CHEMICAL REVIEWS

REVIEW

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Mechanisms of Nucleophilic Organocopper(I) Reactions

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CONTENTS

1. INTRODUCTION

Organocopper compounds in organic chemistry appear most frequently in the form of nucleophilic organocopper(I) reagents, which are used either as stoichiometric reagents or as catalytic species generated in situ from a small amount of a copper(I) complex and a large amount of organomagnesium, -zinc, or other organometallic reagent. The nucleophilic organocopper(I) reagents are commonly described as simple organocopper species, RCu and R_2Cu^-, or metal organocuprates such as R_2CuM (homocuprate) and RCu(X)M (heterocuprate), where R, X, and M stand for a carbanion (e.g., alkyl, alkenyl, aryl), a nontransferable anion (e.g., halide, heteroatom anion, cyanide), and a main-group metal cation (e.g., Li^+, Mg^{2+}, Zn^{2+}), respectively. Such organocuprates serve as uniquely effective synthetic reagents for delivery of hard carbanions such as alkyl, alkenyl, and aryl anions to electrophilic substrates in the form of a variety of reactions such as conjugate addition, carbocupration, alkylation, allylation, alkenylation, and acylation (Scheme 1).[1−9] The chemistry of nucleophilic organocopper reagents has been reviewed many times with emphasis on synthetic utilities since the early 1970s. However, the synthetic applications were developed largely on the basis of intuition and working hypotheses instead of on a solid mechanistic basis because of two problems—the complexity of the multimetallic reactive organocopper(I) species and the instability of tricoordinated organocopper(III) complexes, which have recently been recognized as important

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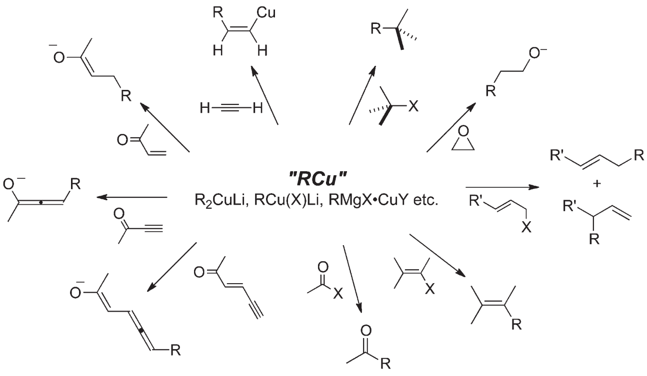
Scheme 1. Nucleophilic C−C Bond Formation Reactions with Organocopper Reagents



intermediates in copper(I)-mediated reactions. First, the organocopper reagents formulated as RCu, R_2Cu^-, R_2CuM, and R(X)CuM per se have recently been found not to be very reactive and are reactive only when they are aggregated with additional Cu and/or M atoms. Second, the existence of an organocopper(III) species was in doubt until the beginning of the 1990s. In addition, comprehensive information on the structure[10−12] and the electronic states of stable copper complexes, reactive intermediates, and transition states of the reactions[13] also only became available in the 1990s. The mechanistic pictures throughout the 1980s were summarized in a comprehensive review by Lipshutz published in 1992,[5] and those in the 1990s in reviews by one of the authors and by others published in 2000.[13a,b,14]

In this review, we will describe what we know in 2011 on the mechanism of the reactions of nucleophilic organocopper(I) reagents as viewed through a window of molecular orbital analysis supplemented by experimental data on structures in solution and in the solid state.[13c] A comprehensive mechanistic picture of representative organocopper(I)-mediated C−C bond-forming reactions in Scheme 1 will be illustrated. It should be noted that, while conventional organocopper reagents continue to be important synthetic tools, the expected depletion of rare metal elements has aroused new interest in the use of copper as a ubiquitous, base metal for organic synthesis and catalysis.[15] In this regard, we hope that this review not only serves as a mechanistic overview of established organocopper reactions but also provides inspiration for designing new organocopper-mediated/catalyzed transformations.

