

An Introduction to Synthesis Using Organocopper Reagents

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Introduction

Organic synthesis generally involves forming or breaking a bond between two carbon atoms and changing one functional group into another. Formation of a carbon-carbon σ -bond using an organometallic reagent has been performed routinely for many years with metals such as magnesium (Grignard reagents), lithium, sodium, and zinc. Transition metals, however, such as palladium, titanium, chromium, iron, cobalt, nickel, and copper are now being used more and more frequently to connect two carbon units efficiently and under especially mild reaction conditions (e.g., at or below room temperature). Organocopper reagents, in particular have become popular among organic chemists for use in synthesis of larger molecules from smaller ones. This widespread acceptance and use of organocopper reagents are largely attributable to their ease of preparation and to their ability to effect transformations difficult or impossible to accomplish effectively with any other reagents. Organocopper reagents often react in a highly selective fashion: stereoselectively, regioselectively, and chemoselectively. These characteristics are especially important in the construction of complex organic molecules, as illustrated by the syntheses discussed later in this book. Several detailed reviews of organocopper chemistry are listed at the end of this chapter.

A. A Brief History of Organocopper Chemistry

Before the mid-1960s organocopper chemistry was studied only in sporadic fashion. Gilman and his students prepared methylcopper in 1936. In 1941 it was observed that the normal course of reaction

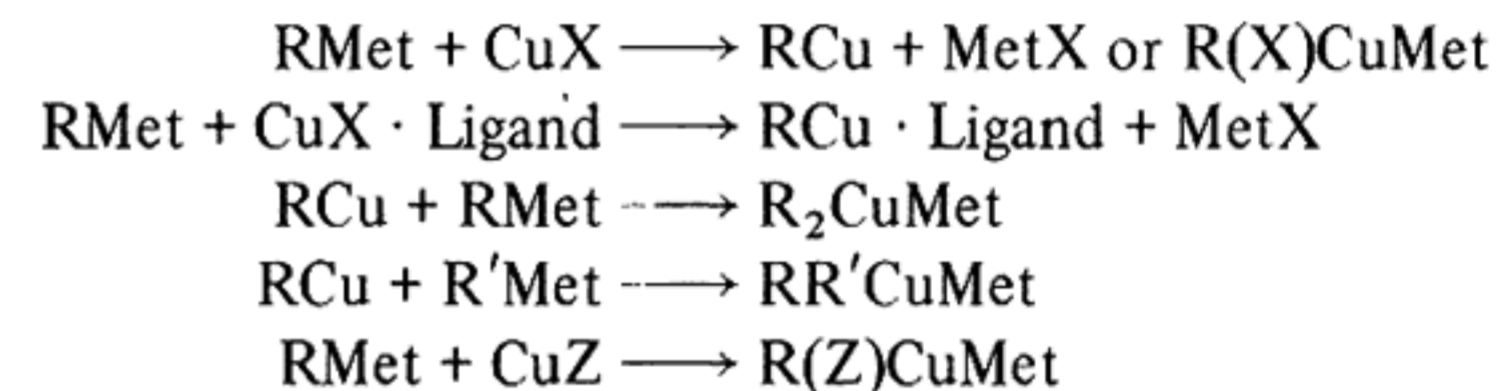
between a Grignard reagent and a cyclohexenone (i.e., 1,2-addition to the carbonyl group) was changed to 1,4-addition by the presence of a catalytic amount of copper(I). In 1952 Gilman and his students prepared dimethylcopperlithium (lithium dimethylcuprate). Not until the mid-1960s, however, did intensive research in the United States (at M.I.T. and Harvard) and in France reveal the broad synthetic potential of organocopper reagents.

In most cases organocopper reagents are prepared by adding an organomagnesium or an organolithium reagent via syringe to a copper(I) species at low temperature in an inert solvent and under an inert atmosphere. Less frequently, organocopper reagents are prepared by starting with organozinc, organoboron, or organozirconium compounds. Very recently, some organocopper compounds have been prepared from organic halides and highly reactive copper powder.

