Copper(III) Intermediates

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Organocuprate Cross-Coupling: The Central Role of the Copper(III) Intermediate and the Importance of the Copper(I) Precursor**

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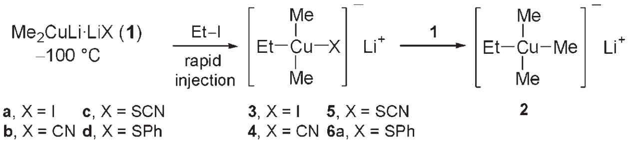
Copper, the humblest of the coinage metals, has nevertheless been the most useful synthetically. Chemists use organocopper compounds, for exmaple, organocuprates (Gilman reagents) R_2CuLi, for a plethora of transformations involving the selective creation of carbon–carbon bonds.[1,2] The two prototypical reactions of organocopper reagents are conjugate addition to α,β-unsaturated carbonyl compounds and cross-coupling with organic halides,[3–5] which has been generalized to include a variety of leaving groups and further extended from S_N2 to S_N2' processes.

The key intermediate in both stoichiometric and catalytic copper-mediated reactions has long been believed to be a so-called "copper(III) intermediate,"[3a,4–6] and theoretical calculations have supported this hypothesis.[7,8] We recently reported the observation of the first example of such a tetracoordinate, square-planar (TCSP) intermediate, lithium cyanobis(methyl)(3-trimethylsiloxycyclohex-2-en-1-yl)cuprate(III), in a conjugate addition reaction (2-cyclohexenone + $Me_2CuLi{\cdot}LiI + Me_3SiCN$) by using rapid-injection NMR spectroscopy (RI-NMR) at −100 °C.[9] It decomposed rapidly at −80 °C to yield the expected enolate.

We have now investigated the reactions of a variety of methyl Gilman reagents, $Me_2CuLi{\cdot}LiX$ (**1**, X = I, CN, SCN, SPh), with a simple alkyl halide, EtI, under RI-NMR conditions, and we have been able to observe a number of TCSP intermediates with a surprising range of stabilities. The most stable of them, lithium ethyltrimethylcuprate(III) (**2**), is the first example of a tetraalkyl copper(III) complex without fluorinated substituents.[10] Since the earliest days of the Ullmann reaction, copper-mediated cross-coupling processes have been notoriously difficult to control and optimize,[5] and our observations in this area have synthetic ramifications as well as mechanistic significance.

When $Me_2CuLi{\cdot}LiI$ (**1a**) or $Me_2CuLi{\cdot}LiCN$ (**1b**; in [D$_8$]THF under nitrogen in an NMR tube, spinning in the probe of an NMR spectrometer at −100 °C) was injected with a [D$_8$]THF solution of EtI, transient new signals were observed in the NMR spectrum. They were assigned to **3** (from **1a**) and **4** (from **1b**), respectively (Scheme 1), on the basis of NMR spectroscopy studies, including 2D techniques (see the Supporting Information) and ^{13}C-labeled analogs (see below). Chemical shift data are summarized in Table 1; they are notable for the extremely deshielded nature of the carbon atom bonded to copper.



Scheme 1. Formation of TCSP intermediates from methyl cuprates.

Table 1: Chemical shifts δ from ^{13}C NMR (^1H NMR) spectroscopy for TCSP species **2–6**.[a]

Complex	δ Me	δ Et (CH_2,CH_3)	δ Cuprate[b]
Me_3EtCu[c]	13.26, 16.03[d]	28.17, 16.13	[e]
(**2**)	(−0.42, −0.29[d])	(0.54, 1.15)	
Me_2EtCuI	16.03	33.67, ND	−9.07
(**3**)	(−0.07)	(1.48, 1.28)	(−1.39)
$Me_2EtCuCN$[f]	14.06	34.66, 16.03	−9.11
(**4**)	(0.00)	(1.54, 1.20)	(−1.41)
$Me_2EtCuSCN$	17.42	39.07, ND	−9.08
(**5**)	(−0.21)	(1.36, 1.26)	(−1.31)
trans-$Me_2EtCuSPh$	18.06	34.21, 17.53	−9.50
(**6a**)	(−0.31)	(1.83, 1.31)	(−1.31)
cis-$Me_2EtCuSPh$	14.83, 20.40	30.04, 15.60	−9.50
(**6b**)	(−0.50, 0.83)	(0.53, 1.14)	(−1.31)

