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Aldehydes and Ketones Form Intermediate π Complexes with the Gilman Reagent, Me_2CuLi, at Low Temperatures in Tetrahydrofuran

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Supporting Information

ABSTRACT: Typical aldehydes and ketones form π complexes with Me_2CuLi at low temperatures in tetrahydrofuran. They range in stability from fleeting intermediates at −100 °C to entities that persist up to −20 °C. Three subsequent reaction pathways have been identified.

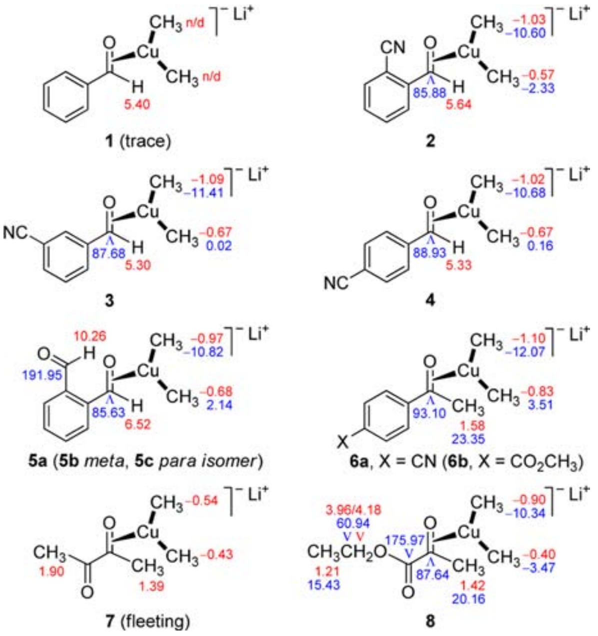
While synthetic applications of organocopper reagents involving nonconjugated aldehydes and ketones are relatively rare,[1] they have been rising in importance with the development of copper-mediated asymmetric induction.[2] For example, Harutyunyan and co-workers recently reported high yields and enantiomeric excesses for copper-catalyzed additions to alkyl aryl ketones,[3] and they invoked intermediate carbonyl π complexes, which had not been observed experimentally.[4] On the basis of theoretical calculations, Nakamura and co-workers predicted such intermediates, for example, in reactions of organocuprates with acid chlorides.[5,6] We have now used the rapid injection method to screen a number of typical aldehydes and ketones and have discovered a diverse group of cuprate−carbonyl π complexes (Chart 1).

In the rapid injection experiment, a solution of substrate is injected pneumatically using dry nitrogen into a solution of reagent with sufficient force to mix them in a fraction of a second as they spin at a controlled temperature in the probe of an NMR spectrometer.[7] Tetrahydrofuran (THF) was chosen as the solvent because it breaks down aggregates, allowing us to focus on the primary structures.[8]

For example, injection of benzaldehyde (60 μL, 0.5 M in THF-d_8) into a solution of $Me_2CuLi \cdot LiI$ (30 μmol) in 7:1 THF-d_8/benzene-d_6 (420 μL) at −100 °C gave the very weak complex **1**. It was recognized thanks to a small, broad ^{1}H NMR peak for its formyl hydrogen centered at ca. 5.40 ppm, accompanied by significant broadening of the cuprate methyl peak [width at half-height ($W_{1/2}$) = 2 Hz before and 20 Hz after injection].

When the probe was warmed to −70 °C, the ^{1}H NMR peak for Me_2CuLi disappeared ($t_{1/2}$ = 4 min) with the simultaneous appearance of a cluster of peaks [ca. 1.30 ppm, MeC(OLi)] for aggregates of the 1,2-adduct;[9] hydrolysis gave a single product, 1-phenylethanol (identical to an authentic sample as determined by GC−MS).[10]

Chart 1. Structures of Me_2CuLi−Carbonyl π Complexes[a]



[a]Also shown are selected ^{1}H (red) and ^{13}C (blue) NMR chemical shifts in ppm relative to tetramethylsilane (TMS) [benzene secondary standard, ^{1}H/^{13}C (ppm): 7.34/128.59]. Some peaks were not detected (n/d). See the text for the chemical shifts of **5b**, **5c**, and **6b**.