There are several different types of useful organocopper reagents, as shown in Table 1-1. The chemical behavior of one type of organocopper compound is sometimes very different from that of another type, and the same organocopper reagent often reacts differently in different solvents. It is often necessary, therefore, to examine empirically several types of organocopper species and to use different solvents and temperatures to arrive at the optimum choice of reagent and conditions for a desired transformation. Nevertheless, based on experience during the past 15 years, some sound generalizations can be made, as follows: (1) catalytic organocopper compounds are most effective when prepared from Grignard rather than organolithium reagents; (2) pure stoichiometric organocopper compounds (RCu) are less reactive than the corresponding cuprate species (R_2CuLi), and among pure RCu species only cuprous acetylides are particularly useful in substitution reactions; (3) phosphorus and sulfur ligands often solubilize organocopper compounds and sometimes allow very pure organocopper(I) compounds to be prepared, but these ligands sometimes make product isolation difficult; (4) homocuprates and mixed homocuprates are by far the most popular types of organocopper reagents; (5) organo(hetero)cuprates are used for special reactions in which the organic group is particularly valuable, or in which an unusually stable organocopper reagent is needed; (6) R_3CuLi_2 and related complex organocopper-lithium species are relatively new and have been used thus far mainly for addition reactions; and (7) organocopper-borane complexes, devel-

Table 1-1 Organocopper Reagents

Types of Organocopper Reagents	General Name
RMet + CuX(catalytic)	Catalytic organocopper compound
RCu	Stoichiometric organocopper compound
RCu · Ligand	[Ligand = R_3P , $(RO)_3P$, R_2S]
R_2CuMet (Met = Li, MgX)	Homocuprate
R_2CuMet · Ligand	
$RR'CuMet$	Mixed homocuprate
$R(Z)CuMet$ (Z = OR', SR', CN, Cl, Br)	Organo(hetero)cuprate or heterocuprate
R_nCuLi_{n-1} ($n > 2$)	Complex organocopperlithium compounds
$RCu \cdot BF_3$	Organocopper-borane complexes
$RCu \cdot BR_3$	