Brief History of Nucleophilic Organocopper Reactions

The history of nucleophilic organocopper chemistry dates back to 1941, when Kharasch and Tawney reported a conjugate addition reaction of a Grignard reagent to an α,β-unsaturated ketone in the presence of a catalytic amount of a Cu(I) salt.[16,17] Gilman and co-workers reported in 1952 that the reaction of 1 equiv of MeLi with CuI resulted in the formation of a yellow precipitate, which then gave a colorless solution upon addition of another equivalent of MeLi.[18] The latter type of reagent is generally formulated as R_2CuLi and often called a "Gilman reagent" or "Gilman cuprate". In 1966, Costa and co-workers isolated phenylcopper(I) and related complexes from a reaction mixture of copper(I) bromide and phenyllithium or phenylmagnesium bromide.[19] Since then, extensive efforts have been devoted to the synthesis, isolation, and structural analysis of organocopper(I) complexes.

The synthetic chemistry of organocuprates started to evolve rapidly in 1966, when House and co-workers showed that the Gilman cuprate Me_2CuLi undergoes a conjugate addition reaction to an enone,[20] which suggests that this and related species are the true reactive species of the Kharasch conjugate addition reaction. Soon after this report, Corey and Posner discovered substitution reactions between the Gilman reagent and alkyl, alkenyl, allyl, or aryl halides,[21] and Whitesides and co-workers reported oxidative homocoupling of Gilman cuprates using molecular oxygen.[22,23] Important initial developments of fundamental transformations, including the substitution reactions of alkyl, alkenyl, and aryl halides,[24] alkyl tosylates,[25] epoxides,[26,27] and allyl,[27,28] propargyl,[29] and acyl electrophiles,[30,31] and addition reactions to electron-deficient alkynes[32] and unactivated alkynes,[33] were achieved by the mid-1970s.[1,2]

During the 1970s and 1980s, several new reagents and concepts for organocuprate chemistry were developed. Representative achievements include (1) a mixed organocuprate reagent RR′CuLi that contains the ligand R′ as a nontransferable "dummy" ligand and hence allows selective delivery of the ligand R (see section 6.3.1),[34−40] (2) an organocopper−BF_3 ($RCu\cdot BF_3$) reagent for accelerated conjugate addition and regioselective allylation (see section 6.1),[41,42] (3) a cyano-Gilman cuprate $R_2CuLi\cdot LiCN$ that exhibits higher reactivity than a standard Gilman reagent in certain reactions (see sections 2.1 and 6.3.2),[43,44] and (4) the use of Me_3SiCl for acceleration of conjugate addition (see section 6.2).[45−52] While organolithium and Grignard reagents were dominant sources of carbanions in organocopper chemistry for a long time, the use of more mildly reactive organometallics, such as organozinc,[53−55] -titanium,[53d,56] -zirconium,[57−59] and -aluminum[60−62] reagents, became popular in the late 1980s.[63] The synthetic utility of the above and other reagents developed in these decades has been amply demonstrated in the context of natural product synthesis.[5]

After the middle of the 1990s, the focus of research in synthetic organocopper chemistry shifted to the development of catalytic asymmetric C−C bond-forming reactions. The efforts of a number of researchers in this field led to the development of synthetically useful enantioselective conjugate addition, allylic substitution, and other reactions by combinations of chiral copper catalysts and a variety of organometallic reagents such as Grignard, organozinc, and organoaluminum reagents.[64,65] Enantioselective reduction through copper hydride chemistry[66,67] and regio- and stereoselective C−C bond formation based on directing group strategies[68] have also reached a considerable level of sophistication. More recently, organoboranes,[63b,64c,69] organosilanes,[63b,64c,70] carboxylic acids,[71] and even simple aromatic and heteroaromatic compounds with acidic C−H bonds[72,73] have rapidly emerged as stable and functional group-tolerant sources of nucleophilic organocopper(I) species for C−C bond formation. Copper(I)-mediated or -catalyzed introduction of poorly nucleophilic perfluoroalkyl groups has also attracted increasing attention.[74−76] Furthermore, organocopper(III) species are now recognized not only as intermediates in nucleophilic organocopper(I) reactions but also as viable reactive species in electrophilic C−C bond-forming reactions.[77]

Although the dominant part of synthetic organocopper chemistry has focused on the synthesis of biologically active compounds, some interesting developments in material science have been reported. Quantitative 5-fold addition to C_{60} and 3-fold addition to C_{70} using magnesium-based organocopper reagents are good examples,[78] providing a new class of cyclopentadienyl and indenyl structural motifs, which serve as versatile platforms for the creation of novel molecules for materials applications.[79]

