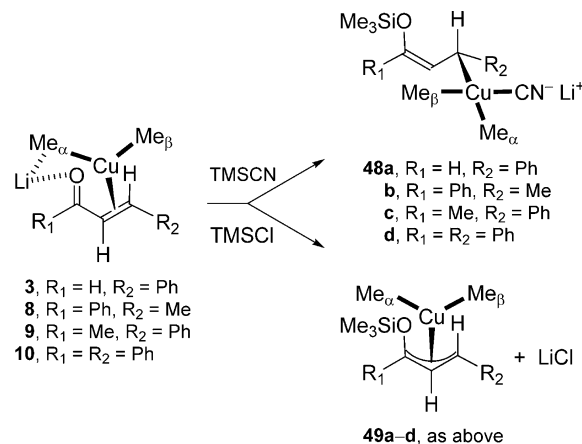
Chart 5. First Examples of  $\eta^1\sigma$ -allyl and  $\eta^3\pi$ -allyl  $\text{Cu}^{\text{III}}$  Intermediates

respectively, were observed along with broadening of the peak for the methyl carbon, which may be attributed to a small, unresolved *cis* coupling to  $^{13}\text{CN}$ .

Similarly, *cis* ( $^2J_{\text{CC}} = 1.4\text{ Hz}$ ) and *trans* ( $^2J_{\text{CC}} = 17.7\text{ Hz}$ ) couplings were observed for the complex of methyl dithio-4-trifluoromethylbenzoate with  $^{13}\text{CH}_3(2\text{-thienyl})\text{CuLi}$ .<sup>8</sup> For the complex of  $^{13}\text{CS}_2$  with  $\text{Me}_2\text{CuLi}$ , we measured *cis* coupling ( $^2J_{\text{CC}} = 4.5\text{ Hz}$ ) to the downfield methyl group and *trans* coupling ( $^2J_{\text{CC}} = 28.8\text{ Hz}$ ) to the upfield methyl.<sup>20</sup>

**Conversion of  $\text{Cu}^{\text{I}}$  to  $\text{Cu}^{\text{III}}$  Complexes and the Key to Stability.** While they frequently had been postulated as intermediates in reactions involving copper,<sup>27</sup> the first  $\text{Cu}^{\text{III}}$  intermediate identified for a major synthetic reaction was reported in 2007.<sup>10</sup> Intermediate 46 (Chart 5) resulted from the reaction of  $\pi$ -complex 6 with trimethylsilyl cyanide ( $\text{TMSCN}$ ) at  $-100^\circ\text{C}$ . This  $\sigma$ -allyl species was characterized as a pseudo-square-planar complex with the aid of two-bond coupling across copper (vide supra). The related  $\pi$ -allyl  $\text{Cu}^{\text{III}}$  complex was not observed, owing to the lack of a  $\beta$ -phenyl substituent (vide infra).

In our study of the reactions of organocuprates with allylic halides and acetates,<sup>11</sup> we found that a phenyl substituent helped stabilize  $\eta^3\text{Cu}^{\text{III}}$  complex 47 (Chart 5). This inspired us to examine cinnamaldehyde, crotonophenone, benzalacetone, and chalcone  $\pi$ -complexes (3 and 8–10, respectively). When these  $\eta^2\text{Cu}^{\text{I}}$  complexes, prepared from  $\text{CuCN}$ , were treated with trimethylsilyl cyanide ( $\text{Me}_3\text{SiCN}$ ), they gave the respective  $\eta^1\text{Cu}^{\text{III}}$  complexes 48a–d (Scheme 8).

Scheme 8. Reactions of Selected  $\pi$ -Complexes with  $\text{TMSCN}$  and  $\text{TMSCl}$ 

On the other hand, when they were prepared from  $\text{CuI}$ , treatment with trimethylsilyl chloride ( $\text{Me}_3\text{SiCl}$ ,  $\text{TMSCl}$ ) or other chlorosilanes ( $\text{Et}_3\text{SiCl}$ ,  $\text{Me}_2\text{PhSiCl}$ ) gave  $\eta^3\text{Cu}^{\text{III}}$  complexes 49a–d (or analogous complexes), respectively. When they were prepared from  $\text{CuCN}$  and then treated with chlorosilanes, they gave mixtures of 48 and 49.<sup>12</sup>

Table 5.  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data for  $\eta^1$  and  $\eta^3$   $\text{Cu}^{\text{III}}$  Complexes<sup>a,b</sup>

