Mechanism of Lithium Cuprate Conjugate Addition: Neutral Tetracoordinate Cu^{I} Cuprates as Essential Intermediates

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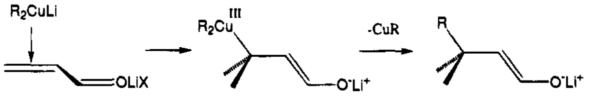
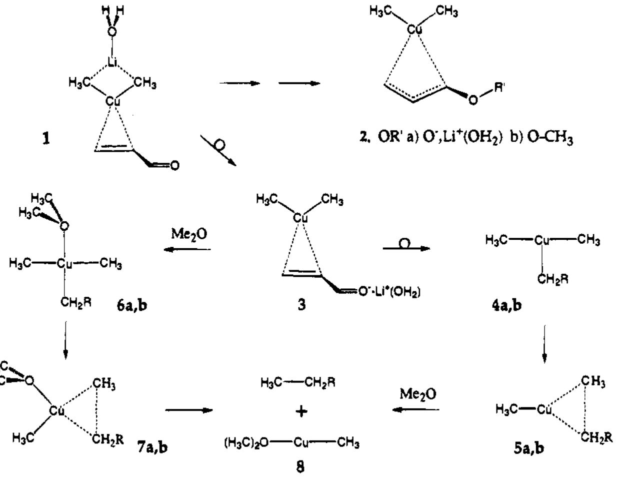
The initial discovery of cuprate conjugate addition was complemented by a mechanistic study ruling out the operation of a cyclic six-centered transition state.[1] In the intervening 30 years, cuprate-facilitated carbon–carbon bond formation has blossomed as a fundamental tool for the synthetic chemist.[2] Full mechanistic understanding of the reaction, however, has yet to be achieved. Early arguments that electron transfer guides the conjugate alkylation[3] continue to receive some attention.[4] However, the bulk of the mechanistic work has suggested the reaction to be initiated by a lithiated enone,[3a,5,7b] a copper olefin π-complex,[6,7] an α-cuprioketone,[7b] a charge transfer complex,[8] a cyclic template,[6a,b,7] or some combination of these along a closed-shell pathway. Spectroscopic studies have detected various species by stopped-flow methodology[7c] or by operating at low temperatures.[6,7b] Subsequent steps are believed to involve an as-yet unobserved "Cu^{III} " intermediate,[6c,8,9] although the latter has been recognized as a high-energy species.[10]



In the present study, we examine a series of structures which model key parts of the potential energy surface for the conjugate addition of dimethyl cuprate to acrolein. Particular emphasis is placed on how the π-complexes are converted to β-alkylated product and on the question of the intermediacy of Cu^{III}. All structures have been optimized without symmetry using density functional theory (DFT),[11] the D95V valence double-ζ basis, and the Hay–Wadt 10-electron relativistic effective core potential on copper (B3LYP/LANL2DZ).[12,13] Key structures have been further subjected to a fixed-point calculation at the MP2/HW3 level of theory[14] and analyzed within the natural population analysis (NPA) framework.[15]

Scheme 1[a]



[a] R = (a) $CH{=}CHO^-Li^+$, (b) H.

Scheme 1 depicts three routes to products stemming from π-complex **1**.[16] The latter carries a molecule of water at lithium as a first solvation shell surrogate for ether solvent and is characterized by a nearly square-planar arrangement around the metal with all Cu–C bond lengths within 2.08–2.14 Å. An effort was made to locate the rearranged allylic complex **2a**, suggested to be capable of reversible complexation with enone and instrumental in directing reaction stereochemistry.[9c,17] All starting points led to the lithium-isomeric π-olefin complex **3**, more stable than **1** by 3.6 kcal/mol. Carbonyl methylation to give **2b** (R′ = CH_3) did, however, lead to a stationary point. This suggests that if complex **1** is sufficiently long-lived, it might be possible to capture the allyl complex as a stable intermediate. Superficially, the calculated result complies with the postulation[7e,9c] and isolation[7d,17b,18] of enol TMS ethers when cuprate addition is carried out in the presence of Me_3SiCl. In fact, recent

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[12] Absolute and zero-point (ZPE, kcal/mol) energies (in au) at the G92/DFT[13]-optimized B3LYP/LANL2DZ geometries: **1**, −551.858 543 (99.4 kcal/mol); **2b**, −509.710 031; **3**, −551.864 312; **4b**, −315.794 473 (66.9); **5b**, −315.794 358 (66.9); **6b,** −470.822 665 (119.3); **7b**, −470.809 557 (118.7); **8**, −391.082 042 (73.4); CH_3CH_3, −79.818 862 (47.2); Me_2O, −155.005 480 (50.0).