Brief Summary of Structural and Mechanistic Aspects of Organocopper Reactions

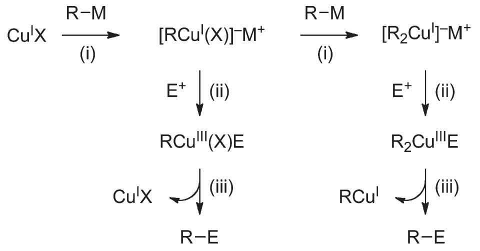
Despite the synthetic utility of organocopper reagents, their reaction mechanisms were poorly understood for a long time. This was primarily because of the difficulty in studying the nature of both organocopper(I) reagents and organocopper(III) intermediates. Organocopper(I) reagents exist as a mixture of structurally complex aggregate species in solution.[12] Although numerous reports described the Gilman reagents as R_2CuLi, the reagent also often contains LiX, which is produced as a stoichiometric side product of the preparation, and LiX complexes with the "Gilman reagent" to form $R_2CuLi \cdot LiX$.[80] Even small differences in solvent and the accompanying salt affect the composition and the aggregation state of the reagent, and also affect the reactivity of the reagent. Because of this complexity, all compounds added to the "soup" are often indicated to describe the copper reagent, such as $CuI \cdot BuMgBr \cdot BF_3$ in ether, tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME).

While structural information on organocuprate reagents in solution and in the solid state has gradually accumulated since the 1970s,[10−12] there has been a lack of information on the nature of reactive intermediates and the transition states involved in organocuprate reactions. Organocopper(III) complexes escaped experimental observation and characterization for a long time because of their low thermal stability in the absence of a strong donor ligand. The experimental and theoretical information available until the beginning of the 1990s was insufficient for comprehension of the whole mechanistic picture.

In the meantime, computational chemistry emerged as a powerful new tool for studying mechanisms of complex organometallic reactions toward the end of the 1980s,[81] when one of us (E.N.) started to seriously think of unveiling the mechanisms behind organocuprate reactions. The development of ab initio and density functional theories (DFT) as well as the increase in computational capacity during the late 1980s and 1990s made it possible to study reactions of first the organometallic monomers (e.g., MeLi, MeCu, and Me_2Cu^-),[82,83] clusters (e.g., $[MeLi]_2$, $[Me_2CuLi \cdot LiCl]$, and $[Me_2CuLi]_2$),[84−88] and finally those involving solvent molecules[89,90] in silico. It was found to be crucial for the calculation to take electron correlation into account for studies in this area.[91] With such new developments, it became possible to understand the behavior of the multimetallic cuprate systems and the essential role of the 3d orbitals of the copper atom. The theoretical studies supported by the new experimental results have revealed a coherent vision of the mechanisms of a number of organocuprate reactions.[13] The attractive feature of the theoretical studies is that the established framework can solve problems in copper catalysis and also for the d-block transition metals nearby in the Periodic Table, such as nickel,[92,93] silver, and gold[94]—a demonstration of the power of theoretical analysis.

Before going into the details, we describe the basics of the mechanisms of nucleophilic organocopper reactions. Regardless of stoichiometric or catalytic processes, the reactions have three elementary steps in common, that is, (i) transmetalation between a copper(I) salt and a main-group organometallic reagent to give either a mono- or diorganocuprate(I); (ii) nucleophilic attack of the d-orbital of the copper(I) atom on an electrophile (E^+) to produce an organocopper(III) intermediate (oxidative addition); and (iii) decomposition (reductive elimination) of the copper(III) intermediate to furnish a product (R−E) and a neutral copper(I) species (Scheme 2). In a catalytic reaction, the last species takes part in the next catalytic step. Thus, the transmetalation and the Cu(I)/Cu(III) redox sequence are common key processes in both stoichiometric and catalytic organocopper reactions.

Scheme 2. General Mechanism of Organocopper(I)-Mediated C−C Bond Formation



Whether a particular reaction involves a mono- or diorganocuprate depends primarily on the nucleophilicity and stoichiometry of the main-group organometallic reagent (R−M). When an organolithium reagent is used, the use of 1 equiv introduces only 1 equiv of the R group on the copper atom, and the use of 2 equiv introduces two R groups to generate a diorganocuprate (Gilman cuprate). Because of the very high reactivity of organolithium reagents, which causes direct coupling with the electrophile in the reaction mixture, organolithium reagents cannot be used for catalytic reactions, with rare exceptions.[95] On the other hand, mildly nucleophilic organometallic reagents such as organozinc reagents usually, if not always, give rise to monoorganocuprates regardless of stoichiometric or catalytic conditions. The nucleophilicity of Grignard reagents being intermediary, they can generate either monoorganocuprates or diorganocuprates as major species depending on the reaction conditions (e.g., the stoichiometry and the speed of addition of the reagent).[96] In catalytic reactions, any of the three elementary steps can be the rate-determining step, but the kinetics of the catalytic organocopper reactions have rarely been studied (see section 6.4).

