Mechanisms of Copper-Mediated Addition and Substitution Reactions

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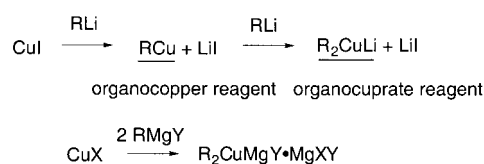
Seiji Mori and Eiichi Nakamura

10.1
Introduction

The use of organocopper chemistry in synthesis dates back to the nineteenth century, when Glaser developed copper-catalyzed coupling of terminal alkynes [1]. Half a century after Kharasch's initial discoveries in the 1940s [2], copper reagents are still the most useful synthetic reagents among the transition metal complexes [3], the key roles of copper having become widely recognized in organic synthesis [4–10]. Conjugate addition [11–14], carbocupration [15], alkylation [16], and allylation [17] represent the reactions that can be achieved readily with organocopper reagents but not with other organometallics. The most important utility of copper in organic chemistry is in the form of nucleophilic organocopper(I) reagents used either in a catalytic or a stoichiometric manner. Generally formulated as [R$_2$Cu]M, with a variety of metal M and R groups, organocuprate(I) complexes and related species are uniquely effective synthetic reagents for nucleophilic delivery of hard anionic nucleophiles such as alkyl, vinyl, and aryl anions (Scheme 10.1).
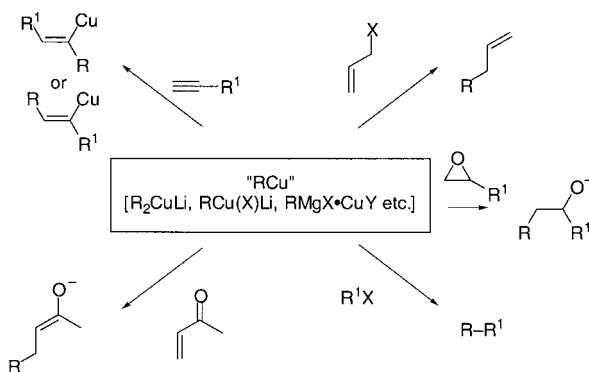
Scheme 10.1. Nucleophilic reactivities of organocopper reagents. R = sp^2, sp^3 carbon anionic centers; X, Y = halogen, etc.

Gilman reported in 1952 that addition of one equivalent of MeLi to a Cu^I salt results in the formation of yellow precipitates, which then afford colorless solutions upon addition of another equivalent of MeLi (Scheme 10.2) [18]. In 1966, Costa isolated a complex between phenylcopper(I) and magnesium, as well as crystals of a lithium diphenylcuprate(I) complex [19]. Although the organocopper reagents derived from Grignard reagents are widely used and may be described as R_2CuMgX, the extent to which to this reflects the reality in solution is still uncertain.

$$CuI \xrightarrow{RLi} \underline{RCu + LiI} \xrightarrow{RLi} \underline{R_2CuLi + LiI}$$

organocopper reagent   organocuprate reagent

$$CuX \xrightarrow{2\ RMgY} R_2CuMgY{\cdot}MgXY$$

Scheme 10.2. Preparation of organocopper reagents.

The organic chemistry of organocuprates started its rapid development in 1966, when House showed that the reactive species in conjugate addition is the lithium diorganocuprate(I) called a Gilman reagent [20]. The foundations for vigorous subsequent synthetic development were laid by Corey, and important initial developments such as substitution reactions on sp^2 carbon atoms or in allylic systems [16, 17, 21–23], and carbocupration of acetylene [24] had been reported by the mid-1970s.

The nature of "Gilman reagents" now needs some careful definition. While numerous reports (older ones in particular) describe Gilman reagents as R_2CuLi, a vast majority of them actually used a LiX complex $R_2CuLi{\cdot}LiX$, prepared by in situ treatment of RLi with CuX (X = bromide, iodide, or cyanide, sometimes with a ligand such as Me_2S and PR_3). Although R_2CuLi and $R_2CuLi{\cdot}LiX$ may display largely the same reactivities, Lipshutz [25] showed that they are in fact different species by analysis of reactivities and spectroscopic properties (the case of X = CN (cyano-Gilman cuprate) is discussed in Sect. 10.6.4). Even small solvent differences may affect the composition of the reagent and hence reactivity [26]. Because of this complexity, it is now customary to indicate all ingredients used when describing a reagent (for example, $R_2CuLi{\cdot}LiI{\cdot}Me_2S/BF_3{\cdot}Et_2O$ in THF/hexane). Understanding of the aggregation state is fundamental for discussion of the reaction mechanism (see Chapt. 1) [27, 28]. In diethyl ether, Gilman reagents largely exist as dimers, but in THF solution, they exist as $R_2CuLi{\cdot}LiX$ or ion-pair species ($R_2Cu^- + Li^+$). These species are in equilibrium with each other [29]. It has been suggested that aggregation of copper species affects enantioselectivities of stoichiometric and catalytic asymmetric conjugate additions [30]. RCu itself is not reactive, and addition of a Lewis acid such as BF_3 is necessary to obtain high reactivities [5, 31]. The latter approach is often used in organic synthesis (see Sect. 10.6.1) in which the identification of the true reactive species has yet to be achieved [32].

Organocopper chemistry is still rapidly expanding its synthetic scope. The scope of carbocupration, previously limited to acetylenes, has recently been extended to olefins [33–36]. 1,6-, 1,8-, 1,10-, and 1,12-Addition and 1,5-S_N2'' substitution reac-

tions of substrates with extended conjugates have been developed (see Chapt. 4) [14, 37–39]. Enantioselective conjugate addition [40] has become truly useful with the aid of dialkylzinc, cationic copper catalyst, and a chiral ligand (Eq. 1, see also Chapt. 7) [41]. Magnesium-based reagents have found use in quantitative fivefold arylation of C_{60} (Eq. 10.2) [42] and threefold arylation of C_{70} [43], paving ways to new classes of cyclopentadienyl and indenyl ligands with unusual chemical properties.

$$(10.1)$$

$$(10.2)$$

R = aryl, methyl
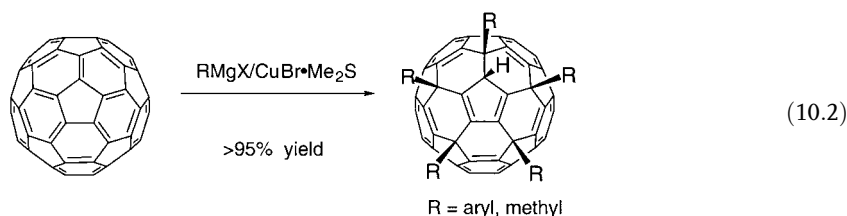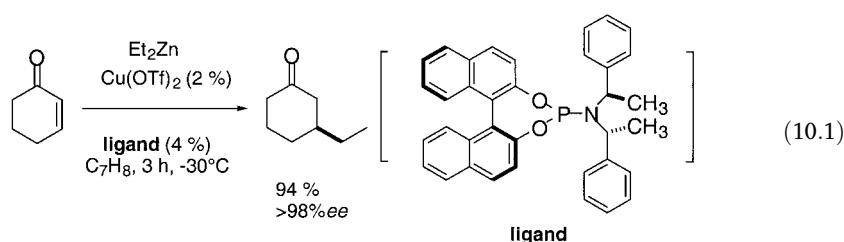
Numerous investigations have been made into the reaction mechanisms of organocopper reactions and the design of efficient copper-mediated reactions, resulting in the reporting of many crystallographic and spectroscopic studies of reactants and products (for analysis of organocopper(I) complexes see Chapt. 1.), as well as examination of solvent effects, substituent effects, kinetics, and NMR spectroscopic data of reactive intermediates. Nevertheless, information about the nature of reactive species in solution and their reactivities is fragmentary and incomplete [44]. The most widely accepted ''resting state'' of lithium organocuprate(I) species in solution is represented by the eight-centered dimer $(R_2CuLi)_2$ shown in Eq. 10.3, but there is little consensus on the ''reactive conformation of a true reactive species'' (see Chapt. 1). Making matters worse, the structures of the final copper-containing products are generally unknown. Those exploring the frontiers of organocopper chemistry in industry and academia desperately require better mechanistic understanding.

$$(10.3)$$
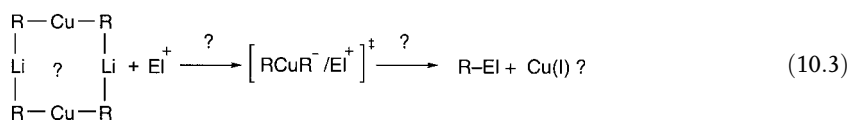
Two sources of mechanistic information, new analytical and new theoretical methods, have surfaced in the past several years. The former class includes new methods in the study of kinetic isotope effects, in NMR spectroscopy, and in X-ray

absorption spectroscopy [EXAFS (extended X-ray absorption fine structure spectroscopy) and XANES (X-ray absorption near edge structure spectroscopy)]. The latter category includes new developments in ab initio and density functional theories. In this chapter, recent progress on mechanisms of copper-mediated addition and substitution reactions is discussed in the context of the following topics:

(1) conventional mechanistic schemes for copper-mediated reactions,
(2) reaction pathways of organocopper-organometallic aggregates as analyzed through combination of theoretical and experimental data,
(3) mechanisms of copper-catalyzed reactions [45, 46].

