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Rapid Injection NMR Reveals η^3 'π-Allyl' Cu^{III} Intermediates in Addition Reactions of Organocuprate Reagents

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Supporting Information

ABSTRACT: By using rapid injection NMR, it has now been possible to prepare and characterize the η^3 'π-allyl' copper(III) intermediate that has been proposed for addition reactions of organocopper(I) reagents and α,β-unsaturated carbonyl compounds.

Copper(III) compounds were long assumed to be intermediates in organic reactions mediated by copper or its salts, as well as modern reactions of organocopper compounds, for example, the extraordinarily useful Gilman reagents, R_2CuLi.[1−6]

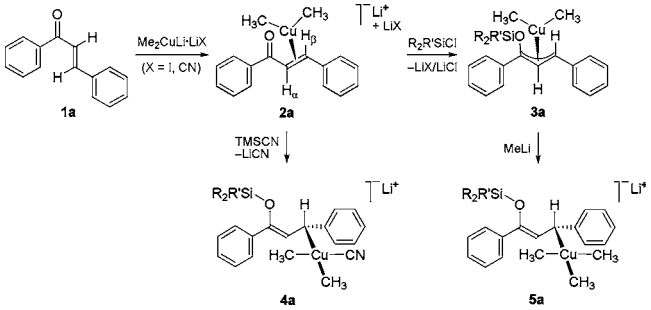
In 2007, Bertz and Ogle reported the direct observation of an η^1 'σ-allyl' organocuprate(III) species by rapid injection of TMSCN from a glass capillary directly into a solution of the η^2 π-complex from 2-cyclohexenone and $Me_2CuLi{\cdot}LiI$ in an NMR tube, spinning under nitrogen at −100 °C in the probe of an NMR spectrometer.[3] By using rapid injection, it was also possible to observe transient Cu^{III} intermediates such as $EtMe_2(I)CuLi$ and $EtMe_2(CN)CuLi$ in the respective reactions of $Me_2CuLi{\cdot}LiI$ and $Me_2CuLi{\cdot}LiCN$ with EtI.[4] In a tour de force of 2D NMR, Gschwind et al. characterized a small amount of $Me_3(CN)CuLi$ in a solution prepared from MeLi and CuCN in the presence of (residual) MeCl.[5]

Both η^1 'σ-allyl' and η^3 'π-allyl' Cu^{III} intermediates were subsequently observed in the reactions of allylic halides and acetates with Me_2CuLi.[6] This raised the question: is an η^3 Cu^{III} species an intermediate in the cuprate conjugate addition reaction, as proposed by Corey and Boaz?[2]

In light of the stability of the phenyl-substituted η^3 complex,[6] we investigated phenyl-substituted α,β-unsaturated carbonyl compounds, specifically 1,3-diphenyl-2-propen-1-one **1a** (chalcone), 1-phenyl-1-buten-3-one **1b** (benzalacetone), 1-phenyl-2-buten-1-one **1c** (crotonophenone), and 3-phenylprop-2-enal (cinnamaldehyde) **1d**. We can now report that by this judicious choice of substrates, it is indeed possible to prepare such η^3 organocopper(III) intermediates.

When a solution of chalcone **1a** in THF-d_8 was injected into a solution of $Me_2CuLi{\cdot}LiI$ in the same solvent at −100 °C, a quantitative conversion to a single cuprate−enone η^2 π-complex **2a** was observed (Scheme 1). Then, injection of a chlorosilane, for example, chlorotrimethylsilane (TMSCl), chlorotriethylsilane (TESCl), or chlorobis(trideuteriomethyl)-phenylsilane [$(CD_3)_2(C_6H_5)SiCl$], gave the η^3 π-allyl complexes **3a** (R, R′ as identified below).

Scheme 1. The Reaction of Chalcone 1a with Lithium Dimethylcuprate(I), Followed by Chlorosilanes ($R_2R'SiCl$) or TMSCN



Structures were assigned using standard 1D and 2D NMR techniques, since organocopper(III) complexes are diamagnetic, square planar or pseudo square planar d^8 species. The ^1H and ^{13}C NMR shifts for Me_α and Me_β, the methyl groups on copper (Me_{Cu}), are summarized in Table 1, along with the double bond shifts for H_α/C_α (DB_α) and H_β/C_β (DB_β).