ID	Me <sub><math>\alpha\text{H}</math></sub>	Me <sub><math>\alpha\text{C}</math></sub>	Me <sub><math>\beta\text{H}</math></sub>	Me <sub><math>\beta\text{C}</math></sub>	DB <sub><math>\alpha\text{H}</math></sub>	DB <sub><math>\alpha\text{C}</math></sub>	DB <sub><math>\beta\text{H}</math></sub>	DB <sub><math>\beta\text{C}</math></sub>	C–O	C $\equiv$ N	$\Delta_\alpha$	$\Delta_\beta$	$\Delta_{\text{CO}}$
48a <sup>c</sup>	0.21	14.07	0.76	21.12	5.66	120.77	N/A	N/A	128.94	152.79	N/A	N/A	N/A
48b <sup>c</sup>	0.04	13.32	0.65	17.72	6.15	129.29	N/A	N/A	139.68	152.72	N/A	N/A	N/A
48c <sup>c</sup>	0.13	14.15	0.70	21.62	5.56	117.87	N/A	N/A	137.48	153.70	N/A	N/A	N/A
48d <sup>c</sup>	0.26	15.28	0.89	21.70	6.67	122.79	N/A	N/A	125.45	152.87	N/A	N/A	N/A
49a <sup>d</sup>	0.05	−5.81	0.06	9.75	5.31	96.36	4.55	78.51	124.69	N/A	20.46	15.56	−45.76
49b <sup>e,f</sup>	−0.51	— <sup>f</sup>	0.30	— <sup>f</sup>	5.63	— <sup>f</sup>	3.67	— <sup>f</sup>	— <sup>f</sup>	N/A	— <sup>f</sup>	— <sup>f</sup>	— <sup>f</sup>
49c	−0.26	3.74	0.03	7.73	5.36	95.59	4.26	74.84	139.37	N/A	24.05	11.74	−45.16
49d	−0.38	9.29	0.20	9.07	6.44	96.20	4.55	78.37	134.44	N/A	26.82	14.17	−44.55

<sup>a</sup>All shifts are in ppm, measured at  $-100^\circ\text{C}$ . <sup>b</sup>Cuprates prepared from CuI unless otherwise noted. <sup>c</sup>Cuprate prepared from CuCN. <sup>d</sup>( $\text{CD}_3$ )<sub>2</sub>( $\text{C}_6\text{H}_5$ )SiCl added, as ( $\text{CH}_3$ )<sub>3</sub>Si peak interfered. <sup>e</sup>( $\text{CH}_3\text{CH}_2$ )<sub>3</sub>SiCl added, as ( $\text{CH}_3$ )<sub>3</sub>Si peak interfered. <sup>f</sup>Fleeting intermediate;  $^{13}\text{C}$  NMR not measured.

In the case of crotonophenone,  $\eta^3$ -complex **49b** was unstable and rapidly went on to 1,4-addition product at  $-100^\circ\text{C}$ .<sup>12</sup> In the case of cinnamaldehyde, *anti-syn* complex **49a** isomerized to the corresponding *syn-syn* complex **49a'**. We use the chemical shifts for **49a** in order to compare them with those for **49c** and **49d**, which also have the *anti-syn* conformation. In contrast to **49b**, complexes **49a'**, **49c**, and **49d** were stable for extended periods at  $-100^\circ\text{C}$ . It appears that a  $\beta$ -phenyl substituent is the key to stability.

Important NMR data for complexes **48** and **49** are summarized in Table 5. For the calculation of  $\Delta$ -values, we use the chemical shifts for **3a**, **9a**, and **10**, which all have the *s-cis* conformation. The conversion of these complexes to  $\eta^3$   $\text{Cu}^{\text{III}}$  complexes **49a**, **49c**, and **49d**, respectively, results in  $\Delta_\alpha \approx 20$ – $27$  ppm and  $\Delta_\beta \approx 11$ – $16$  ppm, which move in the opposite direction from the  $\Delta$ -values for the starting  $\pi$ -complexes (Table 1). Moreover, the larger effect is observed for  $\text{C}_\alpha$  instead of  $\text{C}_\beta$ . The magnitudes of  $\Delta_{\text{CO}} \approx -45 \pm 1$  ppm are significantly larger than those of  $\Delta_\alpha$  and  $\Delta_\beta$  ( $|\Delta_{\text{CO}}| > |\Delta_\alpha| > |\Delta_\beta|$ ), and they are substantially greater than the magnitudes of  $\Delta_{\text{CO}}$  for **3a** ( $-24$  ppm), **9a** ( $-14$  ppm), and **10** ( $-9$  ppm).