Three important categories of copper reactions – conjugate addition, carbocupration, and alkylation – are discussed.

10.2
Conjugate Addition Reaction

Copper-mediated conjugate addition of alkyl anions to α, β-unsaturated carbonyl or related compounds (hereafter called enones) has long attracted chemists' interest because of its synthetic importance and its obscure mechanism. The difficulties inherent in the elucidation of the mechanisms of conjugate additions are due to the complexity of cluster structures of organocopper species. In the light of contrasting reports (one reporting conjugate addition to be slower in THF than in ether [47, 48], another reporting faster reaction in toluene, and further additional reports that, in toluene, 1,4-addition can be promoted over 1,2-addition in the presence of Me$_2$O [49] and Me$_2$S [50]), solvent effects are a difficult subject to deal with. Nevertheless, there have been extensive experimental studies on the reaction mechanisms of conjugate addition.

10.2.1
Four-centered and Six-centered Mechanisms

Four-centered addition of RCu to an enone was widely discussed in the 1960s (Scheme 10.3a) [51–53], while discussions on six-centered transition states have continued until recent times (Scheme 10.3b) [54]. These mechanisms do not, however, explain the formation of E/Z mixtures of enolate stereoisomers [20, 55] and must now be considered obsolete.
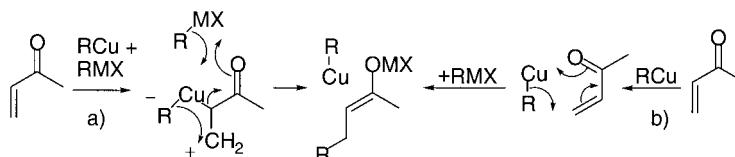

**Scheme 10.3.** a) 1,2-Addition and b) 1,4-addition proposals.

10.2.2
Single-electron Transfer Theorem

House pioneered synthetic and mechanistic studies of cuprate reactions in the 1970s. His papers proposed a mechanism (Scheme 10.4) that assumes a single-electron transfer (SET) from the dimer, producing a Cu^{III} intermediate [56, 57]. The SET/Cu^{III} theorem had a strong following for many years. However, most of the experimental facts listed below, once considered to support the SET process, are now no longer accepted as evidence of SET. Only the Cu^{III} hypothesis has survived the test of time.
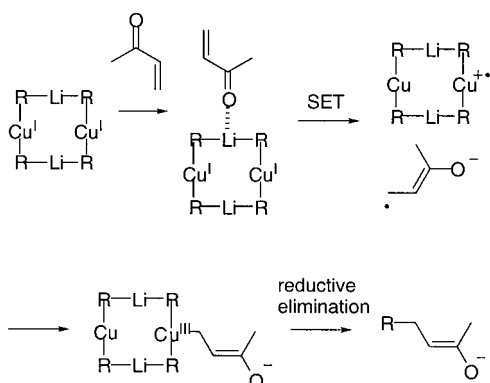
Scheme 10.4. House's 1,4-addition mechanism.

(1) E/Z isomerization of the olefinic part of an enone was once taken as evidence for reversible electron transfer. It was later reported, however, that this isomerization takes place even in the presence of LiI, a common component of the Gilman cluster reagent (for example, $Me_2CuLi \cdot LiI$) [58]. Such an isomerization is also possible through reversible generation of an advanced d-π^* copper/enone complex along the reaction pathway [42, 59], and hence does not represent strong evidence for SET.

(2) Qualitative correlation of the apparent rate of 1,4-addition with the reduction potential of the enone was later proven to be only superficial, through quantitative kinetic studies by Krauss and Smith [60].

(3) β-Cyclopropyl α,β-unsaturated ketones such as the one shown below often give ring-opening products, which was taken as strong evidence for radical anion formation by SET. An elegant study by Casey and Cesa, using a deuterium-labeled substrate, indicated stereospecificity in the cyclopropane ring-opening, which hence refutes the radical mechanism (Eq. 10.4) [61]. On the basis of a series of control experiments, Bertz reinterpreted the results in terms of Cu^{III} intermediates formed by two-electron transfer [62].
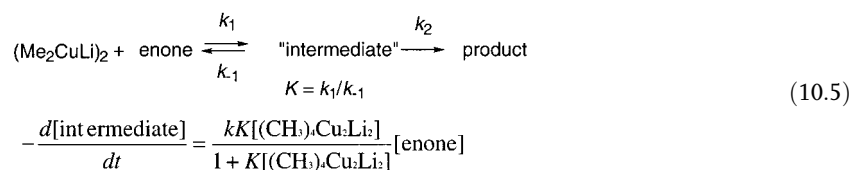
$$(10.4)$$
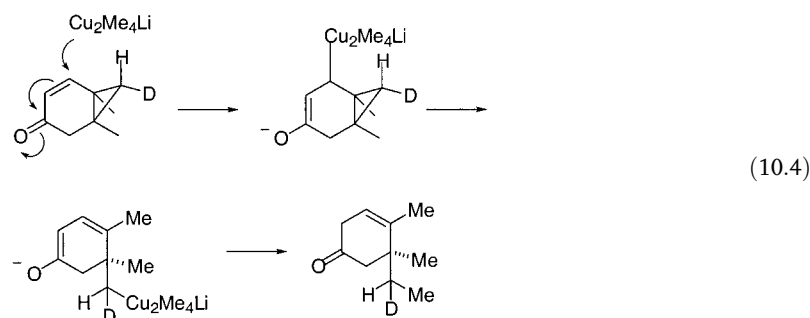
(4) ESR and CIDNP studies intended to detect the radical intermediates failed [63]. Conjugate addition of a vinylcuprate reagent to an enone takes place with retention of the vinyl geometry, indicating that no vinyl radical intermediate is involved [64, 65]. Kinetic isotope effects and substituent effects in cuprate addition to benzophenone indicate that C–C bond formation is rate-determining, which is not consistent with the involvement of a radical ion pair intermediate [66].

SET processes do not occur among moderately electrophilic olefinic acceptors, but are likely to be involved in highly electrophilic substrates. Some recent examples are the polyadditions of cuprate to fullerenes (Sect. 10.1.1). Fluorenone ketyl radical has been detected in a cuprate reaction of fluorenone [20]. Doubly activated olefins [67–69] and bromonaphthoquinone [70] also probably react through SET.

10.2.3
Kinetic and Spectroscopic Analysis of Intermediates

Conjugate additions to α, β-unsaturated ketones and esters are the most important cuprate reactions. Kinetic studies by Krauss and Smith on Me_2CuLi and a variety of ketones revealed the following kinetic characteristics (Eq. 10.5), first order both in cuprate dimer and in the enone [60].

$$(Me_2CuLi)_2 + \text{ enone } \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \text{ "intermediate" } \overset{k_2}{\longrightarrow} \text{ product}$$

$$K = k_1/k_{-1}$$

$$(10.5)$$

$$-\frac{d[\text{intermediate}]}{dt} = \frac{kK[(CH_3)_4Cu_2Li_2]}{1 + K[(CH_3)_4Cu_2Li_2]}[\text{enone}]$$

This rate expression is consistent with the reaction scheme shown in Eq. 10.6, formulated on the basis of the Krauss–Smith paper. Thus, the initially formed cuprate dimer/enone complex with lithium/carbonyl and copper/olefin coordinations [71, 72] transforms into the product via an intermediate or intermediates. A lithium/carbonyl complex also forms, but this is a dead-end intermediate. Though detailed

structures of the intermediates were unknown for a long time, the essence of this scheme was supported by subsequent NMR and XANES spectroscopic studies and recent theoretical investigation. The key ''intermediate'' is now considered to be an organocopper(III) species formed by two-electron, inner sphere electron transfer (Eq. 10.6) (see Sect. 10.2.5).

(10.6)
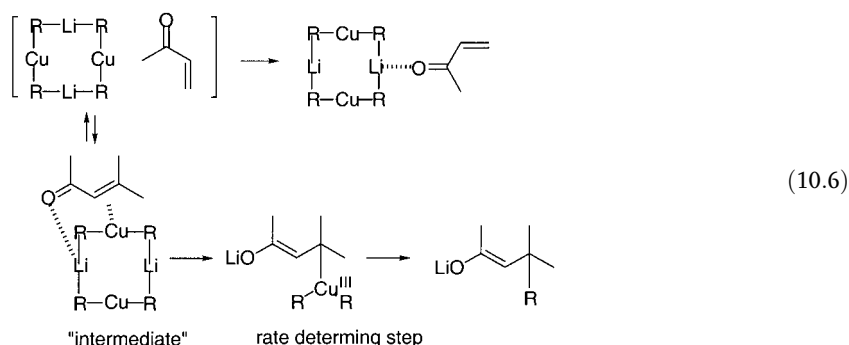
Corey explicitly proposed a Dewar–Chatt–Duncanson (DCD) interaction for such a Cu^{III}/olefin complex [73]. XANES investigation of a complex formed between a *trans*-cinnamate ester and $Me_2CuLi·LiI$ in THF indicated elongation of the C=C double bond and an increase in the coordination number of the copper atom. NMR studies on the organic component in the complexes indicated loosening of the olefinic bond [72, 74]. Very recently, Krause has determined the kinetic activation energies ($E_a = 17–18$ kcal mol^{-1}) of some conjugate addition reactions for the first time [75].

