

EVIDENCE FOR INTERMEDIATE π -COMPLEXES IN THE ADDITION OF TRIALKYLSILYL AND TRIALKYLSTANNYL CUPRATES TO α,β -UNSATURATED ENONES

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Abstract: Low temperature ^{13}C NMR spectra of solutions generated during the addition of metalocuprates $(\text{PhMe}_2\text{Si})_3\text{CuLi}_2$, $\text{PhMe}_2\text{Si}(\text{Me})\text{Cu}(\text{CN})\text{Li}_2$, $(\text{Me}_3\text{Sn})_3\text{CuLi}_2$ and $\text{Me}_3\text{Sn}(\text{Me})\text{Cu}(\text{CN})\text{Li}_2$ to cyclohex-2-en-1-one suggest that these reactions proceed initially *via* unstable lithium coordinated copper(I)-olefin π -complexes. Workup of these reactions results in exclusive delivery of R_3Si or R_3Sn moiety in a 1,4-manner.

The facility with which cuprates bearing alkyl,^{1,2} silyl,^{3,4} and stannyl⁴ anions introduce these groups in a Michael sense to α,β -unsaturated carbonyl compounds (**1**) makes them the reagents of choice for these transformations. Previous mechanistic studies of these processes have centered only on Gilman reagents [i.e., $(\text{R}_2\text{CuLi})_2$, **2**].⁵⁻¹⁶ While initial coordination of the substrate carbonyl with lithium (**1** + **2** \rightarrow **3**) and formation of a β substituted enolate (**4**) are common features, there has been considerable divergence of opinion concerning the intervening steps (Scheme 1).

Kinetic data by Krauss and Smith⁶ as well as Corey's⁷ isolation of an insoluble species that was convertible to products suggest a process involving intermediates that unimolecularly rearrange to the enolate, **4**. On the basis of the correlation of reduction potentials of α,β -unsaturated carbonyl systems with cuprate reactivity House⁸ proposed that initial carbonyl-lithium coordination was followed by a single electron transfer process (**3** \rightarrow **5**) and thence by copper-carbon bond formation to give the Cu(III) species, **6**. A slightly different proposal involving direct formation of **6** from **1** and **2** *via* a charge transfer complex (**7**) was advanced by Smith and Hannah⁹ (Scheme 1).

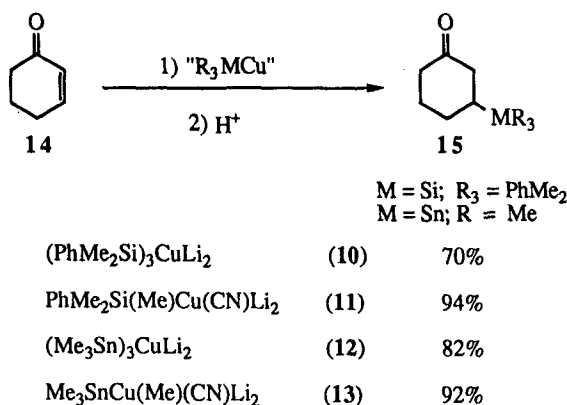
Johnson¹⁰ and Casey¹¹ view the production of the Cu(III) adduct (**6**) as occurring *via* a nucleophilic addition of the reagent to the β carbon atom of the substrate without the intervention of a single electron transfer step. Berlan¹² and Riviere¹³ proposed the formation of a copper(I)-alkene π -complex (**8**). In Berlan's proposal **8** reacts *via* direct carbocupration to give an α -cuprioketone, **9**, which rearranges to the thermodynamically more stable lithium enolate **4**¹² (Scheme 1).

Cogent evidence for binding between copper and π^* MO of the enone as in **8** comes from the infrared¹² and NMR^{14,15} spectroscopic studies of reactions involving unsaturated esters and **2**¹⁴ or $\text{Me}(2\text{-thienyl})\text{CuLi}$.¹⁵ Thus, Ullenius has provided incisive NMR evidence for the reversible formation of **8** *via* (**1** + **2** \rightarrow **3**) in the addition of **2** to methyl cinnamate¹⁴ (Scheme 1). At -70°C this reaction gave an intermediate species in which the

signals due to both the C_2 and C_3 carbons were shifted upfield by 55 and 73 ppm respectively.¹⁶ These shifts are in the range of coordination shifts (~ 60 ppm) for trigonal alkene-transition metal complexes of Ni, Pd and Pt.¹⁷