[a] Chemical shifts δ [ppm] vs. TMS. ND = not determined. [b] Shifts of starting cuprate, **1**, before injection. [c] Shifts for **2** from **4**, see [e]. [d] 2× area of other Me peak. [e] Prepared from **1a–d**. The shifts of the ^{13}C atom bonded to copper in **2** vary with Cu salt by ±0.02 ppm; the corresponding ^1H shifts vary by ±0.1 ppm. [f] Cyanide ^{13}C shifts are δ = 152.66 ppm for **4** and δ = 158.95 ppm for **1b**.

As shown in Figure 1a, **3** had a fleeting existence at −100 °C, where it reached a maximum concentration after about one minute and then disappeared as it was supplanted by **2**. As can be appreciated by comparison of Figure 1b with

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

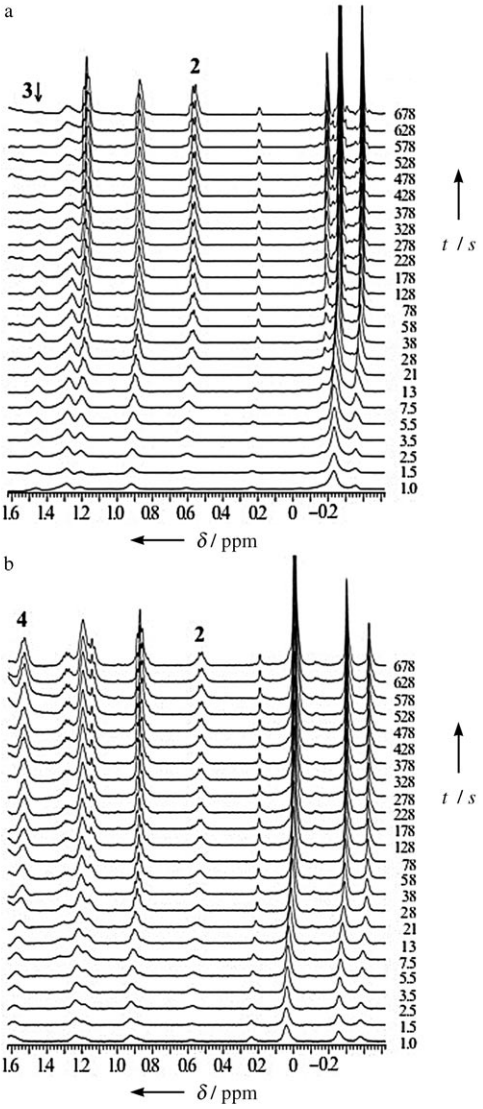


Figure 1. ^{1}H NMR spectra from the rapid-injection treatment of a) **1a** and b) **1b** with EtI. Signals from the methylene groups bonded to Cu are labeled. The minor peak that grows in near $\delta = -0.19$ ppm in (a) is from Me_3Cu_2Li; its other peak (2×area) is at $\delta = -1.13$ ppm. $Me_2CuLi{\cdot}LiI$ appears at $\delta = -1.40$ ppm.