The issues discussed in the ensuing sections are as follows. Section 2 summarizes the structures of organocopper compounds, organocopper(I) ate complexes and organocopper(III) complexes, in particular. Section 3 first discusses the electronic structure of organocuprate(I) complexes and their molecular orbital interactions with electrophiles, to gain insights into the oxidative addition process of the organocuprate reactions. This section then illustrates how Lewis acidic countercations affect the organocuprate reaction, and how organocopper(III) intermediates produce the C−C coupling products. Organocopper reagents will be compared with organosilver and -gold analogues. Sections 4 and 5 are the core of this review, illustrating mechanistic pictures of representative reactions such as carbocupration, conjugate addition, S_N2 alkylation, and allylic substitution. Section 6 discusses the well-known modifications, such as BF_3-modified reagents, Me_3SiCl-modified reagents, and cyano-Gilman reagents to the general mechanistic framework. Plausible mechanisms of catalytic (asymmetric) organocopper reactions are also suggested. Section 7 concludes this review and describes future implications.

We note two points of caution before going into the body of this review. One is on the formal oxidation state of the copper atoms, and another is on the line drawing convention in organocopper chemistry. First, the Cu(I) and Cu(III) oxidation states mentioned frequently in the literature, including this review, are formal as accepted in standard textbooks of inorganic and organometallic chemistry.[97] The theoretical charge on the copper atom in an organocopper(I) complex calculated using natural population analysis[98] is much less than +1, and the charge in an organocopper(III) complex may be around +1 or only slightly more positive.[99] This is because of the donation of a negative charge from the organic ligands (i.e., the significant covalent character of the copper−carbon bond), and the calculated positive charge must not be confused with the convention of a formal oxidation state.[100] Second, the lines that connect atoms to indicate chemical bonding in the structures shown throughout this review need careful attention. The definitions are summarized below with typical examples shown in Chart 1. (1) Solid lines are uniformly used to indicate C−Cu and C−Li bonds in lithium organocuprates (**A**), although the former bond is largely covalent and the latter is largely ionic. Solid lines are also used to indicate coordination of a neutral ligand to copper, according to the accepted convention of (experimental) organotransition metal chemistry (**B** and **C**).[97] (2) Hashed lines are used to show coordination of a neutral Lewis base (e.g., ethereal solvent, carbonyl group, olefin) to lithium or other Lewis acidic main-group metals (**A**). (3) Broken lines are used to show forming, breaking, and other partial bonds (**D** and **H**). (4) Bold and hashed wedges are used to depict stereochemistry, showing bonds to atoms above and below the plane of the drawing, respectively (**H**). (5) A donation/back-donation π-complex of copper and an alkyne is drawn mainly as a metallacyclopropene **E** or partially formed metallacyclopropene **F**, and occasionally as a metal−alkyne complex **G**, depending on the context of the discussion (e.g., experimental observations or theoretical analysis of bonding). A copper−olefin π-complex is also drawn in the same manner. Overall, these drawings are different representations of the same chemical entity. While chemical drawings are mainly used to discuss reaction mechanisms throughout this review, in the Supporting Information is provided a collection of Cartesian coordinates of relevant structures optimized by DFT calculations. Interested readers are encouraged to visualize those structures using modeling softwares including freewares such as MacMolPlt.[101]