The present study involved measurements of the ^{13}C NMR spectra of solutions generated during the addition of metallocuprates $(\text{PhMe}_2\text{Si})_3\text{CuLi}_2$ (**10**),¹⁸ $\text{PhMe}_2\text{Si}(\text{Me})\text{Cu}(\text{CN})\text{Li}_2$ (**11**),¹⁹ $(\text{Me}_3\text{Sn})_3\text{CuLi}_2$ (**12**),²⁰ and $\text{Me}_3\text{Sn}(\text{Me})\text{Cu}(\text{CN})\text{Li}_2$ (**13**)¹⁹ to cyclohex-2-ene-1-one (**14**). These reagents deliver R_3Si or R_3Sn exclusively via 1,4-addition to **14** to give **15** (Table 1).²¹

Table 1. Reaction of metallocuprates with cyclohexenone



Addition of **10** (Figure 1a), to **14** in THF at -85°C gave the ^{13}C NMR spectrum shown in Figure 1b. Signals for C_2 and C_3 of **14** which normally resonate at 120.9 ppm and 150.7 ppm respectively are not present but have been replaced by several signals near 60 ppm and 35 (35.7, 33.8) ppm. Coincident with the appearance of these new signals, is the appearance of four major (-2.3, -2.6, -4.4, -5.1 ppm) and two minor (-3.5, -3.8 ppm) resonances attributable to silyl bound methyls. As the solution is allowed to stand at -70°C , the high field methyl resonances at -2.3 and -2.6 ppm disappear while those at -4.4 and -5.1 ppm grow. This is accompanied by a decrease in the signal intensities near 60 and 35 ppm and the appearance of new sharp signals at 38.6 and 23.7 ppm. The signal originally (-85°C) obtained for the nitrile carbon (159.3 ppm) is replaced (-45°C) by another at 152.7 ppm. Workup of this reaction yields **15** (Table 1).

It is attractive to attribute the signals near 35 and 60 ppm to C_2 and C_3 of a copper-alkene π -complex similar to **8** but containing silyl anion ligands on copper while the signals at 38.6 and 23.7 ppm are attributed to the C_2 and C_3 of the corresponding enolate (**4**). The signal due to the C_3 carbon of the product (**15**) appears at 26 ppm. The upfield methyl signals at -2.3 and -2.6 are assigned to the silicon bound methyls in the copper-alkene π -complex, **8**. The signal due to the carbonyl (C_1) cannot be distinguished from baseline noise.²²

The low-temperature ^{13}C NMR spectrum of mixtures of **11** (Figure 1c) and **14** give similar spectra, the obvious common feature of which is the appearance of the high field doublet at -4.4 and -5.2 ppm attributable to silyl bound methyls in the enolate (**4**, Figure 1d). The signals for C_2 of this adduct also appear around 35 ppm