Chemical shifts for H_α/C_α and H_β/C_β moved dramatically upfield upon going from substrate **1** to η^2 π-complex **2**, and they moved back downfield to an intermediate position upon going from **2** to η^3 complex **3**. The former effect is more pronounced for the β-atoms, and it causes their shifts to move upfield relative to those for the α-atoms in **2** and **3** (vide infra Figure 1).

Stereochemistry, s-*cis* in **2a−d** and *anti−syn* in **3a−d**, was assigned from $^3J_{HH}$ and NOESY; likewise for **3b′** (*syn−syn*), **2d′** (s-*trans*), and **3d′** (*syn−syn*). A NOESY plot for **3a** (R, R′ = CH_3, from CuI) is shown in Figure 1.

Addition of $(CD_3)_2(C_6H_5)SiCl$ to **2a** (from CuCN) at −100 °C gave a mixture of η^3 complex **3a** and η^1 complex **4a** (ca. 2:1). We propose that some of the chlorosilane was converted to the corresponding cyanosilane,[3] which then gave the η^1 complex. By using TMSCN, only **4a** was observed. The ^1H (^{13}C) NMR peaks for **4a** came at 0.26 (15.28) and 0.89 (21.70) ppm for Me_{Cu} *cis* and *trans* to CN (152.87 ppm), respectively.

In the presence of MeLi (1 equiv), **3a** goes on to the η^1 trimethyl complex **5a** (R, R′ = Me). The ^1H (^{13}C) NMR peaks for Me_{Cu} came at −0.12 (18.19, broad; 2Me) and 0.24 (17.93) ppm.

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Table 1. ^{1}H and ^{13}C NMR Shifts for Me_α/Me_β Groups on Copper and H_α/C_α and H_β/C_β of Double Bonds in η^2 and η^3 Complexes[a]

	^{1}H (^{13}C)			
	Me_α	Me_β	DB_α	DB_β
1a	– (–)	– (–)	7.95 (121.00)	8.20 (145.06)
2a	−1.05 (−3.62)	−0.45 (3.99)	5.13 (69.38)	4.40 (64.20)
3a[b]	−0.38 (9.29)	0.20 (9.07)	6.44 (96.20)	4.55 (78.37)
1b	– (–)	– (–)	6.89 (127.93)	7.85 (144.64)
2b	−0.87 (−5.32)	−0.59 (1.89)	4.36 (71.54)	4.14 (63.10)
2b′	−0.79 (−3.55)	−0.41 (4.11)	4.53 (75.26)	4.09 (63.85)
3b[c]	−0.26 (3.74)	0.03 (7.73)	5.36 (95.59)	4.26 (74.84)
3b′[c]	−0.18 (6.19)	0.00 (7.93)	5.43 (98.40)	4.18 (73.58)
1c	– (–)	– (–)	7.34 (126.42)	7.12 (145.58)
2c	−1.26 (−4.47)	−0.26 (0.47)	4.30 (78.70)	3.29 (58.80)
3c[b,d]	−0.51 (–)	0.30 (–)	5.63 (–)	3.67 (–)
1d	– (–)	– (–)	6.95 (129.32)	7.89 (154.39)
2d[e]	−0.62 (−11.68)	−0.41 (4.52)	4.36 (75.90)	4.22 (62.95)
2d′[e]	−0.73 (−1.06)	−0.37 (5.20)	4.49 (81.19)	3.71 (65.99)
3d[f,g]	0.05 (−5.81)	0.06 (9.75)	5.31 (96.36)	4.55 (78.51)
3d′[f,g,h]	0.03 (5.12)	−0.07 (8.89)	6.01 (104.64)	3.82 (76.58)

[a]From CuCN at −100 °C unless otherwise noted. [b]$(CH_3CH_2)_3Si$ derivative. [c]$(CH_3)_3Si$ derivative. [d]Fleeting species (see Figure 3); hence, no ^{13}C shifts. [e]Run at −70 °C, owing to broadness at lower temperatures. [f]From CuI. [g]$(CD_3)_2(C_6H_5)Si$ derivative. [h]For comparison, the shifts for **3d′** from CuCN are Me_α, 0.02 (5.08); Me_β, −0.09 (8.86); DB_α, 6.01 (104.66); DB_β, 3.79 (76.58) ppm.