Chart 1. Drawing Style of Chemical Structures in This Review

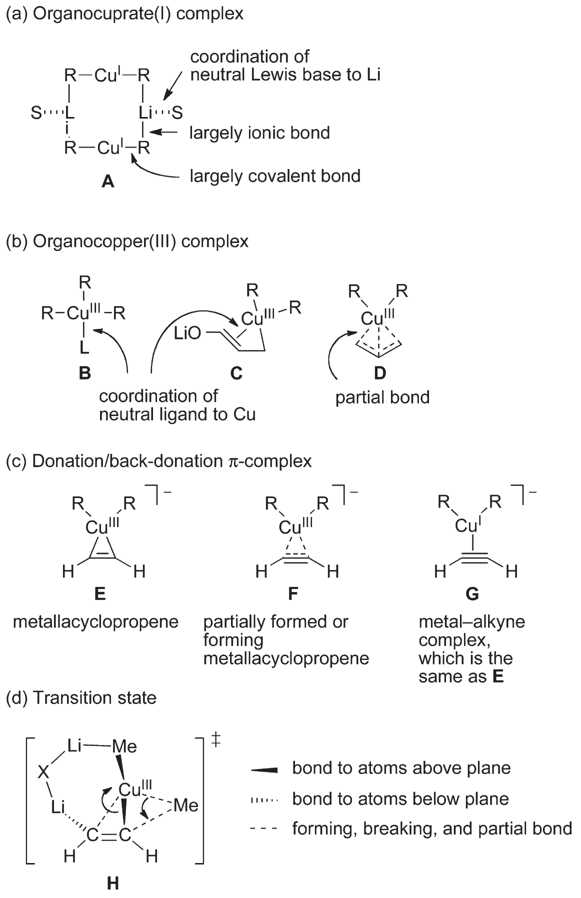
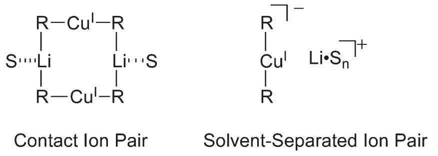


Chart 2. Two Major Structural Types of Lithium Organocuprates



2. STRUCTURES OF ORGANOCOPPER COMPOUNDS

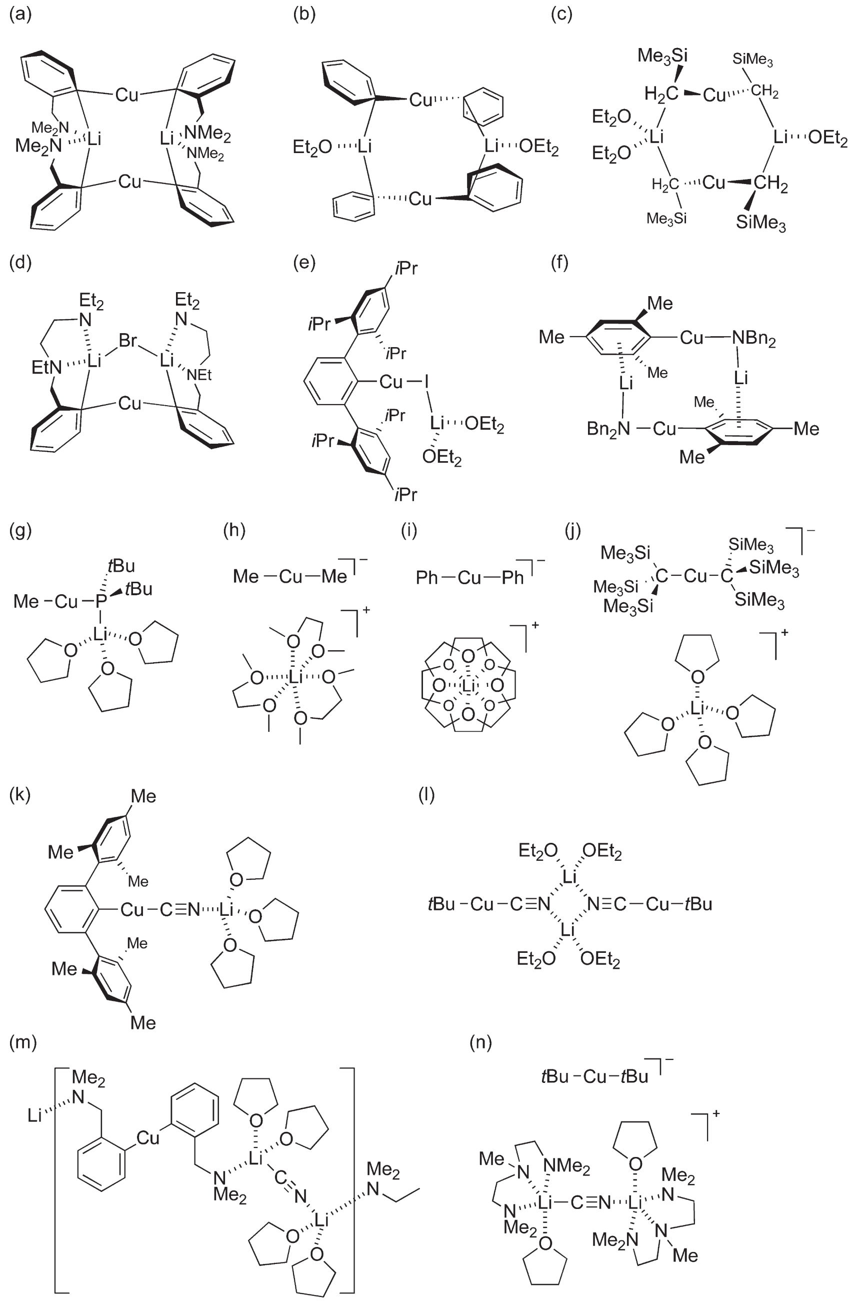
The structures of organocopper compounds in the solid state and in solution have been studied for a long time. This topic was previously reviewed by Power and van Koten focusing on the solid-state structures[10,11] and by Gschwind on the solution structures.[12] This section focuses on the structures of organocopper compounds that are the most relevant to organocopper-mediated C−C bond-forming reactions. First, the structural features of nucleophilic organocopper(I) ate complexes are illustrated. While the structures by themselves are not particularly informative, we can "read" mechanistic information hidden in the structure once we have gained a reasonable idea of the mechanism of their reactivities. Theoretical information on the bonding, vibrational states, and electronic states is particularly powerful for correlating the structures to the reactivities of the complexes. Second, the structures and the reactivities of organocopper(III) intermediates allow us to understand the reductive elimination process that is often a rate-limiting step in the whole reaction pathway of the organocopper reactions.