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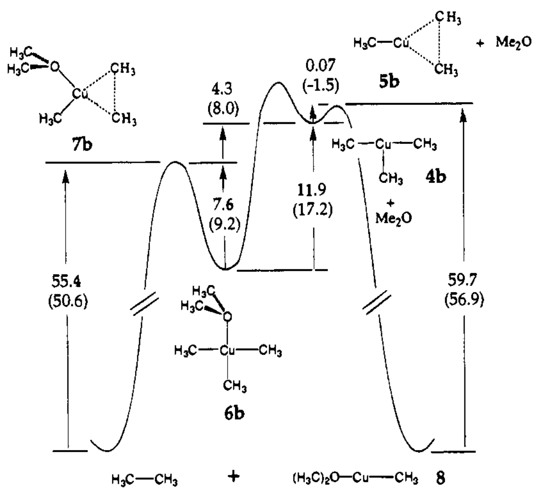

Figure 1. Relative B3LYP/LANL2DZ//B3LYP/LANL2DZ (MP2/HW3//B3LYP/LANL2DZ) energies, kcal/mol, including B3LYP/LANL2DZ zero-point energies for the transformation of **6b** to **4b** and CH_3CH_3 + **8**.

experiments demonstrate that the silylating agent combines with product enolate only after rate-determining cuprate alkylation.[19]

Complex **3** can spontaneously ring-open to the putative Cu^{III} enolate intermediate **4a**, followed by reductive elimination through transition state **5a**. Since the neutral copper center is insulated by CH_2 from the enolate moiety, structure **4** has been modeled as trimethylcopper (**4b**). The T-shaped molecule[20] (no negative eigenvalues of the Hessian matrix) resides in a very shallow local minimum, followed by **5b** (one negative eigenvalue) only 0.07 kcal/mol higher in energy (Figure 1). On the MP2/HW3 surface, **5b** is *less stable* than **4b** by 1.5 kcal/mol. Similar calculations for $RCuH_2$ (R = H and CH_3) are unambiguous in demonstrating that the less-substituted T-structures are transition states between $RCu{\cdot}H_2$ and $HCu{\cdot}RH$ product complexes.[21] Quite clearly, trialkylcopper derivatives have little or no independent existence and, therefore, cannot serve as intermediates in cuprate conjugate addition, reversible[9c] or otherwise.

The remarkable stability of the $[Cu(CF_3)_4]^-$ anion[22] suggested to us that solvent might intercept complex **3** to give the neutral higher order copper species **6**. Treated as the trimethylcopper dimethyl ether solvate, **6b** optimizes without symmetry to give a nearly square-planar structure (Figure 2, supporting information) stable to dissociation to Me_2O and **4b** by 11.9 and 17.2 kcal/mol at the B3LYP/LANL2DZ and MP2/HW3 levels of theory, respectively (Figure 1). Such an intermediate has been proposed previously in connection with cuprate substitution reactions.[2a,4,9a,10] Transition state **7b** yields a single negative eigenvalue, is likewise distorted square-planar, and lies 7.6 and 9.2 kcal/mol higher in energy, respectively, than **6b**.[23] In both **6b** and **7b**, the plane of the Me_2O solvent is perpendicular to the copper–carbon plane (Figure 2). The calculated barrier is in excellent agreement with Krauss and Smith's pseudo-first-order decomposition rates ($k = 0.06-3.9\ s^{-1}$; $E_a = 18-21$ kcal/mol), suggested to apply to a prereductive elimination step.[7c] The result that decomposition of **6b** is energetically less expensive than dissociation to solvent and **4b** ensures that trialkylcopper is not operating by the dissociative reaction channel. The proposed mechanism, then, involves solvent attack on π-complex **3** to give **6**, which, unlike square-planar trialkylphosphine gold complexes,[20] undergoes reductive elimination without prior dissociation to a T-shaped trialkyl metal species, i.e., **4**.

With respect to the oxidation state of the metal in **4**, **6**, and the other copper-containing structures in Scheme 1, a comparative NPA analysis reveals that the 3d metal population ranges from 9.4 to 9.7 electrons as it does for the classical organocopper reagents $CuCH_3$ and $[CH_3CuCH_3]^-$. All structures, neutral and charged, incorporate a d^{10} metal with an atomic charge of $\leq +1.0$. They can be regarded as Cu^I complexes whose bonds are dominated by ionic contributions, but whose structures are determined by a nonvanishing degree of covalent $Cu(d_{x^2-y^2})$ ligand binding. Structures **4** and **6**, for example, show a relatively strong covalent Cu–C bond at the leg of the three-carbon T, while the Cu–C arms are similar to the bonds in $[CH_3CuCH_3]^-$. As for $[Cu(CF_3)_4]^-$,[24] the electron distributions amount to partial oxidation at the ligand centers. NPA analysis for **4** and **6** posits that the T- and leg-methyls have lost 1.0 and 0.5 electrons, respectively, relative to CH_3^-. The intimate interplay between metal and substituent thereby avoids the significant energy penalty associated with copper's putative change from d^{10} to d^8 and back again across the conjugate addition pathway.

The nature of the novel tetracoordinate Cu^I structures represented by **6** eliminates the need to consider Cu^{III} entities as viable intermediates in the conjugate addition process. Furthermore, they provide a basis for understanding the accelerating effects of additives on the reaction.[6b,7e,9c,17-19] It can be confidently predicted that the tetracoordinate intermediates with appropriate substituents will, like $[Cu(CF_3)_4]^-$ and $(CF_3)_2CuSC(S)NEt_2$,[25,26] be observed, isolated, and structurally characterized.

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Supporting Information Available: Figure 2, showing optimized geometries of for **6b** and **7b** (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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