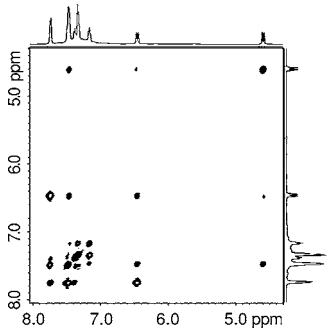


Figure 1. NOESY plot for **3a** (R, R′ = CH_3) at −100 °C, showing strong interactions between H_α (6.45 ppm) and both phenyl groups, whereas H_β (4.60 ppm) interacts only with the 3-phenyl.

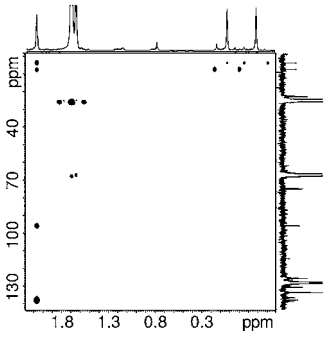
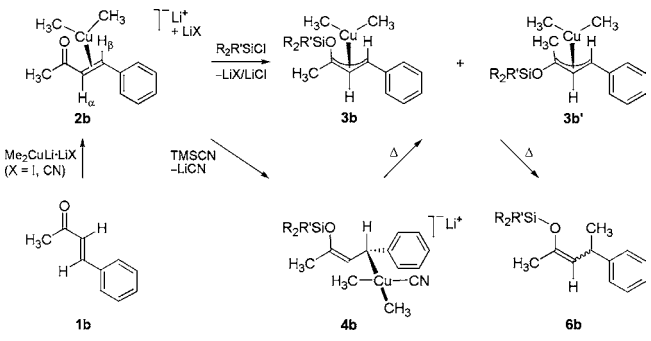


Figure 2. HMBC plot for **3b** (R = CD_3, R′ = C_6H_5) at −80 °C, correlating Hs on C_4 (2.07 ppm, enone numbering) with carbons: Me_α (4.16 ppm), Me_β (7.80 ppm), C_2 (96.40 ppm), and C_3 (138.40 ppm).

Benzalacetone **1b** and $Me_2CuLi{\cdot}LiX$ (Scheme 2, X = I, CN) gave a mixture of several η^2 π-complexes at −100 °C, which simplified to two main species **2b** and **2b′** (ca. 2:1) at −80 °C. They both had the s-*cis* conformation (NOESY), which suggests that they differ in aggregation.[8,9]

Scheme 2. The Reaction of Benzalacetone 1b with Lithium Dimethylcuprate(I), Followed by Chlorosilanes ($R_2R'SiCl$) or TMSCN



Injection of TMSCl into a cold (−100 °C) solution of **2b**/**2b′** from CuI or CuCN gave *anti*−*syn* η^3 complex **3b** (R, R′ = Me) along with a minor amount of *syn*−*syn* isomer **3b′** (1−10%). Injection of $(CD_3)_2(C_6H_5)SiCl$ into a cold (−80 °C) solution of **2b**/**2b′** from CuI gave predominately **3b** (R = CD_3, R′ = C_6H_5); an HMBC plot for this product appears in Figure 2. Also present was a small amount (7%) of **3b′**, which is not visible in the 2D plot.