Strictly speaking, **46**, **48**, and **49** are intermediates in the synthetically valuable and theoretically interesting silyl-assisted conjugate addition of organocuprates.<sup>28</sup> Nevertheless, the facile conversion of cuprate–olefin  $\pi$ -complexes to  $\text{Cu}^{\text{III}}$  intermediates tends to support the oxidative addition/reductive elimination mechanism (Scheme 1b) for the usual conjugate addition reaction of organocuprates to  $\alpha,\beta$ -unsaturated carbonyl compounds.

## PERSPECTIVE AND CONCLUSIONS

The first organocuprates were prepared from CuCN and Grignard reagents, as reported by Kondurov and Fomin in 1915.<sup>29</sup> These presumptive cuprates decomposed without isolation or characterization to hydrocarbon products. The first organocuprate(I) compound to be characterized as such was  $\text{Me}_2\text{CuLi}$ , prepared by Gilman in 1952;<sup>30</sup> however, its chemistry was not explored until more than a decade later. In 1966, House and co-workers showed that this “Gilman reagent” gave 1,4-addition (“conjugate addition”) with  $\alpha$ -enones,<sup>31</sup> and they speculated that organocuprates were intermediates in the Kharasch reaction, the 1,4-addition of Grignard reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds catalyzed by copper salts.<sup>16</sup> We have provided experimental support for this conjecture by preparing a cuprate–olefin  $\pi$ -complex (**6c**) starting from CuCl and  $\text{MeMgCl}$ .

Shortly after the House paper appeared, Corey and Posner reported the cross-coupling reaction of organocuprates with

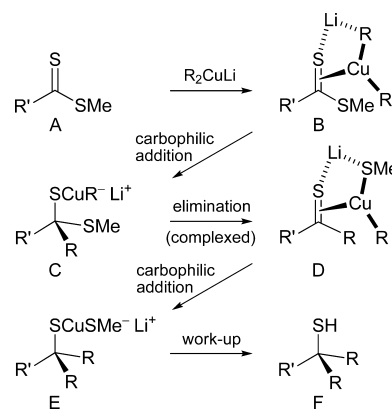
alkyl halides.<sup>32</sup> This reaction has many complications,<sup>33</sup> but it is useful in special cases such as allylic halides and carboxylates.<sup>11</sup>

In 1988, Bertz, Dabbagh, and Williams reported a new kind of reaction of Gilman reagents, namely, carbophilic addition to thiocarbonyl compounds, for example, thioketones and dithioesters.<sup>20</sup> The “double-barreled” carbophilic addition to dithioesters was made possible by the intermediacy of reactive mixed thiocuprates (Posner reagents).<sup>34</sup> This reaction has found some interesting applications;<sup>35</sup> however, it is included here mainly for theoretical reasons. In analogy with the Kharasch reaction, where copper salts change the regioselectivity from 1,2- to 1,4-addition, they change the regiochemistry of the reactions of Grignard and lithium reagents with thiocarbonyl compounds from thiophilic to carbophilic addition.<sup>20</sup>

Scheme 9 lays out a mechanism for the conversion of a typical dithioester **A** to thiolate product **F**, which gives doubly substituted thiol **F** upon workup. We observe intermediate **B**, but not conjectural intermediate **C** or **D**, which intimates that their reactions are very fast. Furthermore, the substrate must remain complexed to copper throughout. Simple thioketones are very unstable,<sup>36</sup> and if a significant amount of **D** were lost via dissociation, the overall yield of product would be measurably diminished. In one paradigmatic reaction, methyl dithiopropionate gave 96–100% yields of 2-methyl-2-butanethiol with  $\text{Me}_2\text{CuLi}$ , prepared from a variety of copper(I) salts ( $\text{CuI}$ ,  $\text{CuCN}$ ,  $\text{CuBr}\cdot\text{SMe}_2$ ,  $\text{CuOTf}$  (copper(I) triflate)).<sup>20b</sup>

This reaction is an example of geminal alkylation. Our first attempt at this genre involved the reactions of lithium and