An intermediate formed on 1,6-addition of a cuprate to a dienone has recently been examined by low-temperature NMR spectroscopy. This reaction passes though a Cu/olefin π-complex intermediate **A**, in which cuprate binds to the α- and the β-carbon. Further 1,3-rearrangement from another intermediate (**B**) to still another (**C**) is proposed (Eq. 10.7) [76].
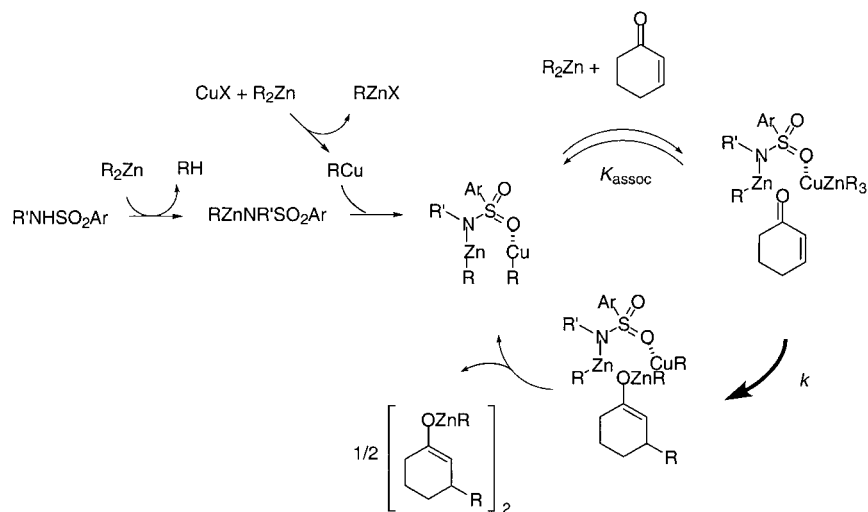

(10.7)
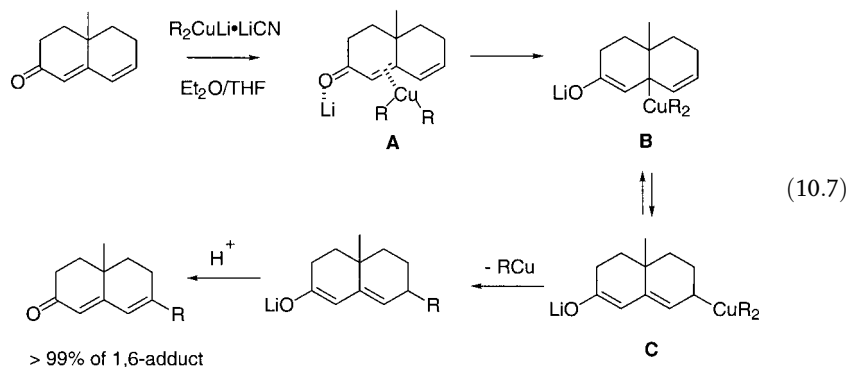
Fig. 10.1. Proposed catalytic cycle of copper-catalyzed conjugate addition.

### 10.2.4
Catalytic Conjugate Addition

There are a large number of reports on copper(I)-catalyzed conjugate additions, yet there is only scant information available about their reaction mechanisms. Recently, the conjugate addition of organozinc compounds to enones was found by Kitamura, Noyori, et al. to be catalyzed by *N*-benzylbenzenesulfonamide and CuCN, and the mechanism was scrutinized (Fig. 10.1). The kinetic rate was found to be first order in the concentrations of the catalyst that exist in equilibrium with R_2Zn and enone [77].

In the enantioselective copper(I)-catalyzed conjugate addition of a cyclic enone with a chiral ligand, the observed nonlinear effects indicate that Cu(I) aggregates participate in the reaction [78].

10.2.5
Theoretically Based Conjugate Addition Reaction Pathway

The reaction pathways of conjugate addition of Me_2CuLi and $Me_2CuLi \cdot LiCl$ have been studied for acrolein [79] and cyclohexenone [80] with the aid of density functional methods, and fit favorably with the ^{13}C NMR properties of intermediates, kinetic isotope effects [81], and the diastereofacial selectivity. A similar mechanism also operates in this reaction, as summarized in Scheme 10.5. The rate-determining step of the reaction (**TScc**) is the C–C bond formation caused by reductive elimination from Cu^{III} to give Cu^{I}.
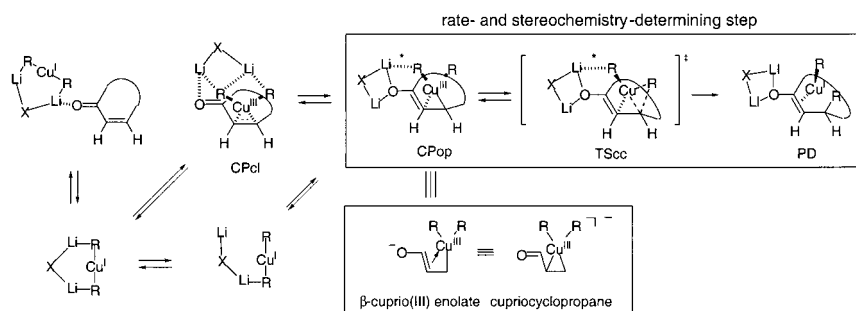
Scheme 10.5. Plausible pathway of conjugate addition of (R₂CuLi)₂ to enones. Solvent molecules are omitted for clarity. The lithium atoms are fully solvated and the R–Li association indicated with a broken line (*) in **CPop** and **TScc** may be extremely small or nonexistent in solution. Here, in Schemes 10.7, 10.9, and 10.10, and in Fig. 10.5, the X group can be RCuR, halogen, etc.

TScc is also the stage at which the enantiofacial selectivity of the reaction is determined [80]. This conflicts with the conventional assumption that the face selectivity is established in the initial π-complexation [40a], which is now shown to represent a preequilibrium state preceding **TScc**. The calculated activation energy taking the solvation of the lithium atoms into account shows reasonable agreement with recently determined experimental data [75].

The central feature of the mechanism is the 3-cuprio(III) enolate **Cpop**, of an open, dimeric nature, as shown by comparison of theory with experimentation involving ^{13}C NMR and KIEs [80, 81]. This species serves as the direct precursor to the product (Scheme 10.5, top box). In this critical **CPop** complex, copper/olefin (soft/soft) and a lithium/carbonyl (hard/hard) interactions are present. The open complex may be formed directly, by way of an open cluster (bottom left of Scheme 10.5), or by complexation of a closed cluster with the enone (**CPcl**). Experiments have shown that the enone/lithium complex (top left of Scheme 10.11) is a dead-end species [60, 74].

The **CPop** intermediate is the "β-cuprio ketone" intermediate widely debated in mechanistic discussions of conjugate addition (cf. Scheme 10.3). On the basis of recent theoretical analysis, two limiting structures for CPop may now be considered; these are shown in the bottom box in Scheme 10.5. The reason for the exceptional stability of **CPop** as a trialkylcopper(III) species can be readily understood in terms of the "β-cuprio(III) enolate" structure, with the internal enolate anion acting as a strong stabilizing ligand for the Cu^{III} state [82].

In spite of the apparent difference between conjugate addition and carbocupration reactions (Sect. 10.3.2), the similarities between the key organometallic features of the two reactions are now evident. In both reactions, inner sphere electron-transfer converts the stable C–Cu^{I} bond into an unstable C–Cu^{III} bond, and the cluster-opening generates a nucleophilic, tetracoordinated alkyl group. The difference is that the product of conjugate addition (**PD**) remains as a lithium enolate complexed with RCu^{I} (Scheme 10.5), while the initial product of carbocupration

(**INT2**, Scheme 10.7) undergoes further reaction (Li/Cu transmetalation) and generates a new organocuprate compound. (Note however that this difference could become more subtle since the product of conjugate addition (**PD**) might behave more like an α-cuprio(I) ketone complexed with a lithium cation [52] than a lithium enolate complexed with copper(I)). In neither reaction was any evidence of radical intermediates (i.e., SET) found by theoretical calculations [79].

Synthetic chemists can now work with three-dimensional pictures of the conjugate addition available on a website [80]. In the absence of steric hindrance (5-methylcyclohexenone, for example), an "axial attack" through a half-chair conformation is favored, while in the cortisone synthesis an "equatorial attack" through a half-boat conformation is favored because of the constraint imposed by the bicyclic rings [83].
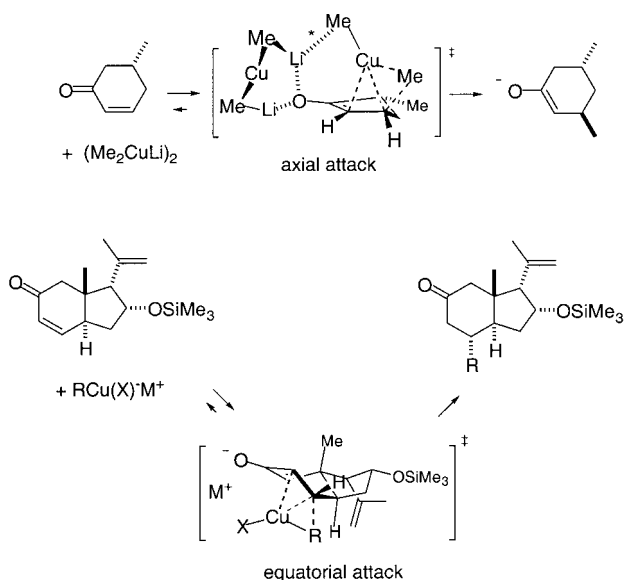
Scheme 10.6. Transition states for diastereoselective conjugate additions. In solution, the lithium and M cations must be fully solvated with solvent molecules. The Me—Li association (indicated with an asterisk) will be extremely weak or nonexistent in solution.