Figure 1a, **4** had a longer lifetime and is significantly more stable than **3**. Gschwind and co-workers have prepared the trimethyl analogue of **4** by an indirect route, and their results comport with ours.[11]

Figure 2 shows the effect of warming the reaction mixture prepared from **1b** and EtI (cf. Figure 1b). At −100 °C, it contained a mixture of **4** (major) and **2** (minor); however, upon warming to −10 °C and re-cooling to −100 °C, **2** predominated with only a trace of **4** still present. Complex **2**, prepared from either **1a** or **1b**, was stable indefinitely at −100 °C, therefore, the propane initially observed at this temperature was from the decomposition of **3** or **4**. The order of stability, $\mathbf{2} \gg \mathbf{4} > \mathbf{3}$, is precisely as predicted by recent theoretical calculations.[7a]

In its reaction with EtI, $Me_2CuLi{\cdot}LiSCN$ (**1c**; prepared from CuSCN and two equivalents of MeLi) gave a TCSP intermediate **5** that was even more ephemeral than **3**, reaching its maximum concentration after about 3 s. In this case, thiocyanate behaves as a pseudohalide and not a thiolate (see below), owing to the electron-withdrawing effect of CN.

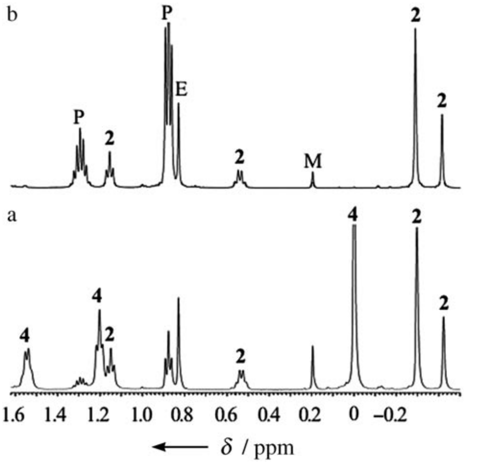
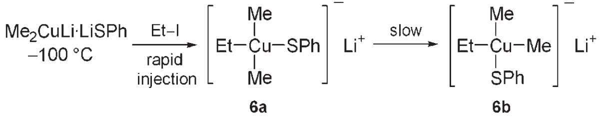


Figure 2. ^{1}H NMR spectrum of a) the reaction mixture from the RI-NMR experiment in Figure 1b at −100 °C, and b) the same reaction mixture after warming to −10 °C (and recooling to −100 °C). M = methane, E = ethane, and P = propane.

Perhaps the most significant results were obtained using $Me_2CuLi{\cdot}LiSPh$ (**1d**), prepared from two equivalents of MeLi based on CuSPh (Posner's precursor for a useful class of heterocuprates, RCu(SPh)Li).[12] When **1d** was treated with EtI at −100 °C, the major product was **6a**. NOESY spectra had cross peaks between the phenyl group of the thiolate ligand and the methyl groups as well as between the methyl groups and the ethyl group, but not between the phenyl and ethyl groups. A trace of **6b** (Scheme 2) was also detected, but in contrast to the experiments with **1a–c**, none of the peralkyl product **2** was observed under the rapid-injection conditions.



Scheme 2. Formation and isomerization of phenylthio complex **6a**.

When the reaction of **1d** with EtI was performed at −90 °C, appreciable amounts of **6b** accumulated in addition to **6a**, which allowed **6b** to be characterized as well (see the Supporting Information). At longer reaction times, **2** was also observed, along with propane. Complex **2** was by far the most stable copper(III) intermediate and could be observed briefly at temperatures as high as 20 °C, where small amounts of ethane and copious amounts of propane were formed, so that all of the TCSP complexes are presumptive intermediates. The amounts of propane and ethane generated at elevated temperatures cannot be measured accurately, because the NMR tube is open in the rapid-injection experiment.

The structures of the TCSP complexes were assigned on the basis of their ^{1}H and ^{13}C NMR spectra with emphasis on

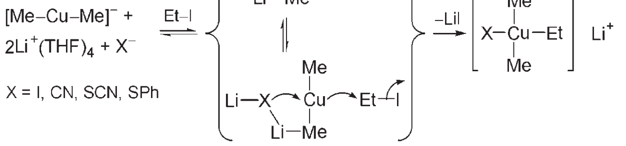
2D techniques such as NOESY and HMQC (see the Supporting Information). In the case of **2**–**6a**, the spectra confirm the presence of an ethyl group and two equivalent methyl groups *trans* to each other. In **6b** we have an example of a TCSP complex with a pair of non-equivalent *cis* methyl groups, which give rise to individual methyl signals.