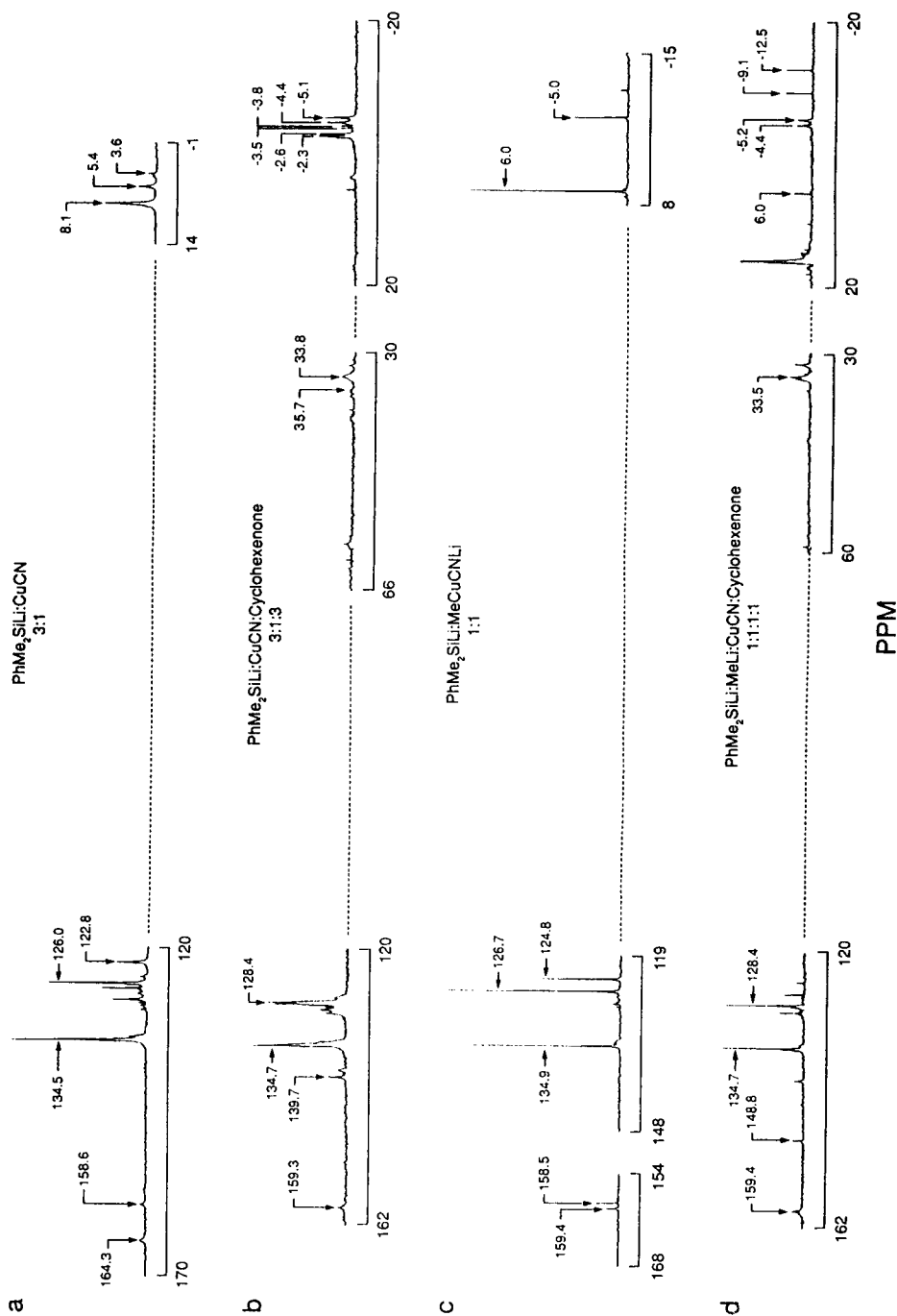


Figure 1. ^{13}C NMR spectra of (a) $(\text{PhMe}_2\text{Si})_3\text{CuLi}_2$ (b) $(\text{PhMe}_2\text{Si})_3\text{CuLi}_2$ + 3.0 equivalents of **14** (c) $\text{PhMe}_2\text{Si}(\text{Me})\text{Cu}(\text{CN})\text{Li}_2$ (d) $\text{PhMe}_2\text{Si}(\text{Me})\text{Cu}(\text{CN})\text{Li}_2$ + **14**; the spectra were run at -85°C .

(33.5 ppm) while those for C3 (24 ppm) cannot be observed due to overlapping of the signal by THF signals. The primary difference between this spectrum and that obtained by mixture of **10** and **14** is the appearance of a signal at -12.5 ppm corresponding to MeCu(CN)Li²³ (**16**) which is formed as a result of exclusive silyl group transfer. The appearance of **16** allows one to deduce that lithium is coordinated to enolate, **4**. The broad signal for the nitrile (159.4 ppm) in this solution is replaced by another at 151.3 ppm as the reaction is warmed from -85°C to -45°C. The set of signals around 60 and 35 ppm (Figure 1d) are hypothesized to be due to a copper-alkene π -complex (corresponding to **8**), the signal at -9.10 ppm is assigned to the methyl of this complex.

The formation of a chiral center on mixing a silylcuprate (**10**) with **14** is a straight-forward basis for the presence of two signals for silyl bound methyls in the ¹³C NMR spectrum assigned to the enolate **4** (-4.4 and -5.1 ppm) and the copper-alkene π -complex **8** (-2.3 and -2.6 ppm; Scheme 1). Thus, the silicon in each species is bound to a chiral center and the silyl bound methyls are diastereotopic. The presence of lithium salt in the solutions of these cuprates may be responsible for the appearance of the additional signals at -3.5 and -3.8 ppm. Coordination with these salts may result in the formation of a stable adduct **9** since no signals were obtained around -3.5 ppm in solutions free of LiCl. Alternatively, the aggregation state of the silylcuprates and the π -complexes could vary and hence give rise to species with the enone carbons in different magnetic environments.