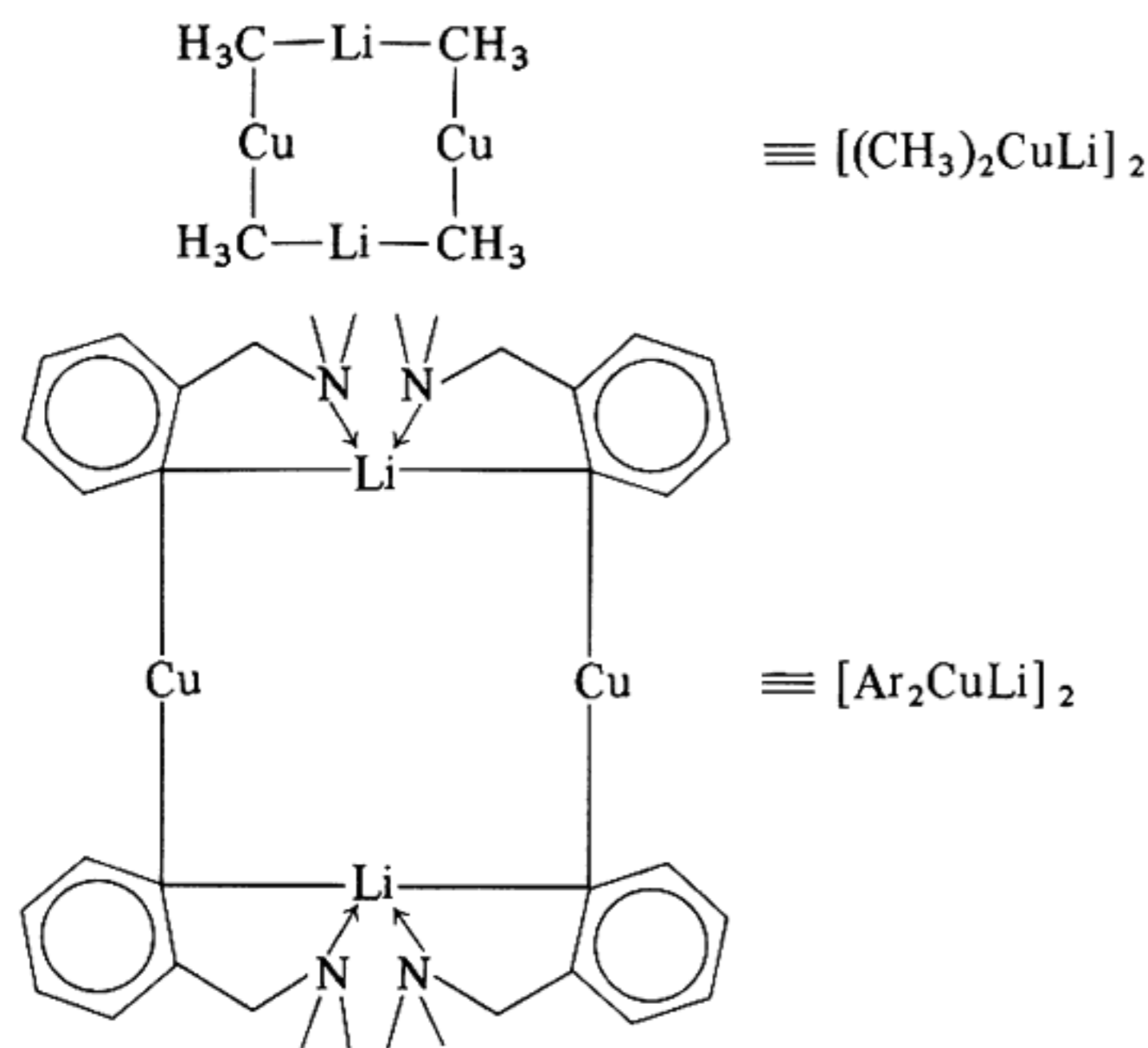


Scheme 1-1 Preparation of Organocopper Reagents

oped recently in Japan, are particularly useful for conjugate addition to acetylenic carbonyl compounds and for substitution of allylic electrophiles (reactivity: $R_2CuLi > RCu > RCu \cdot BR_3$). Many specific examples supporting and extending these generalizations are given in syntheses 1-33 on the following pages.

Their thermal instability (see synthesis 33) and their high reactivity toward oxygen and water make isolation and structural characterization of most organocopper species very difficult. Lithium dimethylcopper, as representative of the homocuprates, has been shown by molecular weight measurement (vapor pressure depression), by NMR spectroscopy, and by solution X-ray scattering methods to exist in diethyl ether solution as a dimer represented in the accompanying structure. Like-

wise, lithium diarylcopper species in which the aryl group carries a coordinating heteroatom side arm have been shown by Dutch researchers using NMR and X-ray methods to exist as Cu_2Li_2 clusters with aryl groups bridging copper and lithium atoms via 3-center-2-electron bonds. Such aggregates are not true "ate" complexes of positive and negative ions; although the name "cuprate" therefore conveys inaccurate structural information, "lithium cuprate" is commonly used and is used here interchangeably with "diorganocopperlithium" and "lithium diorganocopper."



The structures of some fluorinated stoichiometric organocopper compounds (ArCu) were determined at DuPont by kinetic and molecular weight (e.g., mass spectrometry) methods to be tetrameric and in some cases octameric aggregates.