10.3
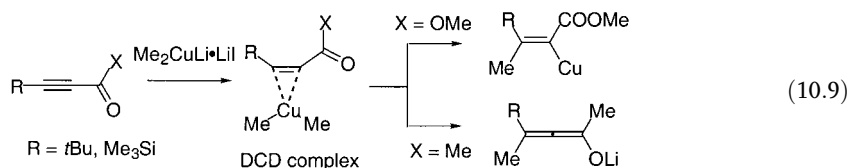## Carbocupration Reactions of Acetylenes and Olefins

10.3.1
Experimental Facts

The carbocupration of acetylene takes place smoothly in a *cis* fashion, providing a reliable synthetic route to vinyl copper species (Eq. 10.8) [24]. Magnesium and zinc,

which are more Lewis acidic than lithium, are better counter-cations for this reaction, and strong coordination of a lithium dialkylcuprate(I) with a crown ether dramatically slows down the reaction [84]. This reaction used to be generally considered to proceed through a four-centered mechanism, and hence to be mechanistically different from conjugate addition.

$$(10.8)$$
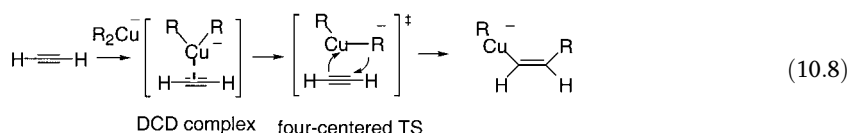
In the addition of Me_2CuLi reagents to electron-deficient acetylenes [85–88], DCD-type complexes have been identified by NMR [84, 89]. As shown below, an ynoate affords a vinylcopper intermediate, while an ynone instead affords an allenolate (Eq. 10.9). The origin of this diversity remains unclear. A related carbocupration mechanism has also been proposed for the reaction with allenylphosphine oxide [53]. Olefin carbocupration of dienes [90] and cyclopropenes [34, 36] is known, but these mechanisms also remain unclear.


$$(10.9)$$

10.3.2
Theoretically Based Carbocupration Reaction Pathway

The carbocupration of acetylene has been studied systematically for five model species – MeCu, Me_2Cu^-, Me_2CuLi, $Me_2CuLi \cdot LiCl$, and $(Me_2CuLi)_2$ [91] – all of which have been invoked once in a while in discussions of cuprate mechanisms. A few general conclusions have been made regarding the reactivities of these reagents with π-acceptors:

(1) The copper d-orbital being very low-lying (hence no redox chemistry available) [92], MeCu can undergo addition only through a four-centered mechanism (Eq. 10.8).
(2) This four-centered pathway requires a large amount of energy, since the covalent Me–Cu bond (55 kcal mol^{-1} [93]) must be cleaved. A neutral RCu species is therefore not a reactive nucleophile.
(3) Being electron-rich (thus with high-lying d-orbitals), lithium cuprates such as $(R_2CuLi)_2$ bind tightly to acetylene through two-electron donation from a copper atom (cf. **CP** in Scheme 10.7). In such complex formation, a cluster structure certainly larger than the parent species R_2CuLi is necessary to achieve cooperation of lithium and copper.
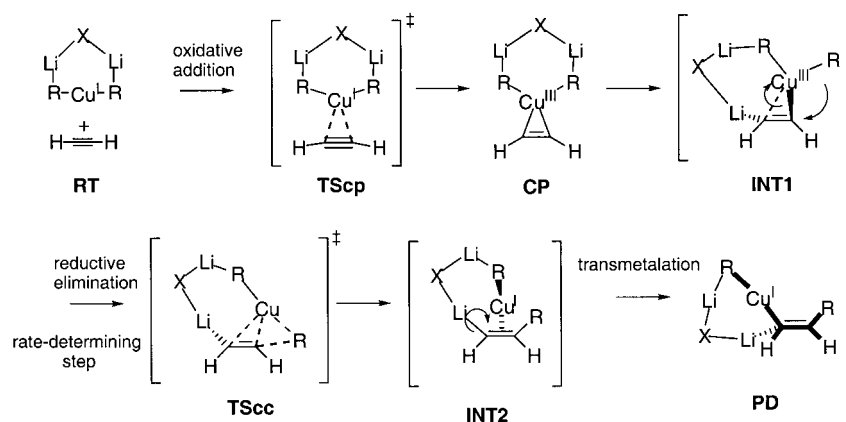
Scheme 10.7. Trap-and-bite pathway of carbocupration.

The reaction pathway may be viewed as a "trap-and-bite" mechanism; the structures involved are shown in Scheme 10.7. The cluster opens up and traps the acetylene (**INT1**), transfers electrons, and then "bites" the substrate to form a C–C bond (**TScc**). The important events include formation of a DCD-complex (**CP**) via a low energy **TS** (**TScp**) [94], inner-sphere electron transfer to form a transient intermediate **INT1**, C–C bond formation through the rate-determining stage **TScc**, and intra-cluster transmetalation from lithium to copper(I) (**INT2**). The DCD character of **CP** is shown by the localized molecular orbitals (LMOs, Fig. 10.2), and has also been found in conjugate addition reactions to enals and enones [79]. Since the C–Cu^{III} bond is very unstable, the activation energy for C–C bond formation via **TScc** becomes small (<20 kcal mol^{-1}). In solution, the reaction may go directly to **INT1**, or to related species through an open cluster.

It should be noted that the depictions of the "organic" arrows and the indications of the valence of the metal as in Scheme 10.7 (and others in the following para-
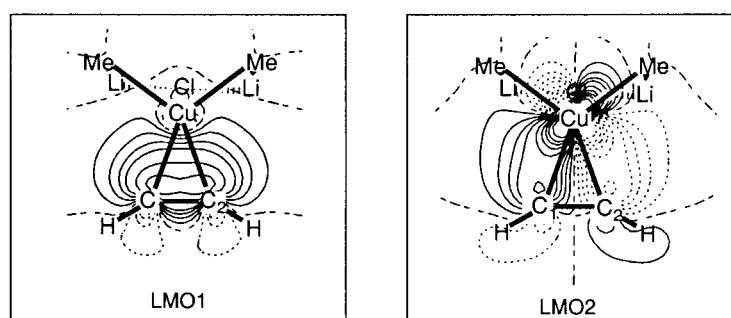

Fig. 10.2. Localized molecular orbitals of the complex (**CP**) between Me$_2$CuLi·LiCl and acetylene.
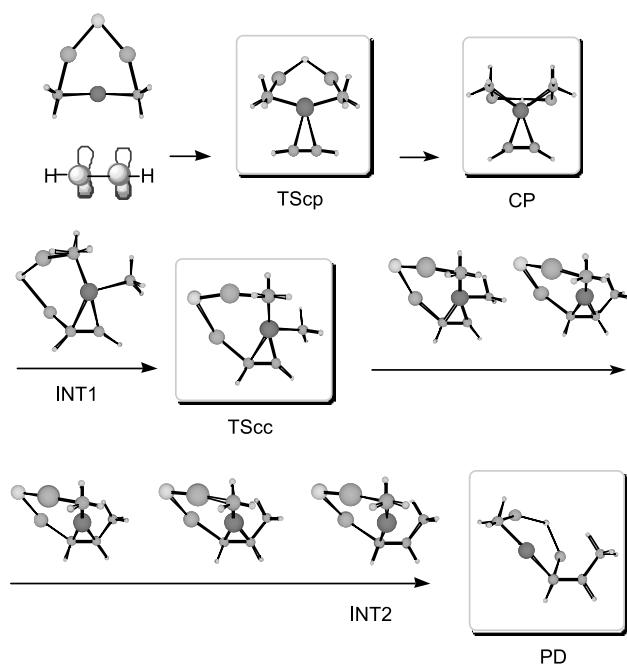
Fig. 10.3. "Snapshots" of intermediates on the potential energy surface of carbocupration of acetylene.

graphs) are necessarily inaccurate from a purely inorganic or theoretical viewpoint. We have nonetheless indicated them, to put the theoretical results into the context of conventional organic chemistry, and to facilitate understanding of the chemistry by organic chemists using the reagents in everyday research.

Figure 10.3 shows "snapshots" of intermediary species on the potential surface of carbocupration to illustrate the transformation of the reacting complex. The formation of the transient carbolithiated intermediate **INT2** is the most striking feature, because recognition of this intermediate provides the key to understanding of the kinship of carbocupration, S_N2' allylation (Sect. 10.4.2), and conjugate addition.