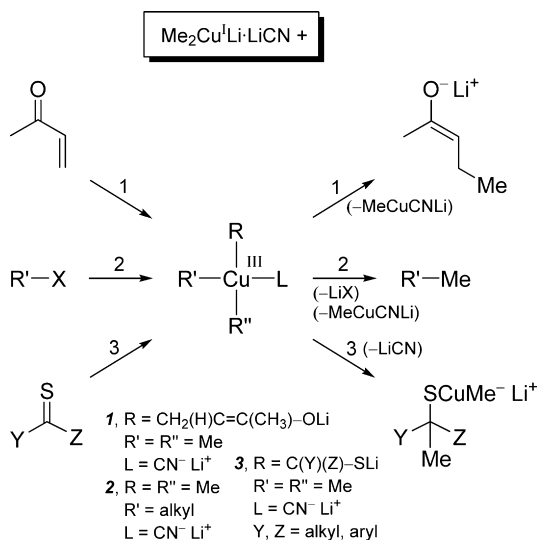
## Scheme 9. Double-Barreled Carbophilic Addition of Cuprates to Dithioesters



copper reagents with ditosylhydrazones, which were not synthetically useful, owing to competing side reactions.<sup>19</sup>

Three apparently unique reactions of organocuprates are (1) conjugate addition to activated olefins, (2) cross-coupling with alkyl halides, and (3) carbophilic addition to thiocarbonyl compounds. It is possible to unite all three reactions into one “unified theory” by showing that they proceed via similar  $\text{Cu}^{\text{III}}$  intermediates, as illustrated for the cyano-Gilman reagent in Scheme 10, where 1, 2, and 3 are the  $\text{Cu}^{\text{III}}$  intermediates in paths 1, 2, and 3, respectively. In the case of path 1, both  $\eta^1$  and  $\eta^3$   $\text{Cu}^{\text{III}}$  intermediates have now been prepared,<sup>10,12</sup> as described above. Likewise,  $\text{Cu}^{\text{III}}$  intermediates have been observed for path 2.<sup>33</sup> In the case of path 3,  $\text{Cu}^{\text{III}}$  intermediate 3 has not yet been observed; nevertheless, we note it is analogous to 1, where the enolate has been replaced by a thiolate. (N.B., cuprate–thiocarbonyl complexes may also be considered  $\text{Cu}^{\text{III}}$  species.<sup>20</sup>)

Scheme 10. Unified Theory of Organocuprate Reactivity



We have established that  $\eta^2$ -complexes are intermediates in conjugate addition (path 1) and carbophilic addition (path 3). The elucidation of the exact nature of these  $\eta^2$ -complexes may require bringing other techniques to bear (e.g., X-ray crystallography). In the meantime, we have conjectured that  $\alpha$ -enones are on the  $\pi$ -side and thiocarbonyls are on the  $\sigma$ -side of the  $\pi$ – $\sigma$  continuum for double-bond complexes of transition metals.<sup>20</sup> The  $\alpha,\beta$ -unsaturated nitriles studied here appear to span virtually the entire range.

In Figure 7 we indicate the relative stabilities of a dozen of the >40 complexes studied here by ordering their ligands. The

approximate position of complexes on the  $\pi$ – $\sigma$  continuum is supported by the observation of two-bond coupling across copper for the “tighter” complexes, such as those of carbon disulfide, fumaronitrile, and methyl dithio-4-trifluoromethylbenzoate. We have not been able to detect  $J$ -coupling across copper in  $\alpha$ -enone  $\pi$ -complex 6a or 6b with  $^{13}\text{C}$ -labeled methyl groups. While we have included a  $\pi$ – $\sigma$  scale, we do not mean to imply quantitative information is presently available.

**Three Controversies.** The first great controversy of organocuprate chemistry concerned the mechanism of the conjugate addition reaction, as discussed in the Introduction. By using rapid injection NMR, we have now been able to make a panoply of cuprate–olefin  $\pi$ -complexes and study their properties. This body of knowledge provides a solid foundation for future mechanistic investigations.