Injection of $(CD_3)_2(C_6H_5)SiCl$ into a cold (−100 °C) solution of **2b**/**2b′** from CuCN gave a mixture of **3b** and **4b** (ca. 2:1, R = CD_3, R′ = C_6H_5). With TMSCN and **2b**/**2b′** from CuI or CuCN, we observed only **4b** (R, R′ = CH_3). The ^{1}H (^{13}C) NMR peaks for **4b** at −100 °C came at 0.13 (14.15) and 0.70 (21.45) ppm for Me_{Cu} *cis* and *trans* to CN (154.01 ppm), respectively.

Injection of crotonophenone **1c** into a solution of $Me_2CuLi{\cdot}LiX$ (X = I, CN) in THF-d_8 at −100 °C afforded a single η^2 π-complex **2c**, which had the s-*cis* stereochemistry (NOESY).

Injection of TESCl into the solution of **2c** from CuI gave a transient η^3 complex **3c** (R, R′ = Et, Scheme 3), which immediately went on to 1,4-addition product **6c** under the

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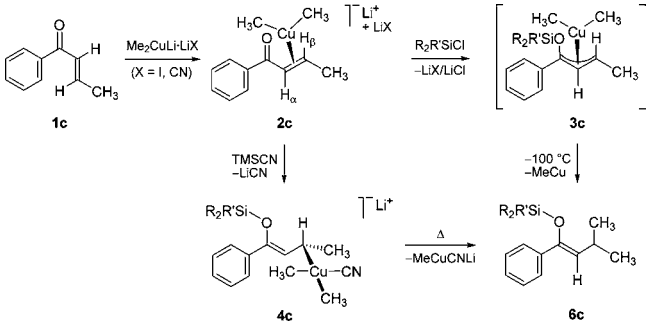
Scheme 3. The Reaction of Crotonophenone 1c with Lithium Dimethylcuprate(I), Followed by Chlorosilanes ($R_2R'SiCl$) or TMSCN



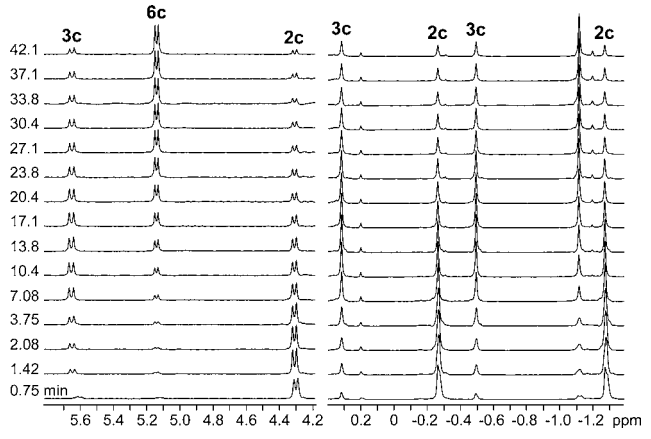


Figure 3. Stacked ^{1}H NMR plots for injection of TESCl into **2c** (4.30, −0.26, −1.26 ppm) at −100 °C. Note the transiency of **3c** (5.62, 0.32, −0.49 ppm) as product **6c** (5.13 ppm) grows. (Note that the magnetic field must be shimmed for a minute or two after injection, which is why the first scan is broad.)

reaction conditions. Stacked plots are shown in Figure 3 for the regions of interest.

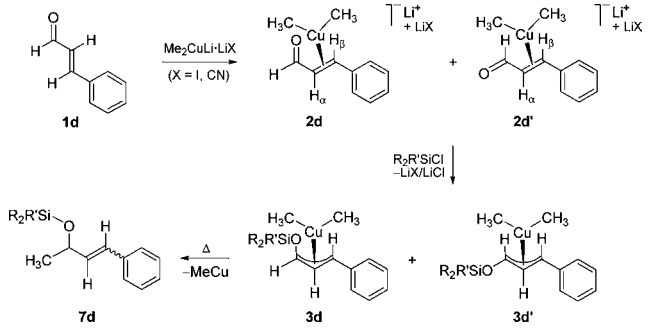
Treatment of **2c** from CuCN with TESCl at −100 °C gave a higher initial concentration of **3c** (R, R′ = Et), which allowed us to measure its rate of decomposition to **6c** ($t_{1/2}$ = 12.5 min at −100 °C). In this case, a small amount of η^1 complex **4c** (R, R′ = Et) grew in and then disappeared as the reaction proceeded.