10.4
Substitution Reactions on Carbon Atoms

10.4.1
S_N2 Mechanism of Stoichiometric Substitution Reactions

S_N2 substitution reactions of alkyl halides with hard nucleophiles such as alkyl anions can be achieved most readily with the aid of organocopper chemistry [95]. S_N2 reactions with epoxides and aziridines are also synthetically useful [96]. The

accelerating effects of $BF_3 \cdot Et_2O$ in the latter reactions indicate the importance of substrate activation (see Sect. 10.6.1) [97].

The alkylation of an alkyl bromide or tosylate, or of an epoxide, with organo-cuprates takes places with 100% inversion of the stereochemistry at the electro-philic carbon, as shown below (Eq. 10.10) [22, 98]. The magnitudes of primary and secondary kinetic isotope effects in the reaction between $Me_2CuLi \cdot LiI \cdot PBu_3$ and CH_3I strongly suggested that the rate-determining step of the reaction is the S_N2 displacement stage [99]. Reactions between R_2CuLi and alkyl halides, aryl halides, and alkyl tosylates have been shown to be first order in the concentration of the R_2CuLi dimer and the alkylating reagent [97, 100, 101]. RCu and $RCu(PBu_3)$ do not react with epoxides [96]. Alkylation reactions of R_2CuLi do not take place in the presence of a crown ether, demonstrating the importance of a Lewis acidic LiX component associated with the cuprate moiety. On the other hand, moderately basic and polar THF is a better solvent than diethylether for alkylation [22].

$$(10.10)$$

Two mechanistic possibilities for the substitution reactions have been suggested (Scheme 10.8). The first assumes simple S_N2 substitution of the R anion group. The second assumes rate-determining displacement of the leaving group with copper bearing a formal negative charge, and subsequent formation of a trialkyl-copper(III) intermediate [82]. This then undergoes reductive elimination to give the cross-coupling product. Though the second mechanism may look pleasing enough to a copper specialist, it leaves a few important questions unanswered; namely the role of the lithium cation, the relative magnitude of k_1 and k_2, and, among other things, the reason why exclusive production of a cross-coupled product $R–R^1$ by way of a symmetrical $R_2(R^1)Cu^{III}$ intermediate is always observed.
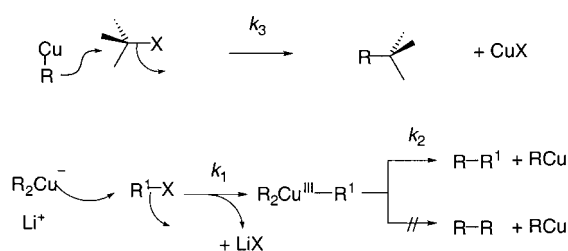

Scheme 10.8. Two proposed alkylation reaction mechanisms.

The proposed participation of a Cu^{III} intermediate is based on an analogy with the chemistry of lithium diorganoaurate(I), R_2Au^ILi [102, 103]. Recent crystallo-graphic data for Cu^{III} species [104] have further supported the similarity between Au^{III} and Cu^{III} [105].

10.4.2
S$_N$2′ Allylation Reactions

Cuprates react rapidly with allylic halides (or acetates) [17, 23], propargyl halides (or acetates) [106–108], and vinyloxiranes, often with S$_N$2′ regioselectivity (Scheme 10.9) [17]. The reaction takes place with *anti* stereochemistry (with respect to the leaving group), while *syn* substitution occurs when an allylic carbamate is employed as the substrate [109].
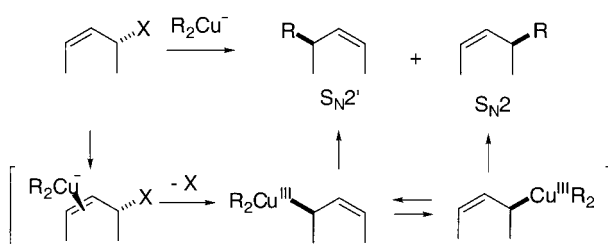
Scheme 10.9. *Anti*-S$_N$2′ Allylation reaction with competing S$_N$2 reaction pathway. X = halogen, OAc, OP(O)Y$_2$.

Reactions of R$_2$CuLi tend to give mixtures of S$_N$2 and S$_N$2′ products, which it has been suggested is due to the involvement of regioisomeric σ-allylic Cu^{III} species, shown bracketed in Scheme 10.9 [106, 110]. Studies on substituent effects in competitive reactions suggested that the rate-determining stage might involve a two-electron transfer from copper to the allylic substrate [107]. The S$_N$2 selectivity of the reaction of Bu$_2$Cu(X)(MgBr)$_2$ is higher with X = I and OTs than with X = Cl and Br, and also higher in ether than in THF [111]. A combination of an organo-copper compound and a Lewis acid, such as RCu·BF$_3$ [5], R$_2$CuLi·ZnCl$_2$ [112], R$_2$CuLi·Ti^{IV} [113], or R$_2$CuLi·AlCl$_3$ [114], greatly enhances the S$_N$2′ selectivity. Cu(I)-mediated reactions of organozinc species also afford high S$_N$2′ selectivities [112, 115–117]. NMR studies on R$_2$CuLi·ZnCl$_2$ and R$_2$CuLi·Ti^{IV} reagents showed only rapid transmetalation from Cu to Zn or Ti, giving little information on any putative Cu/Zn or Cu/Ti mixed species. Scant information is available for the transition state. The stereoselectivity of the S$_N$2′ reaction of δ-substituted allylic halide of the S$_N$2 reaction suggested that the transition state geometry for the delivery of an R group from copper has a four-centered character, as shown below (Eq. 10.11) [112]. This conjecture was supported by theoretical comparison between the TS geometries of olefin carbolithiation and those of acetylene carbocupration (cf. Scheme 10.7) [91].
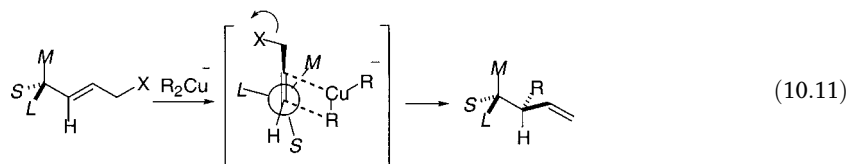

(10.11)

10.4.3
Radical Substitution Reaction Mechanisms

The SET mechanism has been suggested for the alkylation reaction of secondary alkyl iodides, in which the substitution reaction takes place in stereorandom fashion [22, 118]. The reaction between triphenylmethyl bromide and Me_2CuLi generated an ESR-active triphenylmethyl radical, although this may be regarded as a special case [119]. On the basis of trapping experiments using styrene, it was concluded that dialkylcuprate substitution reactions of primary and secondary alkyl iodides may proceed by an SET mechanism, whereas those of primary and secondary bromides do not [120]. This reaction also produces self-coupling products, which is consistent with radicals being involved (Scheme 10.10). The intramolecular cyclization of an olefinic iodide in the presence of an organocopper reagent has been taken as possible but not conclusive evidence of SET [120].
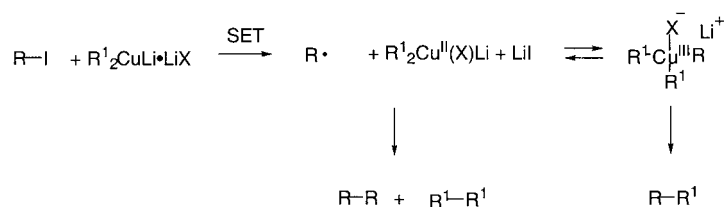
Scheme 10.10. Radical mechanism in alkylation reactions with alkyl halides.

10.4.4
Catalytic Substitution Reactions

Kinetic experiments have been performed on a copper-catalyzed substitution reaction of an alkyl halide, and the reaction rate was found to be first order in the copper salt, the halide, and the Grignard reagent [121]. This was not the case for a silver-catalyzed substitution reaction with a primary bromide, in which the reaction was found to be zero order in Grignard reagents [122]. A radical mechanism might be operative in the case of the silver-catalyzed reaction, whereas a nucleophilic substitution mechanism is suggested in the copper-catalyzed reaction [122]. The same behavior was also observed in the stoichiometric conjugate addition (Sect. 10.2.1) [30].

