Communication

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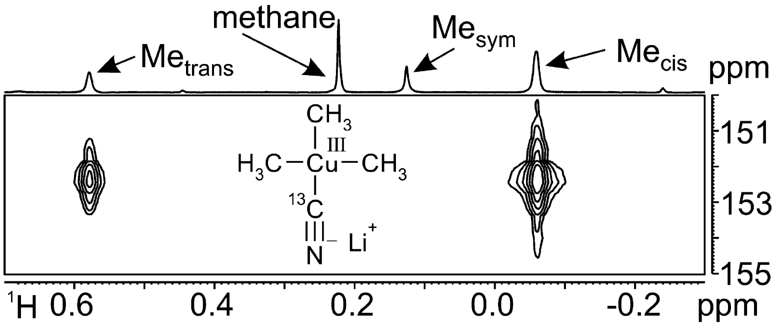

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NMR-Detection of Cu(III) Intermediates in Substitution Reactions of Alkyl Halides with Gilman Cuprates

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For some decades organocopper(I) reagents have provided a uniquely important synthetic methodology for highly selective C−C− bond formation.[1a] Typical reactivity patterns of organocuprates include, for example, conjugate addition reactions to α,β unsaturated enones or S_N2-like substitution reactions of alkyl halides.[1] The formation of the key carbon−carbon bond in these reactions has long been proposed to be mediated by a Cu(III) intermediate.[1−5]

In a very recent publication Bertz and Ogle described the first experimental observation of a Cu(III) intermediate in a conjugate addition reaction of Gilman cuprates to 2-cyclohexenone by rapid injection NMR using THF as solvent.[6] We have now been able to stabilize the first Cu(III) intermediate of a substitution reaction of Gilman cuprates with alkyl halides in diethyl ether. Moreover, we have developed a method of preparing NMR samples and found conditions under which it is possible to stabilize these Cu(III) intermediates for several days, thus allowing for extensive two-dimensional NMR investigations with conventional low-temperature NMR.

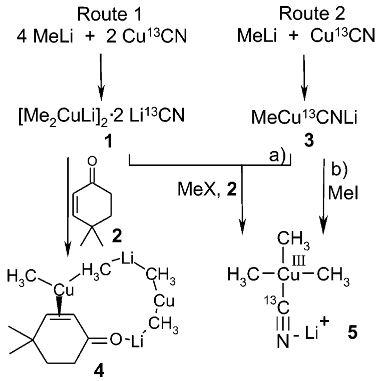
Interestingly, our study started in a similar way to that of Bertz and Ogle, with the stabilization of intermediate species in the conjugate addition reactions of Gilman cuprates to enones. However, the different solvents employed in these two independent studies produce significant differences. In THF mainly solvent separated ion pairs exist[7] inducing slow reaction rates in conjugate addition reactions.[8,9] In contrast, in diethyl ether the dimeric or even oligomeric contact-ion pairs react rapidly.[8] Therefore, the reaction rate has to be slowed down by alkyl substitution of the enones[10] to enable the detection of intermediate cuprate enone π-complexes.[9]

For in-depth investigations of the supramolecular structure of such intermediate π-complexes, as well as the position of the cyano groups therein, we prepared the cyano-Gilman cuprates **1**[11] with isotopically labeled $Cu^{13}CN$, and added 4,4-dimethylcyclohexenone **2** at 180 K (see Scheme 1 , route 1).

Surprisingly, in addition to the expected π-complex **4** we observed very small traces of **5** in a $^1H,^{13}C$ HMBC spectrum. The amount of **5** under these experimental conditions was so small that in the one-dimensional ^1H spectrum no signal of **5** was detected owing to limitations in the dynamic range of the receiver. Only the tremendous signal enhancement of the methyl groups, connected via $^3J_{H,C}$ scalar coupling to the ^{13}C labeled cyanide group, allowed for the observation of **5** in the HMBC spectrum. By using the heteroleptic cuprate **3** and increasing the ratio of the enone relative to **3** (Scheme 1 Route 2a) we were able to suppress the appearance of the π-complex completely and to increase the amount of **5** considerably. This allowed the in-depth investigation of **5** with two-dimensional NMR experiments.

The high field sections of the ^1H spectrum and the $^1H,^{13}C$ HMBC spectrum with the signals and cross-peaks of **5** are shown in Figure 1. From the HMBC section in Figure 1c it is directly evident that one cyanide group shows cross-peaks to two kinds of methyl group.

Scheme 1. Two Routes to Obtain **5** in Diethyl Ether[a]



[a] Addition of enone **2** to a solution of **1** yields π-complex **4** as the main product. MeX represents traces of methyl halides in commercial MeLi solutions (see text).