B. Typical Reactions of Organocopper Reagents

The two most popular reactions of organocopper reagents are (1) additions to carbon-carbon double and triple bonds, and (2) substitutions of organic halides and alcohol derivatives. Thermal and oxidative

dimerization of organocopper compounds is of some use, especially for conversion of copper acetylides into conjugated diynes (Glaser reaction) and for formation of symmetrical biaryls.

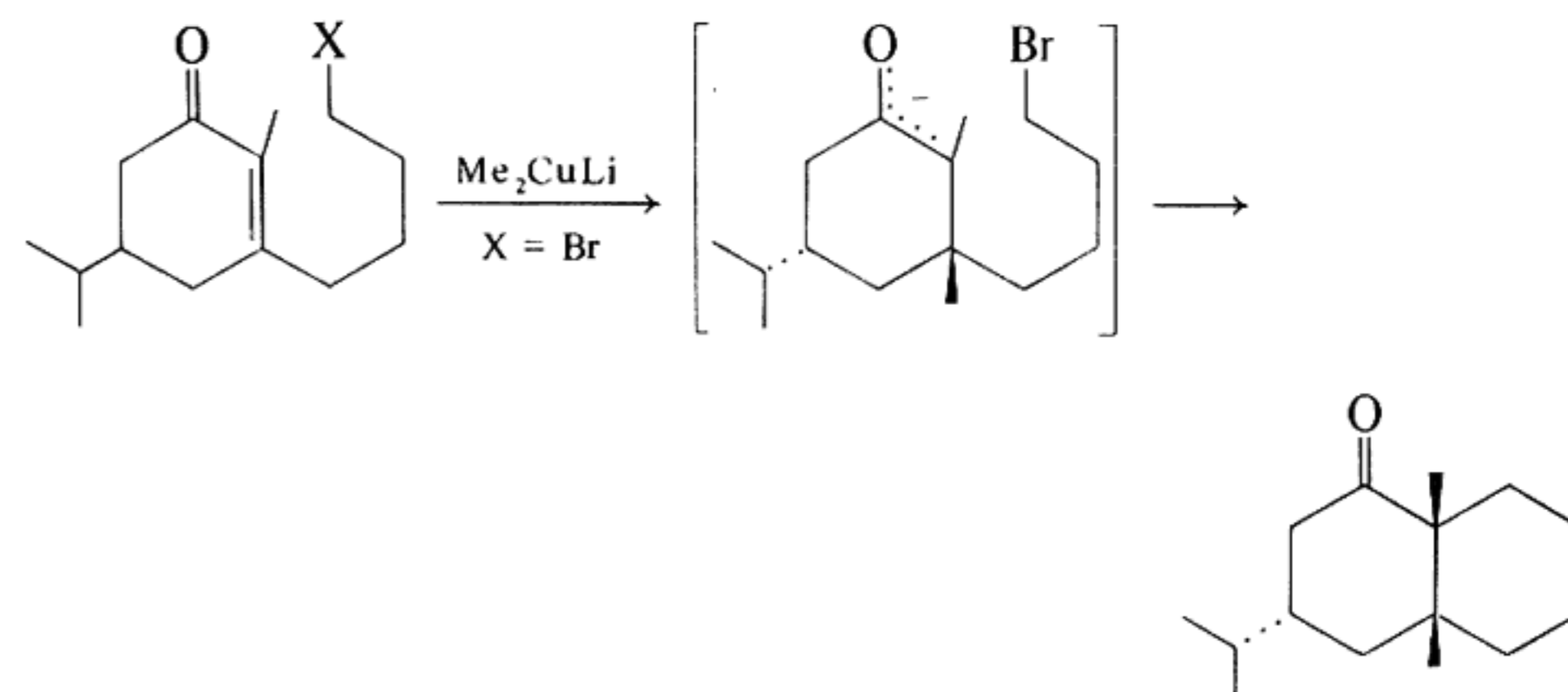
Detailed reviews of organocopper additions to carbon-carbon multiple bonds are listed at the end of this chapter. Although there are a few examples of organocopper addition to olefins and acetylenes activated by nitro, phosphonyl, and sulfonyl groups, in this book we focus attention on the more common cases of organocopper addition to olefins and acetylenes activated by carbonyl groups. We also comment on organocopper addition to unactivated acetylenes (synthesis 10). α,β -Unsaturated carbonyl compounds react with most types of organocopper reagents in a conjugate manner, leading, after aqueous work-up, to a larger molecule in which the new carbon-carbon bond has been formed β to the carbonyl group. Organocopper conjugate addition is therefore like the Michael reaction of enolate ions with unsaturated carbonyl compounds in terms of the *position* of the new carbon-carbon bond and in terms of sensitivity to *steric factors* in the carbonyl compound, but it is unlike the Michael reaction in that a hydrocarbon group becomes attached at the β -carbon, producing a new *monocarbonyl* compound rather than 1,5-*dicarbonyl* compound. In contrast to organocopper reagents, Grignard and organolithium compounds usually react with α,β -unsaturated carbonyl compounds via 1,2-addition to the carbonyl group. Organocopper reagents are generally less basic than the corresponding organolithium and organomagnesium reagents; enolization of carbonyl compounds by organocopper reagents is rare. Unsaturated *ketones* are more reactive than the corresponding unsaturated *esters* toward organocopper reagents, and *acetylenic* carbonyl compounds are more reactive than the corresponding *ethylenic* carbonyl compounds. Other important aspects of organocopper addition reactions are illustrated and discussed in syntheses 1-11.