Repetition of these experiments using (Me₃Sn)₃CuLi₂ (**12**) and Me₃SnCu(Me)Li₂ (**13**) gave similar results in that signals near 35 ppm along with doublets at -10.2 and -10.3 ppm were produced on initial mixing at -85°C. These signals disappeared as those for the stannylated enolate (C₂, 38 ppm; methyl, -11.7 and -11.8) and MeCu(CN)Li (δ -12.5) appeared.

These NMR studies suggests that conjugate addition of mixed metalocuprates to α,β -unsaturated ketones involves initial formation of an intermediate copper(I)-olefin π -complex (**8**) as proposed for alkylcuprates. A carbocupration step to afford a species analogous to **9** is a reasonable alternative and cannot be unambiguously ruled out by any studies, including these, reported to date.

EXPERIMENTAL

All glassware and syringes were dried overnight in an oven at 120°C. Glassware was flame dried under vacuum and flushed with argon immediately prior to use. Syringes were flushed with argon and kept under positive argon pressure until use. Transfers of reagents were performed by syringes equipped with stainless steel needles. Reactions were carried out in three necked round bottom flasks equipped with filtration units and teflon-coated magnetic stirring bars.

Transfer of CuCN took place in a glove bag. All alkyllithiums were freshly titrated before use.²⁴ Cyclohexeneone was distilled before use.

Tetrahydrofuran was freshly distilled over potassium benzophenone-ketyl. Unless otherwise stated, other chemicals obtained from commercial sources were used without further purification.

¹³C NMR spectra were obtained on Varian XL-300 spectrometer with an operating frequency of 75.46 MHz. Parameters for the ¹³C spectral acquisition typically involved a spectral width of 15000 Hz, 32K of memory, an acquisition time of 0.4 s and a 60° pulse of 12 μ s. The spectra were recorded on THF solutions unless otherwise specified and were referenced to THF, α = 25.3 ppm, β = 67.4 ppm.

A vacuum-jacketed, glass dewar measuring 7.5 x 16.0 cm (id 5.5 cm) was designed with tapering bottom to fit in the cup of the vortex mixer. All NMR samples were stirred while cooling at the indicated temperatures in this dewar.

Preparation of PhMe₂SiLi in THF: Dimethylphenylsilyl lithium was prepared from dimethylphenylsilyl chloride and titrated as described in reference 18.

Preparation of CuCN·2LiCl: THF (11.0 mL) was added to a mixture of CuCN (0.98 g, 11.0 mmol) and LiCl (0.95 g, 22.0 mmol) in a round-bottomed flask under argon. A clear, faint yellow solution was obtained after 0.5 h of stirring. This solution was used as the CuCN source for all the ¹³C NMR sample preparations unless otherwise specified.²⁵

Preparation of (PhMe₂Si)₃CuLi₂: The above THF solution of CuCN (0.25 mL, 0.25 mmol) was added to a 5 mm NMR tube, equipped with an argon inlet. The solution was cooled to -78°C and dimethylphenylsilyllithium in THF (0.9 mL, 0.75 mmol) added dropwise. The solution was stirred on a vortex mixer for 20 min before recording the NMR spectra.

Preparation of (Me₃Sn)₃CuLi₂: A THF solution of Me₃SnLi (0.5 mL, 0.25 mmol) was added to a 5 mm NMR tube, equipped with an argon inlet. The solution was cooled to -78°C and a solution of CuCN in THF (0.08 mL, 0.08 mmol) added dropwise. The solution was stirred on a vortex mixer for 10 min before recording the NMR spectra. Inverse addition of the reagents gave similar spectra.

Preparation of (PhMe₂Si)Cu(Me)(CN)Li₂ and (Me₃Sn)Cu(Me)(CN)Li₂: These mixed metalocuprates were prepared in THF as described in reference 19.

