Organocopper Chemistry: Structures, Mechanisms, and Reactivity

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Outline

1. Historical Background
2. Lower-Order Organocuprates
3. Higher-Order Organocuprates
4. Organocopper Reagents
5. Engineering Reactivity
6. Synthetic Utility
7. Conclusions

Lead References:
Why Copper??

"Of all the transition-metal organometallic reagents developed for application to organic synthesis, organocopper complexes are by far the most heavily used and enthusiastically accepted by the synthetic organic chemist."

- copper occupies a unique place on the periodic table, bordering both the main group and transition metal elements
- this position confers special reactivity to Cu(I) that is unavailable to its neighbors [Ni(0), Ag(I), Au(I), and Zn(II)]
  --organonickel and organosilver species are not as stable and less synthetically useful
  --organogold species are too stable
  --zinc(II) lacks a redox system like the Cu(I)/Cu(III) system; as well, the 3d orbitals of zinc(II) are much lower in energy compared with Cu(I)

The Development of Organocopper Chemistry: Historical Background

1941 Kharash and Tawney disclosed the first 1,4-addition of a Grignard reagent to an \(\alpha,\beta\)-unsaturated ketone in the presence of a small amount of a Cu(I) salt

*JACS* 1941 63 2308

1952 Gilman et al. reported the reaction of two equivalents of MeLi with a Cu(I) salt to form a lithium diorganocuprate

*JOC* 1952 17 1630

1966 House and coworkers showed that the reactive species of conjugate addition is Gilman's lithium diorganocuprate (the "Gilman reagent")

*JOC* 1966 31 3128

1968 Corey demonstrates the synthetic utility of organocopper reagents, laying the foundations for subsequent synthetic developments

*JACS* 1968 90 5618

1970's Initial mechanistic studies on reaction pathways of organocopper chemistry

Structure of Lower-Order Organocuprates  
(Lithium Diorganocupper(I) Species)

- Most basic structural property is the linear R-Cu-R arrangement

- Linear free organocuprates: $[R_2Cu]^-$
  --the free organocuprate can be accessed by mixing $R_2CuLi$ with 12-crown-4
  --solvent separated ion pairs, however, are unreactive in many standard organocupper reactions  
  *(JACS 1997 119 4887)*

- Minimum lithium organocuprate clusters: $R_2CuLi$
  --created by coordination of a lithium cation to the linear R-Cu-R anion
  --often dimerize or polymerize to neutralize the partial charges on each end  
  *(JACS 1992 114 1507)*

- Closed clusters: $R_2CuLi$-LiX and $(R_2CuLi)_2$
  --the neutral closed cluster is widely detected in crystals and solution  
  *(JACS 1986 107 697* (first crystal structure of dimer)
  --accepted as the typical resting state of lithium organocuprates in ethereal solution

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Possible Organocuprate Structures

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[R–Cu–R]– + Li⁺ → [R–Cu–R]³⁺ + Li

[R–Cu–R]³⁺ + LiX → [R–Cu–R]– + X–

[R–Cu–R]– + Li → [R–Cu–R]³⁺ + Li

four-centered structure disfavored due to high cost of bending the R-Cu-R bond

R–Cu–R + X– → R–Cu–R + Li

R–Cu–R + Li → R–Cu–R + Li

copper atom covalently bound to alkyl species, which is electrostatically associated with a lithium atom
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*Tetrahedron 2000 56 2805*
Dynamic Equilibria in Solution

- Me$_2$CuLi dimer most carefully studied via X-ray, NMR, and mass spec
  --X-ray absorption spectra (XAS) in solution indicate dicoordination of Cu with very similar bond lengths to the crystal structure (ACIEE 1998 37 1564)
  --cryoscopic and spectroscopic studies on Me$_2$CuLi·LiI indicate a single Cu atom in the organocopper cluster (ACIEE 1997 36 755)
  --presence of LiX in organocopper clusters determined by ESI mass spec (Organometallics 1999 18 1571)
  --NMR studies in Et$_2$O suggest an equilibrium mixture of the dimer and the LiX cluster (Organometallics 1995 14 1213)

- Dynamic properties determined by NMR studies (JACS 1998 120 1333)
  --the Li atom exists in the vicinity of the Me group in [Me$_2$Cu] but rapidly exchanges with other Li atoms
  --the dimer undergoes fast and reversible cleavage of the Me-Li electrostatic bond to yield a high energy "open cluster" intermediate

Mechanistic Studies

- The complex nature of organocopper reagents and the difficulty in monitoring the reagents throughout a reaction have contributed to a relative lack of mechanistic information.