Injection of *o*-, *m*-, or *p*-cyanobenzaldehyde at −100 °C gave the stable complexes **2**−**4**, respectively. The conversion was ca. 100% for **2** and **3** but only 60% for **4**. The ^{1}H NMR shifts for the formyl hydrogens in these complexes (5.64, 5.30, and 5.33 ppm, respectively) bracket the formyl shift for **1** (5.40 ppm), which supports our structure assignment. A complete summary of the ^{1}H and ^{13}C shifts for **2** is given in Scheme 1, and the ^{1}H NMR spectrum of the reaction mixture containing **2** is shown in Figure 1.[11]

The heteronuclear multiple-bond correlation (HMBC)[12] plot for **2** (Figure 2 left) has cross-peaks between the formyl hydrogen (5.64 ppm) and a number of carbon atoms: methyl C (−10.60 ppm, Me$_\alpha$), carbonyl C (85.88 ppm), aryl C2 (104.93 ppm), aryl C6 (121.38 ppm), and aryl C1 (151.21 ppm). The heteronuclear multiple-quantum coherence (HMQC)[12] plot for **2** (Figure 2 right) has cross-peaks between the methyl hydrogens and the methyl carbon for both the upfield [^{1}H/^{13}C (ppm): −1.03/−10.60, Me$_\alpha$] and downfield [^{1}H/^{13}C (ppm): −0.57/−2.33, Me$_\beta$] methyl groups. There is also a cross-peak between the formyl hydrogen and the adjacent carbonyl carbon [^{1}H/^{13}C (ppm): 5.64/85.88, HC(O)]. The rotating-frame

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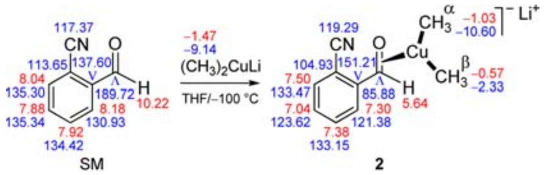
Scheme 1. Reaction of *o*-Cyanobenzaldehyde (SM) To Give 2[a]



[a] Also shown are ^1H (red) and ^{13}C (blue) NMR chemical shifts in ppm relative to TMS.

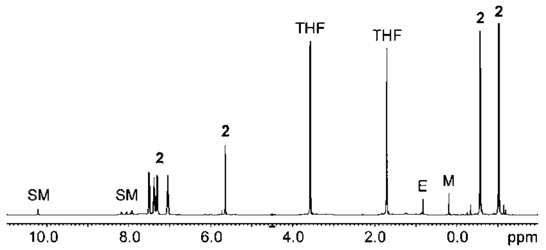


Figure 1. ^1H NMR plot for the reaction solution containing **2** (M = methane, E = ethane).

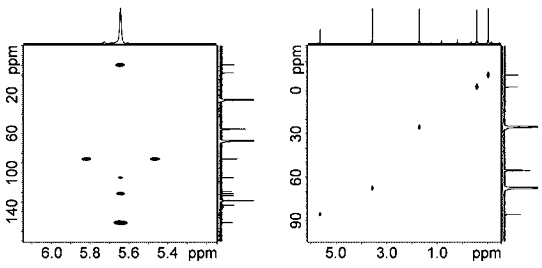


Figure 2. (left) HMBC and (right) HMQC plots for complex **2**.

nuclear Overhauser effect spectroscopy (ROESY)[12] plot (see the Supporting Information) indicated that there was exchange between **2** and the free substrate. The position of Me$_\beta$ cis to the carbonyl carbon (and thus Me$_\alpha$ trans to it) was confirmed by the presence of a nuclear Overhauser effect (NOE) cross-peak between the formyl hydrogen and the hydrogens of Me$_\beta$ without such a cross-peak for Me$_\alpha$. The cuprate−carbonyl π complexes appear to have a pseudo-square-planar geometry, similar to the π complexes of C−C double bonds with cuprates.[13]

When the probe was warmed to −60 °C, the ^1H NMR peaks for **2** disappeared ($t_{1/2}$ = 40 min) as a cluster of peaks [ca. 1.40 ppm, MeC(OLi)] appeared for aggregates of the 1,2-adduct. Hydrolysis gave a single product, 2-(1-hydroxyethyl)-benzonitrile, as confirmed by GC−MS.