2.1. Organocopper(I) Ate Complexes

The simplest organocopper compound, MeCu, is polymeric in an ethereal solvent and is unreactive, while the Gilman reagent Me_2CuLi is soluble and reactive.[18,20] Thus, the nucleophilic reactivities of organocopper reagents have been considered to originate from organocopper(I) ate complexes that are empirically described as R_2CuM (homocuprate) or RCu(X)M (heterocuprate). The crystal and solution structures of lithium organocuprates have been extensively studied by a variety of experimental techniques, including cryoscopic molecular weight determination, NMR, and X-ray crystallographic analysis.

A diorganocuprate(I) complex is characterized by its linear C−Cu−C array, which needs to have a metal countercation. Structures of diorganocuprate(I)/metal cation complexes in crystals can be generally classified into two types, that is, contact ion pair (CIP) and solvent-separated ion pair (SSIP) (Chart 2). The former typically consists of a cyclic structure involving two copper atoms, two lithium atoms, and four organic ligands. The Cu−C bond is covalent, while the Li−C linkage is largely ionic. The lithium atoms are also coordinated by ethereal solvent molecules in many complexes in crystals. In the latter,

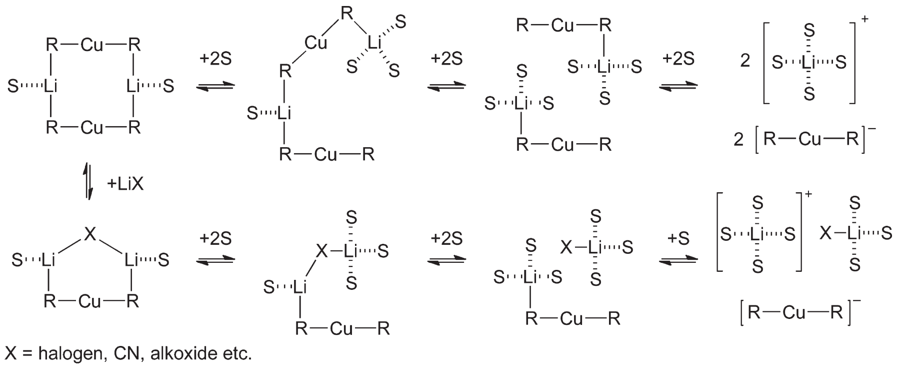
Chart 3. Lithium Organocuprates Structurally Characterized in Crystals



a diorganocuprate anion is separated from a fully solvated lithium cation. Preference for CIP and SSIP strongly depends on the nature of the cuprate and the solvent. CIP is dominant in a weakly coordinating solvent (e.g., Et_2O), while SSIP is preferred in a highly coordinating solvent (e.g., THF) or in the presence of a strong Lewis base. Importantly, these ion-pair structures are in a dynamic equilibrium with each other in solution (vide infra).