- Mechanism elucidation, however, has been aided in recent years by advancements in analytical techniques as well as the development of reliable and accurate theoretical measurements.

Three Major Theories
A. Four- and six-centered transition states

These mechanisms have been discussed since the 1960's but now they are considered obsolete.
Mechanistic Studies

Three Major Theories

B. single electron transfer

--theory based on pioneering work by House and coworkers in the early 1970's

--proposed mechanism assumes a single electron transfer (SET) from the dimer, leading to a Cu(III) intermediate

\[ \text{[RCuLi]} \rightarrow \text{R-Cu-R} \quad \text{Li} \quad \text{Li} \quad \text{Li} \quad \text{O} \quad \text{ET} \quad \text{R-Cu-R} \quad \text{R-Li-R} \quad \text{Cu} \quad \text{Cu} \quad \text{Cu} \quad \text{Li} \quad \text{Li} \quad \text{Li} \quad \text{O} \quad \text{O} \quad \text{Cu(I) species} \]

--most of the supporting experimental evidence accepted in the past is not currently accepted as evidence of SET (except for the hypothesis of a Cu(III) intermediate); ESR and KIE studies are not consistent with a radical mechanism

--while SET processes do not occur among moderately electrophilic olefinic acceptors, they are likely to be involved with highly electrophilic substrates (e.g. fluorenone and doubly activated olefins)

Mechanistic Studies

Three Major Theories


\[ \text{[RCuLi]} \rightarrow \text{R-Cu-R} \quad \text{Li} \quad \text{Li} \quad \text{Li} \quad \text{O} \quad \text{ET} \quad \text{R-Cu-R} \quad \text{R-Li-R} \quad \text{Cu} \quad \text{Cu} \quad \text{Cu} \quad \text{Li} \quad \text{Li} \quad \text{Li} \quad \text{O} \quad \text{O} \quad \text{Cu(I) species} \]

--kinetics: first-order in dimer and enone (JACS 1981 103 141)

--multiple points of contact via copper/olefin (soft-soft interaction) and lithium/carbonyl (hard-hard interaction)

--inner-sphere electron transfer converts the stable C-Cu bond to an unstable C-Cu(III) bond, which is the key intermediate

--rate-determining step is C-C bond formation caused by reductive elimination from Cu(III) to Cu(I)

--product is a lithium enolate complexed with an R_Cu(I) species

--reaction scheme and intermediates supported by NMR studies and theoretical calculations
**A Molecular Orbital Picture**

R - Cu - R goes from a linear species (3d$_{xz}$ is the HOMO) to a bent species (~ 120° bond angle)
--3d$_{xz}$ becomes the new HOMO; favorable overlap with the π* of the olefin
--energy gain via back-donation compensates for energy loss associated with bond bending
--MO picture helps explain why Cu is so effective: d orbitals of Zn are too low-lying to make organozinc compounds as nucleophilic as organocopper compounds

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**Role of Dummy Ligands in the Chemistry of Mixed Cuprates [RCu(Y)Li]**

**Advantages:** conservation of precious R ligand
mediate cuprate reactivity

**Common Ligands:** alkynyl, cyano, phenylsulfanyl, dialkylamino, phosphanyl, thiophene

**Tradition Mechanistic View:** The Y group forms a stronger Cu-Y bond, thus resisting transfer.

**Current Understanding:** The Y group acts as a tight bridge between Cu(III) and Li in the cluster structure, simultaneously binding to both due to strong electrostatic interactions. Thus, the much less bridging organic ligand is transferred preferentially. *(JACS 1999 121 8941)*
Higher-Order Organocuprates

**Definition:** organocupper species bearing three anionic groups, \([R_3Cu]^{2+}\)
  
ex. \(R_3CuLi_2, R_2Cu(CN)Li, RR'Cu(CN)Li\)