By changing the order of addition, it was possible to favor the η^1 complex. Thus, injection of TESCl into a solution of $Me_2CuLi{\cdot}LiCN$ in THF-d_8 at −100 °C, followed by injection of substrate **1c** yielded η^1 complex **4c** (R, R′ = Et). Under these conditions, chlorosilanes are rapidly converted to cyanosilanes.[3]

Injection of TMSCN (natural abundance) into a solution of **2c** (from $Cu^{13}CN$) gave a quantitative conversion to **4c** (R, R′ = Me). The ratio of cyanide from $Cu^{13}CN$ to that from $TMS^{12}CN$ was 44:56, measured from the areas of the relevant peaks. The ^{13}C resonance for Me_{Cu} *trans* to ^{13}CN was a doublet (17.72 ppm, $^2J_{trans}$ = 36.1 Hz), which bracketed a singlet (17.72 ppm) for Me_{Cu} *trans* to ^{12}CN. The peak for Me_{Cu} *cis* to ^{13}CN (13.32 ppm) was a broad singlet, owing to unresolved *cis* coupling ($^2J_{trans} \gg {}^2J_{cis}$ across Cu[3−7]).

Injection of cinnamaldehyde into a solution of $Me_2CuLi{\cdot}LiX$ (X = I, CN) in THF-d_8 at −100 °C gave a 1:1 mixture of two η^2 π-complexes (Scheme 4), which were assigned the s-*cis* and s-*trans* structures **2d** and **2d′**, respectively (NOESY).

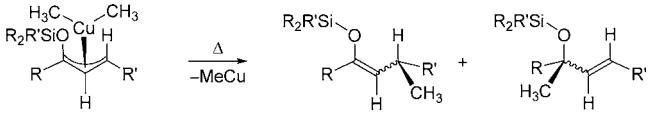
Scheme 4. The Reaction of Cinnamaldehyde 1d with Lithium Dimethylcuprate(I), Followed by Chlorosilanes ($R_2R'SiCl$)



When this mixture was treated with $(CD_3)_2(C_6H_5)SiCl$, the corresponding η^3 π-allyl complexes **3d** and **3d′** were observed. With the iodo-Gilman reagent, the ratio started at ca. 1:1, but with time changed to ca. 1:9. With the cyano-Gilman reagent, only a small amount of **3d** was observed, hence ^{13}C NMR data could not be obtained for **3d** from CuCN (see Table 1). It appears that *syn*−*syn* isomer **3d′** is the thermodynamically stable one in this case (cf. **3b** and **3b′**).

The shifts for H_β/C_β in **3a,b,d** are close to those for the 1-position of the allyl group in dimethyl(η^3-phenylallyl)copper-(III).[6] Given the instability of η^3 complex **3c**, we surmise the β-phenyl in **3a,b,d** is responsible for the stability of these complexes.

Scheme 5. Thermal Decomposition of η^3 Complexes 3



3a, R = R′ = Ph
b, R = CH_3, R′ = Ph
c, R = Ph, R′ = CH_3
d, R = H, R′ = Ph

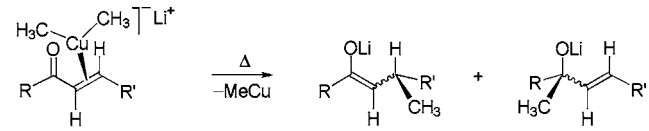
6a-d as in **3**

7a-d as in **3**

We have also established the intermediacy of **3a−d** in addition reactions. Upon warming chalcone η^3 complex **3a** (R = CD_3, R′ = C_6H_5, Scheme 5) to −70 °C, it decomposed to a 1:1 mixture of 1,4-addition products **6a** (*Z*/*E* = 1:1) and 1,2-addition products **7a** in addition to a significant amount (ca. 40%) of ethane and variable amounts of reduction product. Significant amounts of these side products were not observed from the other substrates.