Reaction of (PhMe₂Si)Cu(Me)(CN)Li₂ with cyclohexenone (14) : Dimethylphenylsilyllithium in THF (0.3 mL, 0.25 mmol) was added dropwise at -78°C to a pregenerated solution of MeCu(CN)Li [(0.25 mmol; prepared by the reaction of CuCN (0.25 mL, 0.25 mmol) and MeLi (0.18 mL, 0.25 mmol) in Et₂O)] in a 5 mm NMR tube, equipped with an argon inlet. The reaction mixture was stirred on a vortex mixer for 10 min. Cyclohexenone, **14** (0.25 mmol) was then added neat *via* syringe. The ¹³C NMR spectrum was recorded after stirring for 20 min at -78°C.

Reaction of (Me₃Sn)Cu(Me)(CN)Li₂ with 14: A THF solution of Me₃SnLi (0.5 mL, 0.25 mmol) was added dropwise at -78°C to a solution of MeCu(CN)Li [(0.25 mmol; generated by the reaction of CuCN in THF (0.25 mL, 0.25 mmol) and MeLi (0.18 mL, 0.25 mmol) in Et₂O)] in a 5 mm NMR tube, equipped with an argon inlet. The reaction mixture was stirred on a vortex mixer for 10 min. Cyclohexenone, **14** (0.25 mmol) was then added neat *via* syringe. The ¹³C NMR spectrum was recorded after stirring for 20 min at -78°C.

Typical Procedure for Reactions of PhMe₂SiLi/MeLi/CuCN Solutions with 14: PhMe₂SiLi (1.25 mL, 1.0 mmol) was added dropwise at -70°C to a solution of MeCu(CN)Li [(1.0 mmol, prepared from the addition of MeLi in Et₂O (0.7 mL, 1.0 mmol) and CuCN (0.089 g, 1.0 mmol) in THF (2 mL) at -50°C)] in THF (2 mL) under argon. The resulting deep red solution was stirred for 0.5 h after which cyclohexenone (0.08 mL, 0.82 mmol) was added *via* a syringe. Reactions were stirred for a further 0.5 h and then quenched with saturated NH₄Cl/10%NH₄OH. Workup involved extraction of the organic phase with Et₂O (2 x 2 mL) and washing with brine (2 x 2 mL). The combined extracts were dried over anhydrous MgSO₄ and concentrated *in vacuo*. Column chromatography (4:1 hexanes:EtOAc) yielded 3-(dimethylphenylsilyl)-cyclohexanone in > 90% isolated yield and > 95% purity as judged by gas chromatographic analysis using dodecane as an internal standard. The ¹H NMR and IR data for the 1,4-adduct matched those reported by Fleming *et al.*³ for this compound. ¹³C{¹H} (CDCl₃) δ

212.5 (C=O), 136.6 (*ipso*), 133.8, 129.2, 127.8, 42.3, 41.8, 29.7, 27.5, 26.0, -5.4 (SiCH₃), -5.5 (SiCH₃); MS m/e (rel. intensity) 232 (M⁺, 20), 217 (15), 189 (5), 156 (22), 135 (100); Anal. calc. C₁₄H₂₀OSi 232.1283 found 232.1282.

Typical Procedure for Reactions of Me₃SnLi/MeLi/CuCN Solutions with 14: Me₃SnLi (2.0 mL, 1.0 mmol) was added dropwise at -78°C to a solution of MeCu(CN)Li [(1.0 mmol, generated from the reaction of MeLi in Et₂O (0.75 mL, 1.0 mmol) and CuCN (0.089 g, 1.0 mmol) in THF (2 mL)] under argon. The resulting yellow solution was stirred for 0.5 h after which cyclohexenone (0.08 mL, 0.82 mmol) was added *via* syringe. The reaction was stirred for a further 0.5 h and then quenched with saturated NH₄Cl/10% NH₄OH. Standard workup followed by column chromatography (4:1 hexanes:EtOAc) yielded 3-(trimethylstannylo)cyclohexanone in > 90% isolated yield and > 95% purity as judged by gas chromatographic analysis using dodecane as an internal standard. The ¹H NMR and IR data matched those reported by Still^{4b} for this compound. ¹³C{¹H} (CDCl₃) δ 212.2 (C=O), 45.8, 42.1, 30.8, 29.4, 25.2, -11.7 (SnCH₃); MS m/e (rel. intensity) 246 (M⁺-15, 20); Anal. calc. C₉H₁₈OSn 246.1283 found 246.1282.

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