**Synthesis:** same as for lower-order organocuprates (2 RLi + CuCN)

**Synthetic advantages:** can be more selective/reactive than lower-order organocuprates

- **A.** 1,4-addition
  
  ![1,4-addition reaction](image)
  
  - Me₂Cu(CN)Li₂ in THF, -20 °C
  - Quantitative yield, 100% diastereoselectivity

- **B.** halide displacement
  
  ![Halide displacement reaction](image)
  
  - n-Bu₂Cu(CN)Li₂ in THF, -50 °C
  - 95% yield (compare with 70% for L.O. cuprate)

- **C.** epoxide opening
  
  ![Epoxide opening reaction](image)
  
  - n-Pr₂Cu(CN)Li₂ in THF, 0 °C
  - 86% yield (compare with 30% for L.O. cuprate)

**Reviews:** Tetrahedron 1984 40 5005; Synthesis 1987 325

The Higher-Order Cyanocuprate Controversy: Is the CN Ligand Coordinated to Copper????

- Lipshutz et al. have considered the higher-order cyanocuprates to be dianionic Cu(I) salts with a tricoordinated Cu species.
  
  *JACS* 1993 115 9276

- Utilizing \(^{13}\text{C}, {^6}\text{Li}, \text{and} {^{15}}\text{N} NMR data, Bertz et al. claim that CN is not attached to Cu.
  
  *JACS* 1990 112 4031; *JACS* 1991 113 5470; *ACIEE* 1998 37 314

- Crystallographic data support coordination of the cyanide anion to lithium rather than copper.
  
  *JACS* 1998 120 9688; *ACIEE* 1998 37 1684

- **Conclusion:** The true role of the cyano group in the reactions of higher order cyanocuprates still remains obscure.
Organocopper Reagents

- Neutrally charged species represented as 'RCu'
- Lewis acidic—able to pick up solvent molecules in solution
- Typically unreactive in standard organocuprate-type reactions
  -- a strong neutral donor ligand (like PPh3) may increase reactivity
  (Inorg. Chem. 1995 34 1914)
- Presence of alkali metal salt may cause the neutral RCu to react as a halocuprate complex (JACS 1990 112 5869; JACS 1998 120 8273)

\[
\text{Me-Cu} + \text{LiCl} \rightarrow \text{LiCl-Me-Cu-Cl}
\]

- Employed in cases where reactivity of the organocuprate species needs to be "tamed" (JACS 1990 112 4404)
  -- diallylic cuprates are very reactive and add predominantly in a 1,2-fashion
  (JOC 1986 51 1745)

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Engineering Reactivity

- Source of Cu(I) salt
- Ratio of CuX to R-M (stoichiometric or catalytic)
- Metal source (Li or MgX)
- Solvent (almost always ethereal)
- Additives (for solubilizing, stabilizing, or activating purposes)
  -- Lewis acids (BF3·OEt2 and AlCl3 are most common)
  -- TMSCI

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Synthetic Utility

- Suzuki and Noyori’s synthesis of prostaglandin E$_2$:

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1. Bu$_2$PCu\(\rightleftharpoons\)C$_2$H$_{11}$ \(\rightleftharpoons\)\(\text{TBDMS}\)
2. 78% yield
    \(\text{TBDMS} \rightleftharpoons\)\(\text{TBDMS}\)

1. HF (98% yield)
2. baker's yeast (80% yield)
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JACS 1985 107 3348
JACS 1988 110 4718

In Conclusion...

- Copper occupies a unique position on the periodic table, bordering both the transition metals and the main group elements.
- This position confers special reactivity unavailable to neighboring elements.
- Organocopper reagents provide the most general synthetic tools in organic chemistry for nucleophilic delivery of hard carbanions to electrophilic carbon centers.
- Although much progress has been made to determine the structure and mechanism of organocopper compounds, many areas remain to be studied.

"The unified view on the nucleophile reactivities of metal organocuprate clusters thus obtained has indicated that organocuprate chemistry represents an intricate example of supramolecular chemistry, which chemists have exploited without even knowing it."

~Nakamura and Mori, *ACIEE* 2000 39 3750