In contrast, when chlorosilane was omitted and η^2 complex **2a** was warmed to −10 °C, only *Z*-enolate **8a** was observed (Scheme 6), and no 1,2-adduct **9a** was detected.

Scheme 6. Thermal Decomposition of η^2 Complexes 2



2a, R = R′ = Ph
b, R = CH_3, R′ = Ph
c, R = Ph, R′ = CH_3
d, R = H, R′ = Ph

8a-d as in **2**

9a-d as in **2**

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Upon warming to −60 °C, benzalacetone η^3 complex **3b** (R, R′ = Me) went on to a mixture of 1,4-addition products **6b** (*Z*/*E* = 12:1). No 1,2-adduct **7b** was observed in this case. Upon warming η^2 complex **2b** to −10 °C, it was converted to a mixture of enolates **8b** (*Z*/*E* = ca. 1:1), which were characterized by converting them to silyl enol ethers **6b** with TMSCl. 1,2-Adduct **9b** was not observed.

The η^3 crotonophenone complex **3c** (R, R′ = Et) decomposed immediately at −100 °C (Scheme 3) to 1,4-addition product **6c** (*Z* only). 1,2-Adduct **7c** was not observed. Upon warming η^1 complex **4c** (R, R′ = Me) to −40 °C, only **6c** was observed. When η^2 complex **2c** was warmed to −60 °C, enolates **8c** (*Z*/*E* = 5:1) were formed. 1,2-Adduct **9c** was not observed.

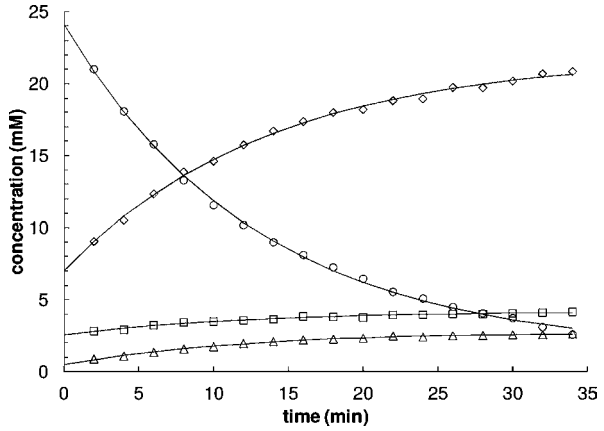

Figure 4. Plots of concentration vs time for the decomposition of **3d′** (○) from CuI at −50 °C to give *E*-**6d** (Δ), *E*-**7d** (◇), and *Z*-**7d** (□). The half-life of **3d′** is 9.2 ± 0.3 min at this temperature.

Upon warming to −50 °C, the usual mixture of cinnamaldehyde η^3 complexes **3d** and **3d′** (R = CD_3, R′ = C_6H_5, Figure 4) gave predominately 1,2-addition products **7d** (*Z*/*E* = 1:6) and a minor amount (<10%) of 1,4-addition product **6d** (*E* only). In contrast, when η^2 complexes **2d**/**2d′** were warmed to −20 °C, 1,2-adducts **9d** and 1,4-adducts **8d** were observed in a 3:7 ratio.

Corey and Boaz proposed an η^3 Cu^{III} intermediate to explain the effect of TMSCl on the 1,4-addition of organocuprates to α-enones.[2] Typically, η^2 π-complexes such as **2** are in equilibrium with the corresponding starting materials, and owing to the high electron density on oxygen,[10] they can be trapped via silylation. Thus, by employing rapid injection NMR and choosing relevant substrates, we have been able to intercept the η^3 'π-allyl' species and show it is an intermediate in 'silyl-assisted' 1,4- and 1,2-addition reactions of a typical Gilman reagent. It joins the previously reported η^1 'σ-allyl' species[3] on the sparsely populated 'copper(III) plateau',[6,7] as it completes another piece of the mechanistic puzzle.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Selected 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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