10.4.5
Theoretically Based Alkylation Reaction Pathways

Alkylation reactions reveal a mechanistic aspect of the cuprate reactions different from that of addition reactions. Theoretical analyses of reactions of alkyl halides (MeI and MeBr) [123, 124] and epoxides (ethylene oxide and cyclohexene oxide) [124] with lithium cuprate clusters (Me_2CuLi dimer or $Me_2CuLi \cdot LiCl$, Scheme 10.11) resolved long-standing questions on the mechanism of the alkylation reaction. Density functional calculations showed that the rate-determining step of the
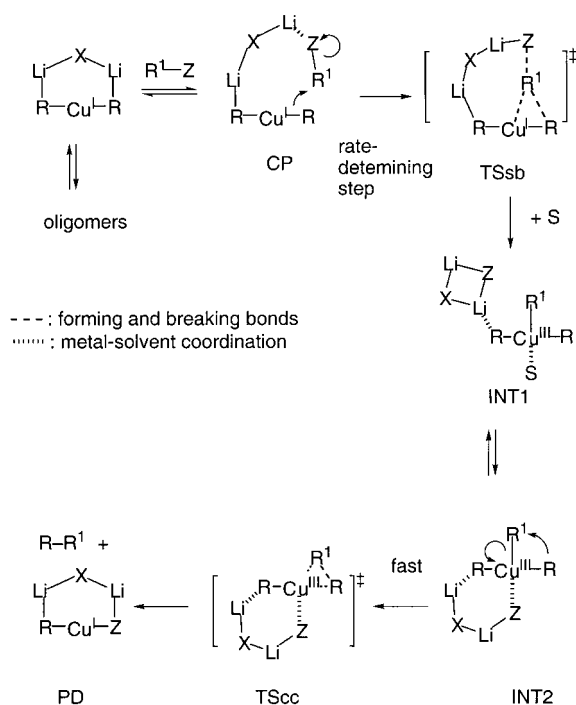
Scheme 10.11. Reaction between $R_2CuLi \cdot LiX$ and an alkylating agent R^1Z. Solvent coordinated to lithium atoms is omitted.

alkylation reaction (**TSsb**) is the substitution of the C–Br bond with an incoming Me–Cu σ-bond. The linear $3d_{z2}$ orbital of copper acts as the nucleophile here, as shown by the LMO in Fig. 10.4. The computed and experimental kinetic isotope effects for the reaction of methyl iodide showed good agreement with each other, supporting this conclusion. It is notable that it is again possible to identify an open cluster structure in **TSsb**, with the lithium atom electrophilically activating the leaving group. A trialkylcopper(III) intermediate (**INT**) may form after the rate-
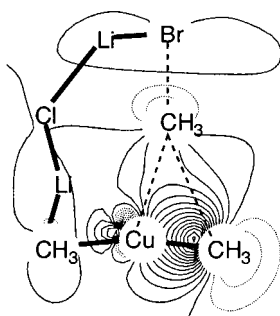

Fig. 10.4. Localized transition structure molecular orbital in the S_N2 reaction between $Me_2CuLi \cdot LiCl$ and MeBr.

determining, halide displacement step but only as an unstable transient species **INT1** or **INT2** (Scheme 10.11). These are trialkylcopper(III) complexes of T-shape geometry, with the fourth ligand (solvent of a halide) making the square planar structure [82]. The *trans* relationship of the two alkyl groups (R) is assured by the linear geometry of the cuprate moiety in the transition state **TSsb**, which guarantees cross-coupling between R and R^1 in **TScc**. Interestingly, this mechanism is a hybrid of the two previous proposals shown in Scheme 10.8.

A similar reaction pathway was found for the S_N2 substitution of an epoxide with a lithium cuprate cluster [124]. In contrast to that in the MeBr reaction, the stereochemistry of the electrophilic carbon center is already inverted in the transition state, providing the reason for the preferred ''*trans*-diaxial epoxide-opening'' widely observed in synthetic studies. The TS for the S_N2 reaction of cyclohexene oxide is shown in Eq. 10.12.

$$(10.12)$$
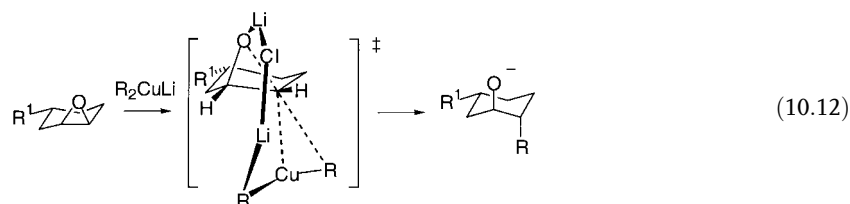
10.6
Other Issues

10.6.1
Counter-cation Lewis Acid Effects

For all major categories of lithium cuprate reactions, it has been shown that addition of a crown ether results in significant retardation [79, 94, 125]. In addition to this, sodium cuprates are much inferior to lithium cuprates for conjugate addition [126]. $BF_3 \cdot Et_2O$, on the other hand, accelerates conjugate additions [31] and alkylations of epoxides and aziridines [97, 127]. In allylation chemistry, zinc-based [128], titanium-based [113], and aluminum-based [114] organocopper reagents show much higher S_N2' selectivities than lithium cuprate does. The Lewis acidities of cuprate counter-cations are undoubtedly important, but their mechanistic roles still need further investigation (Eq. 10.7).

Recent theoretical studies of reductive elimination from $Me_3Cu \cdot S$ in the presence of BF_3 suggest that reaction rate of the conjugate addition can increase if one of the Me groups is detached from the copper(III) to bind with a boron atom (Scheme 10.12) [129].

The origin of the acceleration produced by BF_3 in epoxide alkylation reactions has been examined theoretically [124]. A plausible pathway for BF_3 participation in the epoxide-opening is shown in Fig. 10.5. An epoxide/BF_3 complex **CP1** may encounter the cuprate cluster to form a ternary complex **CP2**, or such a complex may
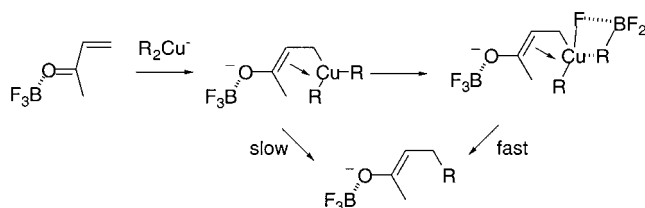
Scheme 10.12. Proposed mechanism of BF₃ activation in the conjugate addition.

X = halide, R-Cu-R etc.
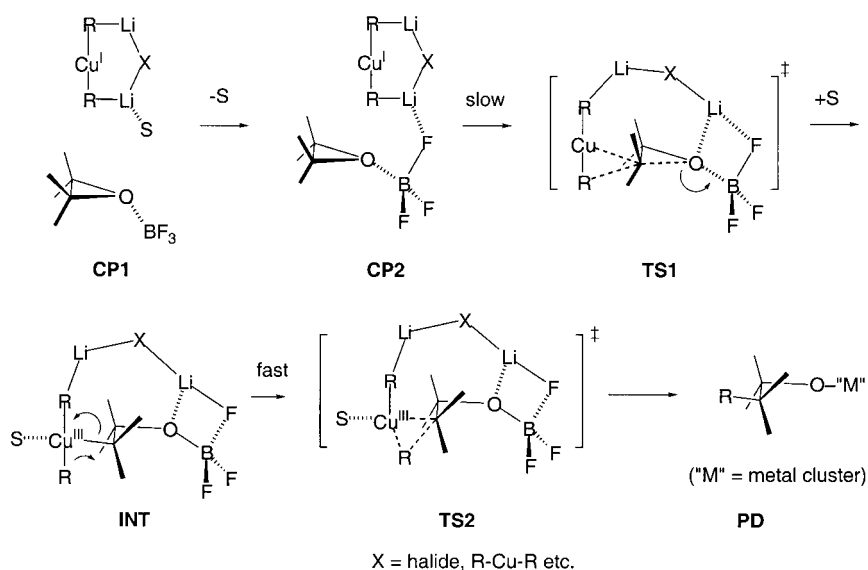
Fig. 10.5. Mechanism for the acceleration of an epoxide alkylation reaction by BF₃.

also be formed from a cuprate/BF₃ complex and the epoxide. Displacement to TS
(**TS1**), followed by the formation of a Cu(III) intermediate (**INT**), gives the alkyla-
tion product **PD**. The cooperative interaction of BF₃ fluorine and boron atoms with
the cuprate and epoxide system is responsible for the acceleration and stabilization
of products. The activation energy is reduced by ca. 10 kcal mol⁻¹ compared to the
process in the absence of BF₃.

10.6.2
Me₃SiCl Acceleration

Since Nakamura and Kuwajima's initial discovery in 1984 [130], Me₃SiCl has be-
come a standard reagent for acceleration of conjugate additions. The effect was first
reported for copper-catalyzed conjugate additions of the zinc homoenolate of pro-
pionic acid esters, as shown in Scheme 10.13, and utilized in a total synthesis of
cortisone [131]. Application to Grignard-based catalytic reagents and stoichiometric
lithium diorganocuprate(I) followed [132]. Acceleration of conjugate additions and

modification of their selectivities by means of silylating agents are now well established [132].
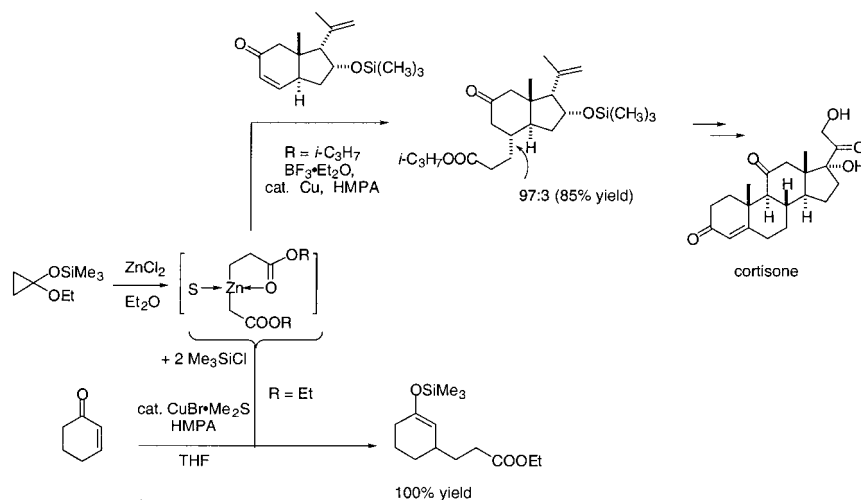
Scheme 10.13. Me$_3$SiCl- and BF$_3$-accelerated catalytic conjugate addition and a cortisone synthesis.

