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Rapid Injection NMR in Mechanistic Organocopper Chemistry. Preparation of the Elusive Copper(III) Intermediate[1]

Steven H. Bertz,*,† Stephen Cope, Michael Murphy,* Craig A. Ogle,* and Brad J. Taylor

Department of Chemistry, University of North Carolina—Charlotte, Charlotte, North Carolina 28223

Received October 20, 2006; E-mail: sbertz@complexitystudycenter.org; cogle@uncc.edu

Following the pioneering work of Gilman,[2] House,[3−5] Whitesides,[4,5] Corey,[6,7] Posner,[6,8] and a phalanx of other researchers,[9−11] organocopper reagents are now a vital part of many of the synthetic methods that organic chemists depend upon to selectively form carbon−carbon bonds. Paradigmatic examples include conjugate addition to α-enones,[3,4] S_N2-like reactions of organic halides,[5,6] and S_N2' reactions of allylic carboxylates.[12] The seminal step that forges the carbon−carbon link in these and related organocopper reactions has long been posited to be reductive elimination from a putative copper(III) intermediate,[3,5,8,12−18] where the prospective partners have been brought together in a *cis* relationship. Both square planar[15−18] and T-shaped[19] complexes have been proposed.

We have previously reported that rapid injection NMR (RI-NMR) is an excellent way to access highly reactive and thermally unstable species.[20] By using RI-NMR in conjunction with a typical substrate, 2-cyclohexenone **2**, and common Gilman reagents, $Me_2CuLi\cdot LiI$ **3a** or $Me_2CuLi\cdot LiCN$ **3b**, we have now been able to prepare the first example of this crucial intermediate, lithium cyanobis(methyl)(3-trimethylsiloxycyclohex-2-en-1-yl)cuprate(III) **1** (Figure 1). Moreover, we have found conditions under which it is stable indefinitely and can therefore be studied in great detail. In 1995, Snyder unequivocally predicted that it should be possible to prepare and characterize such a species,[21] and the latest calculations from his group underpin our conclusions.[22]

Before our introduction of RI-NMR into organocopper chemistry, relatively stable π-complexes had been prepared from cinnamate esters[23] and 10-methyl-$\Delta^{1,9}$-2-octalone.[24] However, conventional techniques were not sufficient to prepare "clean" solutions of π-complexes from substrate **2**. By using rapid injection, a solution of **2** was introduced directly into the NMR tube containing **3a** or **3b**, spinning in the spectrometer probe under nitrogen at −100 °C, where we were able to prepare highly reactive π-complexes **4** and **4**·LiX (X = I, CN) and study them spectroscopically.[20] Now, we have investigated the chemical reactivity of these π-complexes by making a second rapid injection, and this has led us to the efficient preparation of **1**.

Two routes can be used to prepare **1** (Scheme 1), both of which are made possible by the double application of the rapid injection technique. In route A, a solution of iodo-Gilman reagent **3a** in THF-d_8 in an NMR tube at −100 °C was injected with a THF-d_8 solution of **2** in order to obtain the usual mixture of π-complexes **4** and **4**·LiI.[21] Then, a second injection introduced a THF-d_8 solution of trimethylsilyl cyanide (TMSCN), which induced an essentially quantitative conversion of the π-complexes to **1**.

In route B, a solution of cyano-Gilman reagent **3b** in THF-d_8 in an NMR tube at −100 °C was injected with a THF-d_8 solution of trimethylsilyl chloride (TMSCl). While superficially similar to the procedure of Corey and Boaz,[7] who treated iodo-Gilman reagents with TMSCl before adding α-enones, our experiment gave a serendipitously different result: the TMSCl reacted rapidly with the LiCN present in **3b**[25] and quantitatively generated chloro-Gilman reagent $Me_2CuLi\cdot LiCl$ and TMSCN in situ. Then, a second injection introduced a THF-d_8 solution of **2**, which underwent essentially complete conversion to **1**.

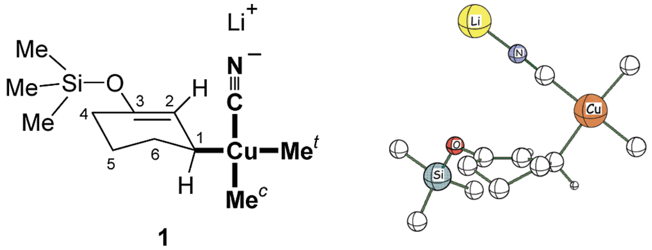

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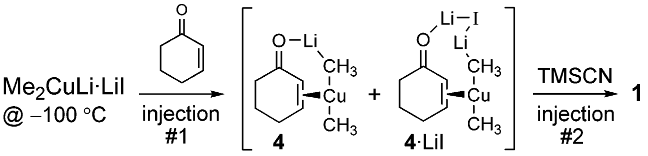
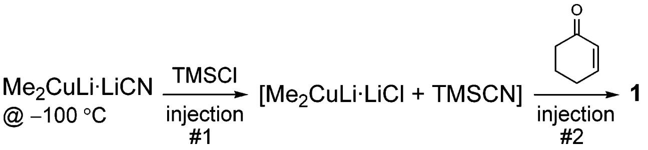
Figure 1. Representations of copper(III) intermediate **1** in the form of its contact ion pair. For the solvent-separated ion pair, see ref 22.