Reviews of organocopper substitution reactions are listed at the end of this chapter. A generalized reactivity series of electrophiles toward lithium diorganocopper reagents is as follows: acid chlorides > aldehydes > tosylates \approx epoxides > iodides > bromides > chlorides > ketones > esters > nitriles \gg alkenes. The relative reactivity of alkyl halides is allylic > primary > secondary \gg tertiary, and the kinetics of displacement are roughly first order in organocopper reagent and first order in substrate. Based on these relative reactivity series, chemo-

selective reaction of organocopper reagents has been achieved in many cases with one functionality in a bifunctional or polyfunctional compound. Organocopper substitution with alkyl halides is like the Wurtz coupling reaction ($\text{RX} + \text{Na}$) in that two *hydrocarbon* groups are joined, but it is unlike the Wurtz coupling in that union of two *different* hydrocarbon groups R (from R_2CuLi) and R' (from $\text{R}'\text{X}$) can be achieved without concomitant formation of the undesired symmetrical dimer $\text{R}'\text{R}'$.

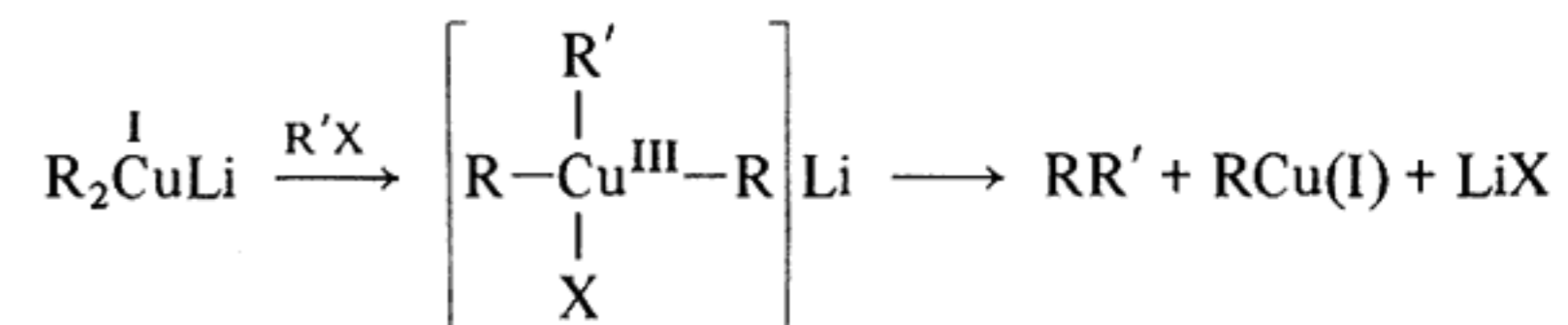
The organocopper substitution reaction can be accomplished with a wide variety of nucleophilic R groups: R = alkyl (primary, secondary, tertiary), alkenyl, aryl, heteroaryl, alkynyl, allylic, and with many R groups carrying remote functionalities (e.g., ethers, acetals, ketals, sulfides). The stereochemical result of this substitution reaction is inversion of configuration with secondary alkyl halides and retention of configuration with vinylic halides. In all known examples the nucleophilic R group is transferred from the organocopper reagent with retention of configuration. In contrast to organocopper reagents other highly nucleophilic organometallic reagents (e.g., lithium and magnesium alkyls) are usually also strongly basic and therefore often undergo other reactions besides substitution. Other important aspects of organocopper substitution reactions are discussed in syntheses 12-33.