Me$_3$SiCl also affects the stereoselectivity of 1,2-additions to carbonyl compounds [133]. With the aid of suitable activators, these mildly reactive reagents show selectivities unattainable by the conventional reagents, as illustrated below for Me$_3$SiCl-dependent chemoselectivity (Eq. 10.13) [134].

(10.13)
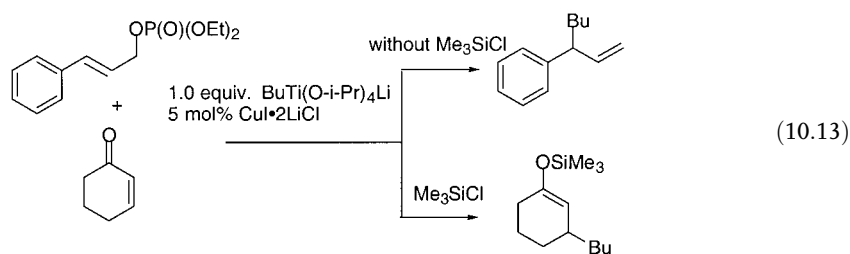
Considerable mechanistic discussion has appeared in the literature [135]. One argument assumes simple Lewis acid activation of the starting enone with Me$_3$SiCl [136] (**A** in Scheme 10.14), although it is supported neither by experiment nor by theory [137]. On the contrary, Me$_3$SiCl has indeed been shown to be Lewis acidic but rather to act as a base toward the lithium atom in the lithium cuprate cluster [135a] (**C** in Scheme 10.14). The second proposal, by Corey [73], which takes into account an inner sphere electron-transfer hypothesis, assumes in situ trapping of an enolate-like intermediate by the silylating agents, making the process irreversible (**B** in Scheme 10.14). The third and most recent proposal assumes theoretical

justification for chloride coordination to copper (**D** in Scheme 10.14) [135b]. The magnitude of such coordination, however, was recently shown to be very small [129]. While these proposals failed to provide a direct answer to the mechanism of Me_3SiCl acceleration, the positive correlation between the silylating power of the reagent and the magnitude of rate acceleration [138] strongly suggests that the rate-determining step of the reaction is the silylation step rather than the C–C bond-forming step. Recent studies of kinetic isotope effects by Singleton fully supported this observation [139]. Mechanistic data – such as reaction rate, stereochemistry, and theoretical analysis – are still awaited, however.
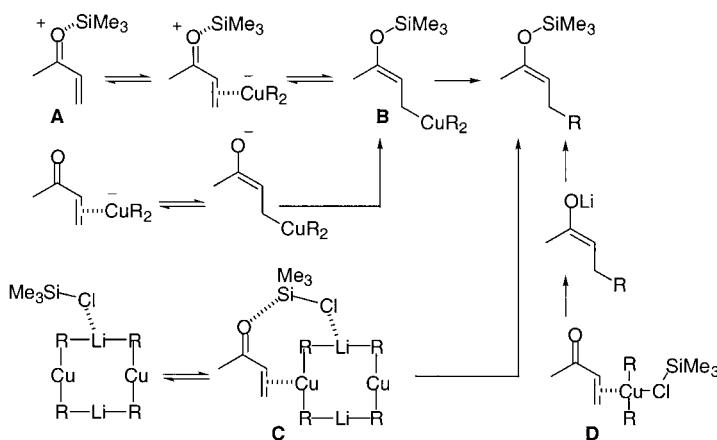
Scheme 10.14. Various proposed mechanisms for Me_3SiCl acceleration of conjugate additions to enones ($X = Me_3SiCl$).

10.6.3
Dummy Ligands

A synthetic problem associated with the use of homocuprates R_2Cu^- is that the reagent can transfer only one of the two possibly precious R ligands to the target electrophile (E^+, for example, to α,β-unsaturated carbonyl compounds), with one R ligand being lost as an unreactive RCu species. The introduction in 1972 of mixed organocuprates $[RCu(X)]^-$ [140], in which the X group acts as a nontransferable dummy ligand, provided the first general solution to this problem (Eq. 10.14). Typical dummy ligands include alkynyl [141], cyano [142], phenylthio [143], di-alkylamino, and phosphino groups (Chapt. 3) [143, 144]. The selectivity of ligand transfer was considered to be a function of the ligand-ligand coupling process in an intermediate bearing three ligands: R, X and E. A widely accepted hypothesis was that an X group forming a stronger Cu–X bond acts as a better dummy ligand (resisting transfer). While this hypothesis has successfully been applied to the design of dummy ligands, recent theoretical studies by Nakamura revealed an entirely different controlling factor in dummy ligand chemistry [145].

$$(10.14)$$
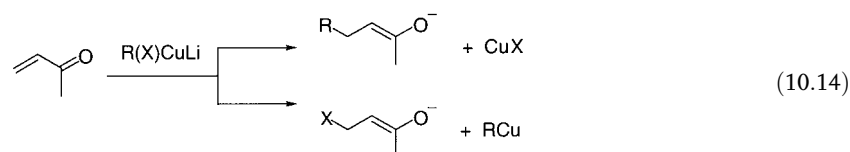
The recognition of the importance of cluster structure has resulted in a new understanding of the role of a dummy ligand (Y) in the chemistry of mixed cuprates MeCu(Y)Li [145]. As shown in Scheme 10.15 for the case of Y = alkynyl, the
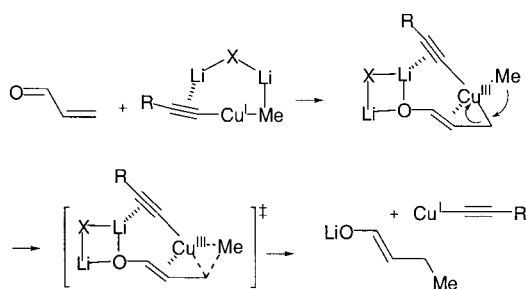
Scheme 10.15. Dummy ligands: selective transfer of the methyl (or alkyl, alkenyl, aryl) group in preference to transfer of the alkynyl group.

transfer of the methyl group is overwhelmingly favored over the transfer of the alkynyl group. This is because the alkynyl group acts as a tight bridge between Cu^{III} and Li^+ (Fig. 10.6). In other words, the alkynyl dummy group simultaneously binds to Cu and Li atoms (strong electrostatic interaction between the Li and the alkynyl group), and so remains on the copper atom. By default, the much less effective bridging organic ligand is transferred to the enone substrate. This runs

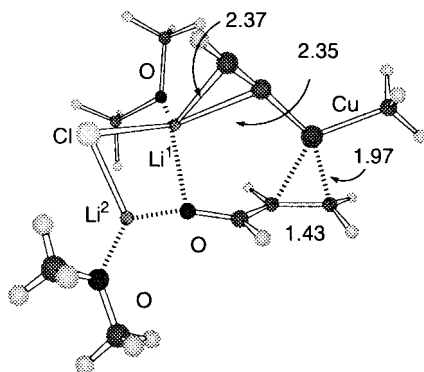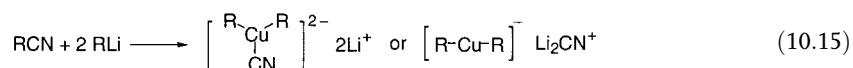**Fig. 10.6.** 3D structure of the open complex between acrolein and Me(ethynyl)CuLi·LiCl, with Me_2O coordinated to each lithium atom (B3LYP/631A). Bond lengths are in ångstroms.

contrary to the conventional hypothesis that the Y group forming a stronger Cu–Y bond acts as a better dummy ligand (resisting transfer), and has provided an fur- ther illustration of the critical roles of cluster structures in organocopper chemistry.

10.6.4
The "Higher Order" Cuprate Controversy

Organocopper(I) species bearing three anionic groups, ($[R_3Cu]^{2-}$), are termed "higher order" cuprates [146, 147]. For purposes of differentiation, conventional cuprate(I) species (R_2Cu^-) may be referred to as "lower order" cuprates. Whether or not a "higher order cyanocuprate ($R_2Cu(CN)Li_2$)", bearing two carbanionic res- idues and a cyanide anion on copper, exists as a stable species has been the subject of controversy (Eq. 10.15). This controversy has also spawned numerous mecha- nistic and structural studies on cuprates in general.

$$\text{RCN} + 2\,\text{RLi} \longrightarrow \left[\begin{array}{c} R \diagdown \underset{|}{\overset{}{Cu}} \diagup R \\ CN \end{array} \right]^{2-} 2\text{Li}^+ \ \ \text{or} \ \ \left[R\text{-Cu-R} \right]^- \ \text{Li}_2\text{CN}^+ \tag{10.15}$$

It was reported in the 1970s that a "higher order" cuprate reagent, prepared by the use of more than two equivalents of an alkyllithium reagent with a copper(I) salt, was more reactive [20, 146] and more selective than ordinary cuprates [148]. Using NMR and cryoscopy, Ashby showed that species that could be regarded as higher order cuprates were formed [149]. Bertz demonstrated the presence of a triply coordinated Cu(I) complex ($[R_3Cu]^{2-}$) for the first time, by solution NMR studies [150], while Power demonstrated the existence of a triply coordinated cup- rate [$Ph_5Cu_2Li_3(SMe_2)_4$] in the crystalline state [151, 152].