The simultaneous presence of methyl and ethyl groups on the same Cu atom was confirmed by using two-bond ^{13}C–^{13}C coupling constants, ^2J. This method was first used to show that R and CN are both bonded to the same Cu atom in RCuCNLi,[13] and it has subsequently been applied to a number of other systems.[9,14] The magnitude of two-bond coupling across metal atoms depends on stereochemistry: $^2J_{trans} \gg {}^2J_{cis}$.[15]

Isotopomers of selected TCSP complexes were prepared from the corresponding ^{13}C-labeled reagents; thus, **4*** was prepared from $(^{13}CH_3)_2CuLi{\cdot}Li^{13}CN$ and $CH_3{}^{13}CH_2I$. It had a large coupling ($^2J = 40.4$ Hz) between the cyano C atom and the methylene C atom, which therefore must be *trans* to each other. The small coupling H_5 ($^2J = 6.8$ Hz between CN and Me and $^2J = 1.5$ Hz between methylene and Me) indicate *cis* relationships. The methylene C atom of **2*** was coupled to the methyl C atom *trans* to it with $^2J = 44.6$ Hz and to the methyl C atoms *cis* to it with $^2J = 2.2$ Hz. The unique methyl C atom was coupled to the other two with $^2J = 2.6$ Hz. The methylene C atom of **6a** was coupled to the methyl C atoms with $^2J = 1.2$ Hz. In **6b**, the methylene C atom was coupled to the *trans* methyl C atom with $^2J = 38.8$ Hz and to the *cis* methyl C atom with $^2J = 1.6$ Hz; the methyl C atoms were coupled to each other with $^2J = 2.0$ Hz.

Both consecutive displacement and pseudorotation mechanisms have been proposed for the isomerization of TCSP complexes (e.g. **6a** to **6b**), and evidence has been presented for pseudorotation in pentacoordinate intermediates in the *cis*–*trans* isomerization of d^8 complexes of Pt^{II} and Au^{III}.[16] New organocopper complexes **2**–**6** are formally d^8 Cu^{III} compounds, and a pentacoordinate square pyramidal intermediate has precedent among stable Cu^{III} complexes.[17]

The observation that the initial reaction of $Me_2CuLi{\cdot}LiI$ and EtI results in what appears to be the product of *trans* addition requires comment, as oxidative addition normally results in *cis*-addition products. The key to understanding this outcome is found in the analogous reactions of **1b**–**d**, which initially result in TCSP complexes that also have the Et group *trans* to the ligand X. By postulating that the I ligand in **3** is also from the copper reagent and not from EtI, we have a unified mechanism for all cases studied (Scheme 3).



Scheme 3. Proposed mechanism for the formation of TCSP intermediates.

In solution, $Me_2CuLi{\cdot}LiX$ exists as a dynamic equilibrium between solvent-separated ion pairs (SSIPs) and contact ion pairs (CIPs), and the former predominate in THF.[18] Therefore, we conjecture that these reactions proceed by way of a small equilibrium concentration of heterodimer,[19] which could be either cyclic [20] or linear, as shown in brackets in Scheme 3.

From a synthetic perspective, any process that scrambles the alkyl groups (e.g. **6a** to **6b**) or that replaces a "non-transferable" ligand with a transferable one (e.g. **6a** to **2**) may result in diminished yields of the desired product. The final outcome of a copper-mediated cross-coupling reaction depends upon the relative rates of such side reactions versus the desired reductive elimination, and therefore even when these scrambling processes are operating, they may not be observed in all cases. Based on the intriguing results with cuprate **1d** from CuSPh, more research into novel organocuprate precursors is warranted.

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