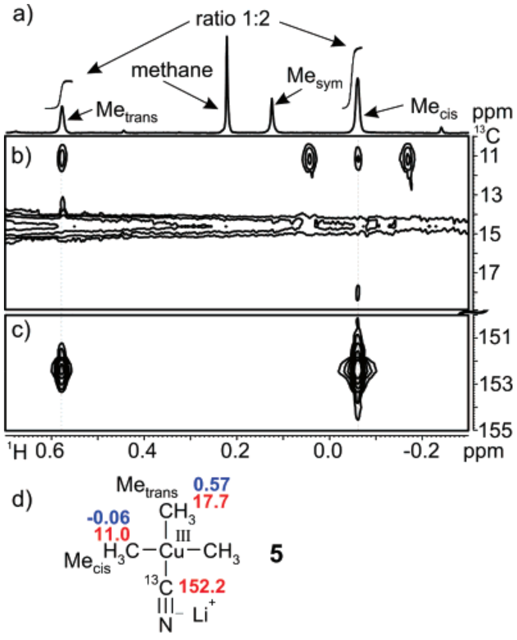


Figure 1. Selected high-field sections of a 1D ^1H spectrum (a) and a $^1H,^{13}C$ HMBC spectrum (b,d) of the products obtained by route 2a at 180 K in diethyl ether. The proton spectrum (a) shows for **5** a 1:2 ratio of Me_{trans} and Me_{cis} as well as signals of methane and a species Me_{sym}; the methyl section (b) and the cyanide section (c) of the HMBC spectrum show that two chemically equivalent methyl groups together with a third methyl group and a cyanide group are attached to copper. This indicates a square planar copper (III) intermediate **5** (d) in its form as a monomeric contact-ion pair with ^{13}C (red) and ^1H (blue) chemical shifts.

In the corresponding proton spectrum (Figure 1a) the integrals of these methyl groups show a 1:2 ratio indicating that two out of the three methyl groups attached to copper are chemically equivalent.

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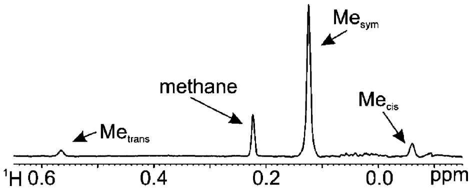

Figure 2. High-field sections of a 1D ^1H spectrum of the products obtained by route 2b at 180 K in diethyl ether. The signal intensities of **5** and methane are significantly reduced compared to route 2a; the signal of Me_{sym} is significantly larger.

Also, the methyl section of the HMBC spectrum (Figure 1b) confirms the structure of **5** to be a square planar coordinated Cu(III) species with three methyl groups and one cyano group attached, showing cross-peaks between Me_{trans} and Me_{cis} as well as cross-peaks from both $^3J_{H,C}$ and $^1J_{H,C}$ scalar couplings for Me_{cis}.

The relative values of the proton and carbon chemical shifts of **5** (Figure 1d) are in good agreement with the chemical shifts reported for the conjugate addition Cu(III) intermediate by Bertz[6] and Snyder.[12] There, Bertz, Ogle and Snyder claim that the copper coordination sphere is square planar on the basis of precedent[13−15] and on high level theoretical calculations.[12] In our experimental setup using exclusively methyl groups as alkyl substituents the square planar coordination of **5** is directly evident from the proton spectrum and the HMBC spectrum discussed above. In addition our results are in perfect agreement with crystal field theory. Square planar d^8 Cu(III) complexes are expected to be diamagnetic with quite sharp NMR signals and chemical shifts close to those of organic compounds as shown in Figure 1. In contrast, tetrahedral d^8 Cu(III) complexes would be paramagnetic, with two unpaired electrons among the three t_2 orbitals. This would lead to very broad signals and extreme low-field shifts of the protons close to the paramagnetic center.

In the beginning of our study the mechanistic origin of the detected Cu(III) intermediate was less evident. Experiments with entirely ^{13}C-labeled MeLi showed that all three methyl groups in **5** originate from the MeLi solution and neither the NOESY nor the HMBC spectra of both isotopically labeled and unlabeled **5** showed any cross-peaks to the enone indicating no detectable interaction between **5** and enone **2** (data not shown). However, in the HMBC spectra of the ^{13}C labeled compounds small amounts of $^{13}CH_3I$ were observed originating from the synthesis of MeLi (see Supporting Information (SI)). The commercially available solution of MeLi used in the previous experiments also contains traces of halides.

Considering the well-known substitution reactions of alkyl halides with Gilman cuprates[1c,16] it was highly probable that we stabilized the first Cu(III) intermediate of a substitution reaction with Gilman cuprates. To prove this hypothesis we prepared **5** according to Scheme 1 Route 2b. The corresponding proton spectrum is shown in Figure 2.

The two methyl signals of **5** are clearly visible and the HMBC spectrum of this substitution reaction also shows an identical pattern to that discussed above for **5** (see SI). Compared to the first approach the signal intensity of **5** is significantly reduced, indicating a beneficial influence of the enone in the generation or stabilization of **5**. The substitution reaction also produces, besides **5**, the proton signals of ethane (data not shown), methane, and a quite large amount of a third species (hereafter named Me_{sym}) compared to Figure 1a. The corresponding HMBC pattern (see SI) indicates a symmetrical species with a proton−carbon chemical shift combination very similar to those methyl groups in the two square planar coordinated Cu(III) intermediates known so far which are located trans to alkyl groups (Figure 1d and ref 6). Additionally, on the basis of theoretical calculations Snyder predicted that tetraalkyl square planar Cu(III) complexes are more stable than **5** by approximately 20 kcal/mol.[12] Therefore, we speculate that the ^1H and ^{13}C signals of Me_{sym} might belong to a tetramethyl Cu(III) species.

In summary, we present the first experimental observation of the long proposed Cu(III) intermediate in a substitution reaction with organocuprates. The one-dimensional proton and the HMBC spectrum for the first time provide direct experimental evidence for a square planar coordination of the Cu(III) intermediate in solution. The presence of 4,4-dimethylcyclohexenone increases the detectable amount of the trimethylcyano Cu(III) species significantly, whereas in pure substitution reactions the proposed tetraalkyl Cu(III) species seems to be more stable in diethyl ether.

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Supporting Information Available: Experimental section and ^1H, ^{13}C HMBC of the products of route 2b. This material is available free of charge via the Internet at http://pubs.acs.org.

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