Lipshutz reported in 1981 that reagents formed by addition of two equivalents of RLi to CuCN give higher yields than the corresponding Gilman cuprates (R_2CuLi) or lower order cyanocuprates (RCu(CN)Li), and described them as "$R_2Cu(CN)Li_2$" to imply a triply coordinated structure [147]. With the aid of ^{13}C, ^{6}Li, and ^{15}N NMR data [153], Bertz was able to point out that cyanide was not attached to copper(I) in the Lipshutz mix, and started the controversy [154, 155]. Physical measurements by Penner-Hahn [156] and Lipshutz [157], and theoretical studies by Snyder [158], Penner-Hahn, and Frenking [159] contributed much to the discussion. All the crystallographic data for cyanocuprates of "higher-order stoichiometry" recently reported by Boche [160] and van Koten [161] indicated that the cyanide anion is coordinated to lithium and not to copper. Evidence along the same lines was found in sodium and potassium derivatives [162]. The consensus, therefore, after many years of studies, is that triply coordinated $[Cu(CN)R_2]^{2-}$ is not a stable structure in ethereal solution [153, 163–165]. Despite this conclusion, the Lipshutz mixed reagent still remains the one of choice in many synthetic transformations, and the presence of a triply coordinated cuprate(I) dianion was recently indicated by ^{13}C–^{13}CN carbon coupling in cyanostannylvinylcuprate(I) dianion in a THF/ HMPA mixture [166]. In addition, the cyanide anion finds its way onto copper at the end of the reaction, forming RCu(CN)Li, while it is not known when the

cyanide/copper coordination starts. The true role of the cyano group in the reactions of "higher order cyanocuprates" remains obscure [164, 167].

10.6.5
Further Issues

While a large number of studies have been reported for conjugate addition and S_N2 alkylation reactions, the mechanisms of many important organocopper-promoted reactions have not been discussed. These include substitution on sp^2 carbons, acylation with acyl halides [168], additions to carbonyl compounds, oxidative couplings [169], nucleophilic opening of electrophilic cyclopropanes [170], and the Kocienski reaction [171]. The chemistry of organocopper(II) species has rarely been studied experimentally [172–174], nor theoretically, save for some trapping experiments on the reaction of alkyl radicals with Cu(I) species in aqueous solution [175].

10.7
Orbital Interactions in Copper-mediated Reactions

Recent theoretical analysis has revealed an intriguing difference between the addition reactions and the S_N2 alkylation reactions, in the geometry of the nucleophilic C–Cu–C moiety. As summarized in Sect. 10.2, the C–Cu–C bonding in doubly coordinated organocuprate(I) anions found in stable structures is always linear. As the HOMOs of linear R_2Cu^- molecules are largely $3d_{z2}$ copper orbitals [92, 94], linear C–Cu–C groups are suitable for interaction with the σ^*-orbital of MeBr, as illustrated in Fig. 10.7a [94]. Bending of the C–Cu–C bond to $<150°$ causes mixing of the $3d_{xz}$ copper orbital with the 2p methyl orbital, to make it the HOMO of the cuprate (Fig. 10.7b), which is now suitable for interaction with the π^*-orbitals of enones and acetylenes. The energy gain through back-donation largely compensates for the energy loss associated with the bending (ca. 20 kcal mol^{-1} to achieve an angle of 120°).
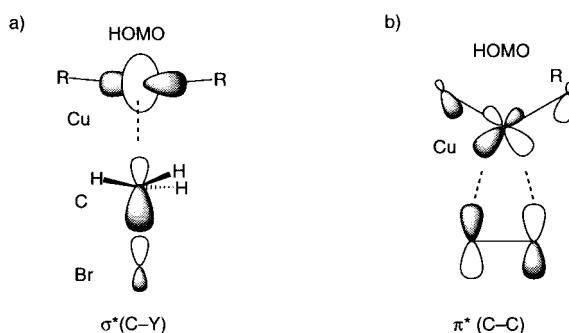

Fig. 10.7. Orbital interactions between R_2Cu^- and substrates in (a) an early stage of interaction of the cuprate with methyl bromide, and (b) π-complexation to acetylene or olefin.

The above analysis for copper chemistry also applies to the same-class element gold, which, however, forms much more stable C–Au^I bonds [176] and so is unreactive. On the other hand, the d-orbitals of zinc(II), a main group neighbor, are too low-lying to make organozinc compounds as nucleophilic as organocopper compounds [92].

10.8
The Roles of Cluster Structure in Copper-mediated Reactions

The experimental and theoretical data below indicate several important characteristics of cuprate structures and their reaction mechanisms.

(1) The C–Cu–C angle in a covalently bound R$_2$Cu$^-$ fragment in a stationary state is always close to 180° [94]. In ethereal solution, R$_2$CuLi exists as higher aggregates, the Li–R bonds of which are fractional [26, 177–179]. It is invariably possible to identify a neutral fragment, R–Cu–R–Li, in crystals of cyclic oligomers and higher polymers (Scheme 10.16). Depending on the nature of the reacting electrophiles (σ^* or π^*), either linear or bent conformations of the C–Cu–C moiety become important in nucleophilic reactions (Fig. 10.7) [94].
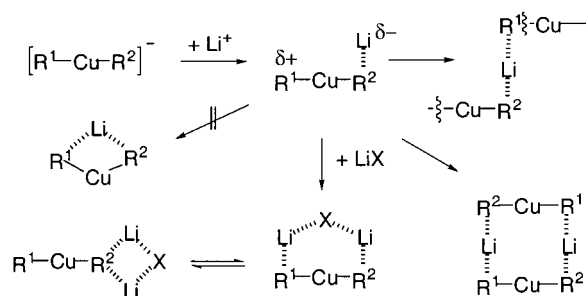
Scheme 10.16. Various structural possibilities for cuprates. Solid lines indicate (largely) covalent bonds, and dashed lines (largely) electrostatic bonds between a metal cation and an organic or heteroatomic anion. X = RCuR, halogen, CN, etc.

(2) Because of the fractional R–Li bond, clusters and polymers can reversibly form an open cluster, which traps the unsaturated substrate through multiple-point bonding (cf. Schemes 10.5 and 10.7). Lithium cations assist the electron flow from the cuprate to the electrophile and, to achieve such cooperative action, a cluster of a particular size may be necessary. Lewis acid metals other than lithium (Zn^{II}, for example) will also play similar roles.

(3) A C–Cu^I bond is a stable covalent bond, and is difficult to cleave by itself [93]. After charge transfer from cuprate(I) to substrate, however, cleavage of the resulting R–Cu^{III} bond becomes easy. The reductive elimination reaction regenerates RCu^I, which may take part in further catalytic cycles. Thus, in copper-

catalyzed reactions, excess R^- anion will react with RCu to regenerate the necessary cuprate species.

(4) Although acetylene carbocupration and conjugate addition have previously been considered to be two separate reactions, they have been shown to share essentially the same reaction mechanism. The kinship of carbocupration, conjugate addition, S_N2' allylation, and S_N2 alkylation has now been established, through the theoretical studies of Nakamura, Mori, and Morokuma.

(5) Demonstration of the critical roles of the open conformations of polymetallic clusters highlights theoretical analysis in cuprate chemistry. Polymetallic clusters in various synthetic reactions are currently attracting the attention of synthetic and mechanistic chemists alike [40, 180–183].

10.9
Summary and Outlook

As summarized in the preceding sections, numerous experimental studies have indicated active participation by large organocopper clusters. These typically bear nucleophilic alkyl residues, copper(I) atoms, and counter-cations (typically lithium). The uniqueness of organocopper chemistry stems primarily from the fact that it lies on the border line between main group elements and transition metals. Comparisons may be made for the neighboring elements – Ni^0, Cu^I, Ag^I, Au^I and Zn^{II} – all of which exist in d^{10} configurations. The energy levels of the copper(I) 3d orbitals are much higher than those in zinc(II), and become even higher upon mixing with the 2p orbital of the alkyl ligand through R_2Cu^- formation [94]. Redox systems like the Cu^I/Cu^{III} cycle are unavailable for zinc(II). Organonickel and silver species are less stable, and so much less synthetically viable than organocopper(I) reagents, while organogold(I) species are too stable to be synthetically useful. The C–Cu–C angle is intimately connected with the reactivities of diorganocuprate(I) species, and the Lewis acid (Li^+) in cuprate clusters provides push-pull electronic assistance for charge transfer from Cu^I to the electrophile. The diversity of coordination structures revealed by calculations indicates that organocopper chemistry represents the ultimate "supramolecular chemistry", long but unwittingly exploited by chemists. Numerous other aspects of organocopper chemistry await further mechanistic study. The importance of R_3Cu^{III} species is now fully recognized, and needs more careful attention in future studies of mechanistic and synthetic organocopper chemistry.

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