In multifunctional molecules that are both alkyl electrophiles and α,β -ethylenic carbonyl compounds, the relative amounts of organocopper substitution and conjugate addition can be changed by changing the alkyl-X leaving group and by changing the solvent. For example, we have shown that the accompanying enone mesylate, $\text{X} = \text{Ms}$, undergoes mesylate displacement by dimethylcopperlithium, whereas the corresponding enone bromide, $\text{X} = \text{Br}$, undergoes mainly conjugate addition (followed by intramolecular displacement). House and his co-workers recommend diethyl ether as solvent for organocopper conjugate addition reactions and diethyl ether-hexamethylphosphoramide (purified by distillation from BaO) for organocopper substitutions with alkyl halides. Most organocopper substitutions proceed well with tetrahydrofuran (THF) as solvent. Because there are some exceptions to these generalizations, however, review articles or the primary literature should be consulted before choosing a solvent for a particular organocopper reaction.



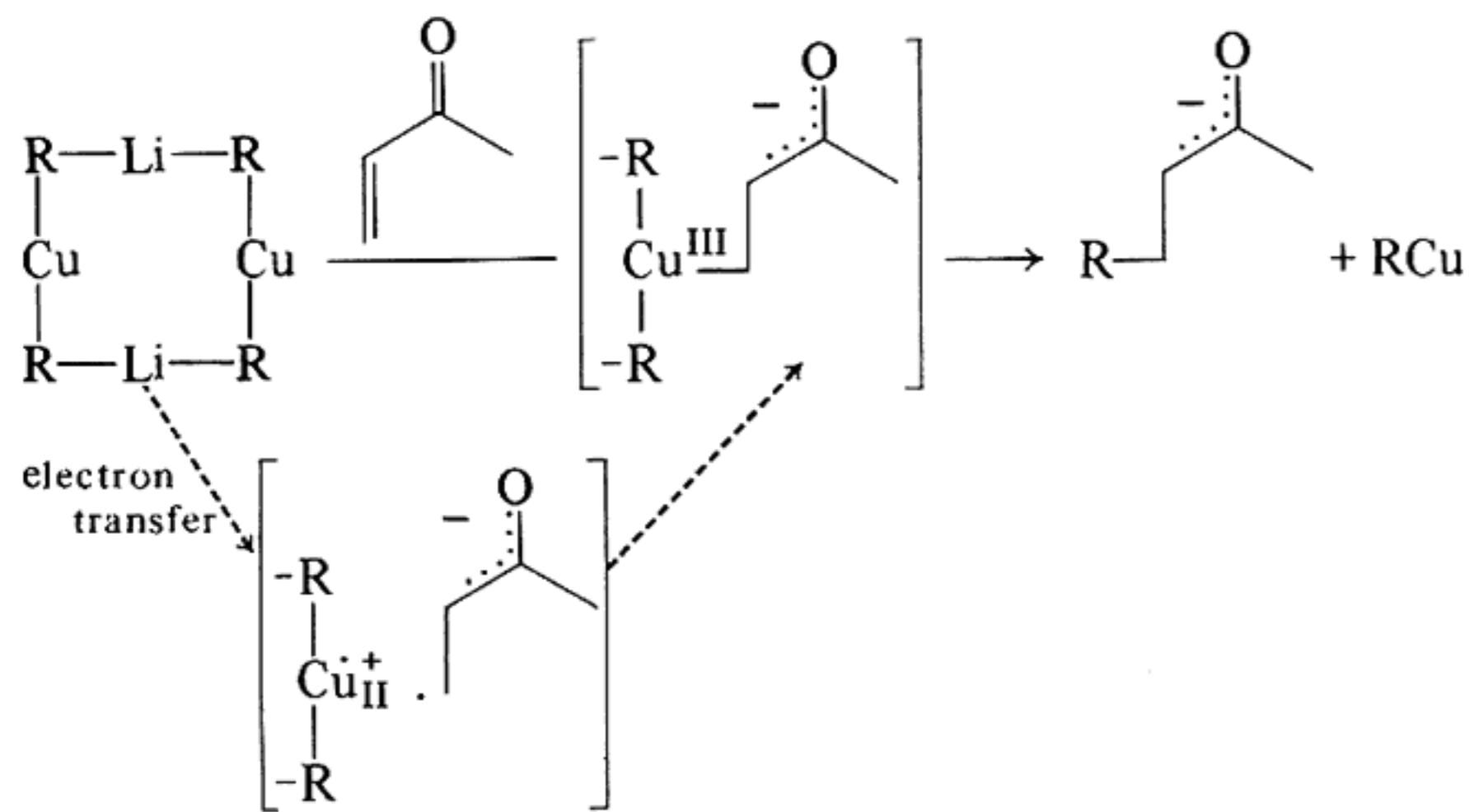
C. Mechanisms

Despite substantial efforts since 1965, the *detailed* mechanisms of organocopper addition and substitution reactions remain uncertain. There is widespread agreement, however, about the *general* mechanism of organocopper substitution reactions. Oxidative *trans*-addition of a d^{10} cuprate to an $\text{R}'\text{X}$ electrophile produces a planar copper(III) (d^8) intermediate whose lifetime is influenced by the nature of X; reductive *cis*-elimination leads to the unsymmetrical coupling product RR' and the RCu(I) and LiX as shown in the following equation:



Although there is widespread agreement about the likelihood that transient copper(III) intermediates are involved also in organocopper conjugate addition reactions, there are differences of opinion regarding how the copper(III) intermediates are formed. Direct nucleophilic oxidative addition of an organocopper(I) compound to the β -carbon atom of an α,β -ethylenic carbonyl compound produces a copper(III) intermediate; indirect oxidative addition proceeds via electron transfer from the organocopper(I) compound to the carbonyl substrate, generating a copper radical cation and an enone radical anion which then

combine to produce the copper(III) intermediate. Reductive elimination causes attachment of an R group to the β -carbon atom and generation of an enolate, as shown in the accompanying equation. Unfortunately, there is only indirect evidence thus far for copper(III) intermediates in these reactions.



As a more exact picture of the mechanisms of organocopper substitution and addition reactions develops, there will emerge a more thorough understanding of why copper is one of the most effective transition metals in promoting carbon-carbon σ -bond formation. Undoubtedly, the uniqueness of copper is attributable in large part to the relatively low ionic character of a copper-carbon bond, to the low oxidation potential (0.15 V) separating cuprous from cupric ions, and to the tendency of copper to form polynuclear copper clusters and mixed-valence copper compounds.

Organocopper Reviews

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