Injection of phthalaldehyde at −100 °C resulted in rapid conversion to **5a** (75% after 10 s; see Chart 1 for ^1H and ^{13}C chemical shifts). Isophthalaldehyde and terephthalaldehyde also formed the corresponding π complexes **5b** [53% after 10 s, 75% after 30 min; $^1H/^{13}C$ (ppm): −1.16/−11.54, Me$_\alpha$; −0.73/−0.18, Me$_\beta$; 5.36/88.49, HC(O)] and **5c** [50% after 10 s; $^1H/^{13}C$ (ppm): −1.01/−10.55, Me$_\alpha$; −0.69/−0.23, Me$_\beta$; 5.38/89.56, HC(O)]. The formyl ^1H peaks were very broad for **5a** ($W_{1/2}$ = 30 Hz vs 10 Hz for the free substrate) and **5b** ($W_{1/2}$ = 25 Hz) but not for **5c** ($W_{1/2}$ = 8 Hz).

In the case of ortho isomer **5a**, ethane was evolved[11] very slowly at −100 °C and more rapidly at −80 °C ($t_{1/2}$ = 12 min); its evolution from the para isomer **5c** was rapid at −100 °C ($t_{1/2}$ = 14 min). The meta isomer **5b** was stable at −100 °C but disappeared upon warming to −60 °C ($t_{1/2}$ = 1 min) as the 1,2-adduct appeared [^1H NMR: cluster of peaks at ca. 1.40 ppm, MeC(OLi); confirmed by GC−MS after hydrolysis].

Acetophenone did not form a complex under our conditions. Nevertheless, upon injection of the *p*-cyano- or *p*-methoxy-carbonyl derivatives at −100 °C, we observed small amounts of the corresponding π complexes **6a** [15%; see Chart 1 for ^1H and ^{13}C chemical shifts] and **6b** [2%; $^1H/^{13}C$ (ppm): −0.90/−3.13, Me$_\alpha$; −0.49/8.64, Me$_\beta$; 93.34, C(O)]. They were stable at −100 °C but disappeared upon warming (**6a**, $t_{1/2}$ = 7 min, −40 °C; **6b**, $t_{1/2}$ = 8 min, −20 °C; measured for the disappearance of starting materials) as the enolates appeared along with methane.[11] The catalytic system, which gives 1,2-addition with acetophenones, appears to involve a phosphine-complexed organocopper(I) intermediate.[3]

Injection of diacetyl at −100 °C gave **7** (50% after 10 s), which disappeared rapidly ($t_{1/2}$ = 4 min) with the formation of ethane.[11] No Cu^0 (red mirror or black precipitate) was observed; therefore, the copper remained complexed, presumably as Cu^I.

Ethyl pyruvate afforded **8** (49% after 10 s, 95% after 3 h), which was stable at −100 °C. A NOE cross-peak between the hydrogens of Me$_\beta$ and those of the acyl methyl group was observed. Complex **8** disappeared upon warming ($t_{1/2}$ = 2 min, −20 °C) as the 1,2-adduct appeared [^1H NMR: singlet at 1.35 ppm, MeC(OLi)].

In contrast to thiobenzophenone, which gave a very stable π complex,[14] benzophenone did not yield a detectable amount of one. On the other hand, fluorenone formed a stable π complex.[15]

In the presence of Me_2CuLi, diverse aldehydes and ketones form cuprate−carbonyl π complexes with wide variations in yield and stability. Three subsequent reaction pathways are possible: (i) 1,2-addition, (ii) evolution of ethane, and (iii) enolate formation. These observations confirm theoretical calculations and provide experimental support for mechanistic schemes involving cuprate−carbonyl π complexes.

■ 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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