Scheme 1. Two Routes to Copper(III) Intermediate **1**

Route A



Route B



A number of formally Cu(III) compounds are known,[26] but only a few of them involve Cu−C bonds. Examples include difluoromethyl[27] and trifluoromethyl derivatives,[28] diazamacrocyclic[29] and triazamacrocyclic complexes,[30] and a bis(dicarbollide) sandwich.[31] Most of the characterized Cu(III) complexes are square planar, and theoretical calculations indicate this geometry for our case as well.[22]

Table 1 summarizes the NMR chemical shift data for **1**−**4**. The salient feature of the ^{13}C NMR spectrum of **1** is the presence of Me peaks at 12.43 and 25.31 ppm, which are dramatically downfield from their positions in **3** or **4**. The Me group at 25.31 ppm has NOESY cross-peaks with the ring (H atoms on C_1, C_2, C_5, and C_6) and with the Me group at 12.43 ppm; the latter has no cross-peaks with the ring. Hence, the downfield peak is from Me^c, *cis* to the ring, while the upfield peak is from Me^t, *trans* to it.

The large chemical shift difference between Me^c and Me^t can be rationalized by observing that they are *trans* to cyano and

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[†] Complexity Study Center, 88 East Main St., Suite 220, Mendham, NJ 07945.

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Table 1. ^{13}C NMR (^{1}H NMR) Chemical Shifts for **1**−**4**[a]

group	**2**	**3a**	**3b**	**4**	**4**·LiI	**4**·LiCN	**1**
CH_3 (CH_3^t)[b]		−**9.12** (−1.40)	−**9.04** (−1.35)	−**5.02** (−1.12)	−**5.56** (−1.16)	−**5.76** (−1.15)	**12.43** (0.05)
CH_3 (CH_3^c)[b]		−**9.12** (−1.40)	−**9.04** (−1.35)	−**0.57** (−0.10)	−**1.85** (−0.24)	−**2.14** (−0.21)	**25.31** (0.53)
CN			158.89			159.20	**153.78**
C_1 (C_3)[b]	198.65			194.75	193.34	193[c]	144.73
C_2−H (C_2−H)[b]	130.12 (5.90)			**77.45** (3.77)	**75.82** (3.68)	**75.27** (3.71)	116.28 (5.02)
C_3−H (C_1−H)[b]	151.65 (7.08)			**61.50** (3.26)	**61.50** (3.19)	**61.51** (3.17)	**39.68** (2.74)

[a] Parts per million from TMS. Values for C atoms attached to Cu are in boldface. [b] Labeling for **1**. Note that C_1 of **2** becomes C_3 of **1** and C_3 of **2** becomes C_1 of **1**. [c] Shift could not be measured accurately, owing to broadening.

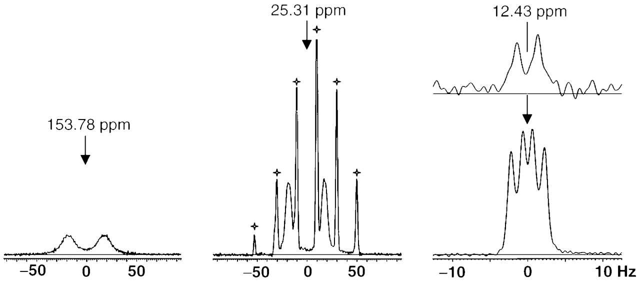
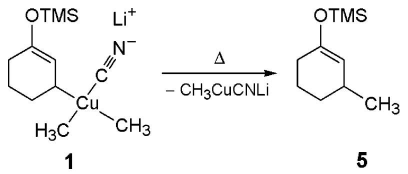


Figure 2. Selected ^{13}C NMR traces for labeled **1** (+ solvent peaks). The lower are for $RCu(^{13}CH_3)_2{}^{13}CNLi$. The upper is for $RCu(CH_3)_2{}^{13}CNLi$. Note the different scale for the rightmost traces. R is defined in the text.

Scheme 2. Further Reaction of Copper(III) Intermediate **1**



R = 3-trimethylsiloxycyclohex-2-en-1-yl ligands, respectively, which are very different electronically.

The ring methine and cyano carbon resonances are shifted upfield, the former owing to a change in hybridization (from ~sp^2 to sp^3). The latter appears at 153.78 ppm, between the values of 158.89 ppm for **3b** (no Cu−CN bond[32]) and 148.99 ppm for MeCuCNLi (demonstrable Cu−CN bond[33]).

The presence of the TMS group was confirmed by a NOE between the H atoms of the Me groups on Si and the H atoms on C_2 and C_4 of the ring.[34]

The preparation of **1** was repeated with $^{13}CH_3Li$ and $Cu^{13}CN$ in order to measure $^{13}C-^{13}C$ coupling constants ^2J across Cu (Figure 2). This method was first used to prove that both CH_3 and CN are attached to the same Cu in $CH_3CuCNLi$.[33] The ring methine is coupled to Me^t with $^2J = 38.1$ Hz, and the cyano is coupled to Me^c (*trans* to it) with $^2J = 35.4$ Hz; the cyano is coupled to Me^t (*cis* to it) with $^2J = 5.4$ Hz, and Me^c is coupled to Me^t with $^2J = 2.9$ Hz. The methine−cyano and methine−Me^c couplings are not resolved under our conditions; they are predicted to be the smallest of the six possible ones.[22] The relative magnitudes of the calculated ^2J values agree with experiment: methine−Me^t > cyano−Me^c ≫ cyano−Me^t > Me^c−Me^t > methine−cyano ~ methine−Me^c.[22] The pattern, *trans* ≫ *cis*, is consistent with a square planar complex.[35]

Finally, when the spectrometer probe was warmed from −100 to −80 °C, **1** was converted smoothly into MeCuCNLi and **5**, the expected conjugate addition product (Scheme 2).

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Supporting Information Available: NMR spectra (^{1}H NMR, ^{13}C NMR, HMQC, COSY, and NOESY). This material is available free of charge via the Internet at http://pubs.acs.org.

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