The second great controversy concerned the existence of “higher order cyanocuprates”, which were first questioned by a Bell Laboratories chemist.<sup>37</sup> Thanks to a number of experimental techniques (NMR, IR, EXAFS, and single-crystal X-ray),<sup>38</sup> as well as theoretical calculations,<sup>39</sup> we now know that they do not exist; nevertheless, it is worth considering why people believed in them in the first place. In many examples, the cyano-Gilman reagents,  $\text{R}_2\text{CuLi-LiCN}$ , were more reactive than the previous iodo-Gilman reagents,  $\text{R}_2\text{CuLi-LiI}$ . Consequently, we are well aware of the danger inherent in the use of reactivity to assign structures, and we only use it to highlight major differences, for example, the use of methanol to differentiate qualitatively “loose” versus “tight” complexes (i.e., very weak vs very strong bonding).

Figure 8 provides a simple way to understand the problem with “higher order cyanocuprates”. In structures A and B the negative charges from the methyl groups are balanced by the positive charges on  $\text{Cu}^{\text{I}}$  or  $\text{Cu}^{\text{III}}$ , respectively, and the remaining negative charge is localized on N, the most electronegative atom, and balanced by a  $\text{Li}^+$  ion. The  $\text{Cu}^{\text{I}}$  atom in A is  $d^{10}$ , and coordination of two lone pairs gives a total of 14 electrons; the  $\text{Cu}^{\text{III}}$  atom in B is  $d^8$ , and coordination of four lone pairs gives a total of 16 electrons. In C and D, we attempt to add an extra Me anion to the Cu atoms in A and B, increasing the canonical electron counts to 16 and 18, respectively, which appear acceptable. However, calculations for C show that no low-energy configuration is available.<sup>39</sup> This is essentially an application of the Pauling electroneutrality principle.<sup>40</sup> Our efforts to prepare D have proven unsuccessful, as were many attempts to prepare C.<sup>37</sup>

Finally, we come full circle by settling a third controversy, concerning the hapticity of bonding in cuprate–olefin complexes, which we have supported as intermediates in the conjugate addition reaction. It has been suggested that they are

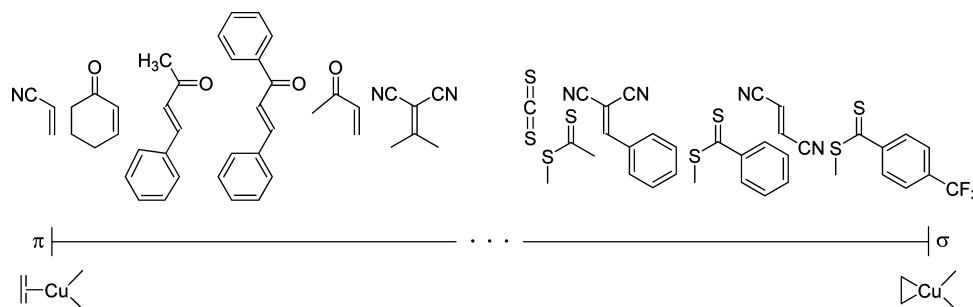
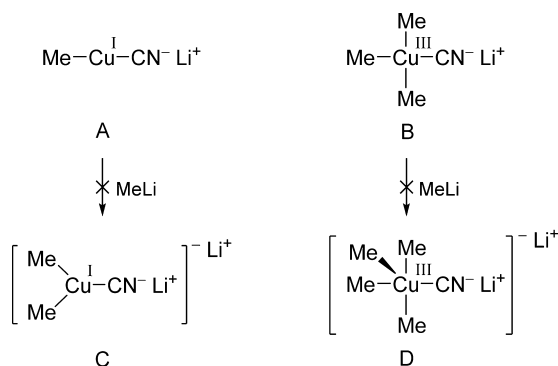


Figure 7. Relative stabilities of selected substrates in dimethylcuprate complexes. Each is displaced from its complex by those to the right of it. The scale is not quantitative.



**Figure 8.** Ate-complexes of  $\text{Cu}^{\text{I}}$  and  $\text{Cu}^{\text{III}}$ : A and B are known compounds; C and D are hypothetical “higher order cyanocuprates”.

$\eta^3 \text{Cu}^{\text{III}}$  complexes.<sup>18</sup> Figure 9a illustrates how the chemical shifts of relevant carbon atoms change upon complex formation. It is clear that the carbonyl group (CO) remains essentially the same and that the olefin is the focus of bond formation. In contrast stands Figure 9b, where the carbonyl group is significantly affected by  $\pi$ -allyl complex formation. Therefore, regardless of where organocuprate–double-bond complexes may be on the  $\pi$ – $\sigma$  continuum, we conclude that they all involve dihapto-coordination.