2.1.1. Structures in the Solid State. Representative CIP and SSIP structures of organocuprates determined in crystals are illustrated in Chart 3. The first dimeric cuprate structure was determined in 1985 for a diarylcuprate $(2\text{-}Me_2NCH_2C_6H_4)_4Cu_2Li_2$, in which the dimethylaminomethyl groups serve as chelating ligands for the lithium atoms (Chart 3a).[102,103] The dimeric structure of a simple diarylcuprate $Ph_4Cu_2Li_2(OEt_2)_2$, suggested earlier by molecular weight measurement and NMR studies,[104] was confirmed by X-ray analysis in 1990 (Chart 3b).[105] A similar dimeric diphenylcuprate containing Me_2S instead of Et_2O, $Ph_4Cu_2Li_2(SMe_2)_3$, was also characterized.[106] A diarylcuprate dimer, $Mes_4Cu_2Li_2$ (Mes = mesityl), was determined to be a solvent-free cuprate cluster.[107] Thus far, the dimeric structures of dialkylcuprates have been characterized by X-ray crystallography only for compounds containing Me_3SiCH_2 groups; for instance, the crystal structures of trimethylsilylmethylcuprates containing Et_2O or Me_2S molecules have been determined (Chart 3c).[108,109] The common structural feature of these dimeric cuprates is close-to-linear (≥165°) C−Cu−C moieties that are twisted with respect to each other and bridged by lithium cations. Organocuprate clusters containing LiX units (X = halogen, CN, etc.) had often been

Scheme 3. A Part of Plausible Equilibria among CIPs and SSIPs in Solution[a]



[a] The number of solvent molecules on the lithium atoms may vary depending on the R group and other factors.

suggested by theoretical studies.[110−115] Such a crystal structure containing a LiBr bridge was obtained using an aryl ligand containing a bidentate nitrogen chelating group (Chart 3d).[116] Other notable CIP-type homocuprates include the only example of a higher-order cuprate $Ph_5Cu_2Li_3(Me_2S)_3$[117] and the only example of a magnesium cuprate $Ph_6Cu_4Mg(OEt_2)$.[118]

CIP structures of heterocuprates (RCu(X)Li) have also been determined by X-ray crystallography. Representative complexes of this type include a monomeric iodocuprate 2,6-$Tip_2C_6H_3CuLiI(OEt_2)_2$ (Tip = 2,4,6-(iPr)$_3C_6H_2$) (Chart 3e),[119] a dimeric amidocuprate $Mes_2Cu_2Li_2(NBn_2)_2$ (Chart 3f),[120a] a monomeric phosphidocuprate MeCuLiP(tBu)$_2$(THF)$_3$ (Chart 3g),[121] and others.[122] These heterocuprates also feature a linear C−Cu−X bonding.

Besides the CIP structures mentioned above, several SSIP-type crystal structures of organocuprates have been determined. Typical SSIP homocuprates $[Li\cdot S_n][R_2Cu]$ (S = solvent or ligand) among them include $[Li(DME)_3][R_2Cu]$ (R = Me, $CH(SiMe_3)_2$) (Chart 3h),[108] [Li(12-crown-4)$_2$][R_2Cu] (R = Me, Ph) (Chart 3i),[123] and $[Li(THF)_4][((Me_3Si)_3C)_2Cu]$ (Chart 3j).[124] Without any influence of lithium cations, the C−Cu−C moieties of these SSIP cuprates are close to perfect linearity. An SSIP-type heterocuprate, [Li(12-crown-4)$_2$][Cu(Br)$CH(SiMe_3)_2$], was also isolated and structurally characterized.[123]

Organocuprates prepared from CuCN and one or two equivalents of organolithium reagents serve as important synthetic tools in organic synthesis (see section 6.3). The reagents generated by these stoichiometries were once called "lower-order" or "higher-order" cyanocuprates,[5,44] because the latter stoichiometry could generate an unusual tricoordinated dianionic reactive species,[125−129] which has, however, been unambiguously characterized only for a single case, that is, $Ph_5Cu_2Li_3(Me_2S)_3$.[117] The crystal structures of the cyanocuprates RCu(CN)Li have been determined for monomers such as 2,6-$Mes_2C_6H_3Cu(CN)Li(THF)_3$ (Chart 3k)[130,131] and dimers such as [tBuCu(CN)Li$(OEt_2)_2$]$_2$ (Chart 3l).[132−135] These cuprates commonly feature a linear C−Cu−CN unit and coordination of the cyanide anion to the copper and lithium atoms by the carbon and nitrogen atoms, respectively. The C−Cu−CN structural unit of such a cyanocuprate was deduced first from NMR studies.[136]