In this paper we have presented our results for organocuprate complexes with C–C, C–N, and C–S double bonds, which are intermediates in reactions of synthetic and theoretical interest. A copious amount of NMR data strongly supports the conclusion that all of them are fundamentally based on dihapto-coordination to copper, although they vary dramatically in the strength of the ligand–copper bond from very weak to very strong, indeed. The weaker complexes are useful for the synthesis of stronger, functionalized ones that are difficult to prepare directly. Finally, this study makes significant contributions to understanding the three most important controversies in the history of organocopper chemistry.

## EXPERIMENTAL SECTION

NMR spectra were obtained with a JEOL ECA-500 spectrometer. All NMR tubes (Norell) were dried in an oven (150 °C) and cooled under Ar. In order to get consistently good results, it is critically important that the NMR tubes be unused. We have experimented with used NMR tubes that had been cleaned thoroughly by washing with concentrated nitric acid, deionized water, concentrated ammonium hydroxide, deionized water, and finally acetone. The lifetime of  $\pi$ -complex **6** in these tubes was measured in seconds rather than hours,

as when virgin NMR tubes were used. In fact, were it not for rapid injection NMR, we would not have seen this  $\pi$ -complex at all.

$\text{Me}_2\text{CuLi}$  was prepared by adding 2.00 equiv of  $\text{MeLi}\cdot\text{THF}-d_8$  in benzene- $d_6$  (ca. 1 M) to a suspension of  $\text{CuI}$  or  $\text{CuCN}$  (30.0  $\mu\text{mol}$ , Aldrich, best grade available) in 420  $\mu\text{L}$  of  $\text{THF}-d_8$  (freshly distilled from Na/K) in a septum-sealed NMR tube, cooled to  $-80^\circ\text{C}$  in a dry ice/acetone bath. The suspension of copper salt was sonicated for 1 min at  $0^\circ\text{C}$  before addition of the lithium reagent at  $-80^\circ\text{C}$ , and the resulting cuprate solution was agitated for 10 s outside the cold bath with a vortex mixer (VWR). The sample was checked for purity by  $^1\text{H}$  NMR at  $-100^\circ\text{C}$ . When a satisfactory sample was obtained, the septum was removed in a stream of dry nitrogen, and the tube was immediately lowered into the probe, which was filled with the dry nitrogen used to spin the sample. The substrate, dissolved in  $\text{THF}-d_8$ , was then injected (60  $\mu\text{L}$  per standard injection), and single-pulse  $^1\text{H}$  NMR spectra were obtained periodically (2–20 s, depending on the rate of reaction).  $^1\text{H}$  NMR ( $^{13}\text{C}$  NMR) spectra were referenced to benzene at 7.34 (128.59) ppm.

## ASSOCIATED CONTENT

### Supporting Information

Typical 1D and 2D NMR plots. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

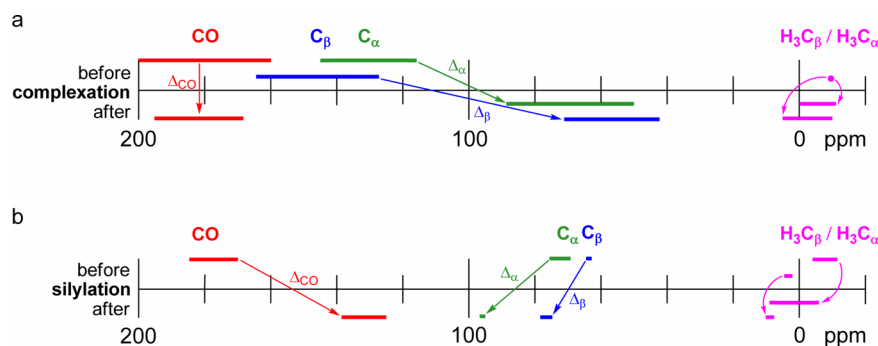
The authors declare no competing financial interest.

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**Figure 9.**  $^{13}\text{C}$  NMR chemical shift ranges for CO (red),  $\text{C}_\alpha$  (green), and  $\text{C}_\beta$  (blue) of the substrate and  $\text{Me}_\alpha$  (top magenta) and  $\text{Me}_\beta$  (bottom magenta) of the cuprate before and after (a) complexation giving  $\eta^2$ -complexes and (b) silylation converting  $\eta^2$ - to  $\eta^3$ -complexes.



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