The crystal structures of cyanocuprates that were for some time interpreted as "higher-order" cyanocuprates having a tricoordinated copper(I) dianion are known only for $[Li_2CN(THF)_4][(2\text{-}Me_2NCH_2C_6H_4)_2Cu]$ (Chart 3m)[137] and [$t$$Bu_2$Cu][$Li_2CN$(PMDTA)(THF)] (PMDTA = pentamethyldiethylenetriamine, Chart 3n).[132] These two examples share common structural features, such as linearity of the C−Cu−C moiety and coordination of the lithium cations to both ends of the cyanide anion. The former is a part of the polymeric chain and the latter consists of a monomeric SSIP structure. Therefore, these cuprates do not show a "higher-order" structure (i.e., tricoordinated dianionic structure $[R_2Cu(CN)]^{2-}\cdot 2Li^+$);[44] instead, they are simply R_2Cu^- having a cyanide anion outside of the coordination sphere of the copper atom and are commonly referred to now as cyano-Gilman cuprates.[138,139] Pieces of evidence supporting the ordinary R−Cu−R structure rather than a tricoordinated dianionic structure also came from ^1H and ^{13}C NMR studies in solution,[115,140,141] EXAFS and XANES measurements,[113,142−144] and computational analysis.[111,113−115,145]

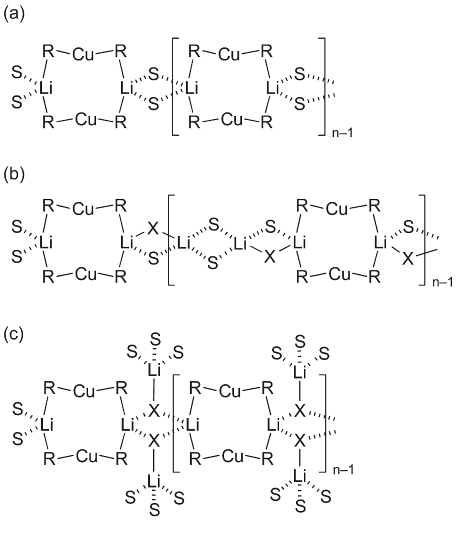
2.1.2. Structures in Solution.

Besides the crystal structures of organocuprates, their structures in an ethereal solution have also been extensively studied because these are more relevant to their reactivities. The linear bonding geometry of the C−Cu−C moiety in cuprates such as MeCu(CN)Li, Me_2CuLi, and $Me_2CuLi\cdot LiX$ (X = I, CN) has been established by NMR studies.[136,141] Fast chemical exchange of the lithium atoms was also revealed, while the Cu−C bonding is covalent and static on the time scale of NMR.[141] This chemical exchange is the origin of rapid structural reorganization and equilibrium among various organocuprate species, making their analysis in solution challenging. In contrast to the case of Gilman cuprates, the chemical exchange of lithium atoms was slowed down in amidocuprates $RCu(NR_2)Li$, permitting detection and analysis of the individual species involved in the equilibrium process.[120,146,147]

The aggregation levels of cuprates in solution have been studied by various methods, including colligative measurements,[127,148,149] mass spectrometry,[150,151] and most extensively by NMR spectroscopic measurements.[108,152−156] Me_2CuLi exists dominantly as a dimeric CIP in Et_2O, while SSIP is the major species for Me_2CuLi and $Me_2CuLi\cdot LiCN$ in THF.[153] The NMR studies in THF also indicated equilibrium between SSIP and CIP. The equilibrium shifts toward SSIP at lower temperatures, as expected from Scheme 3. The effect of a lithium salt on the SSIP−CIP equilibrium turned out to be minor.[108] Extensive analysis of Me_2CuLi (salt-free) and $Me_2CuLi\cdot LiCN$ in Et_2O indicated that both of the cuprates prefer to take a homodimeric CIP core structure, that is, $[Me_2CuLi]_2$,[154] whereas a CN-bridged heterodimeric structure was often suggested by theoretical studies (see Chart 3d for an example of the Br-bridged structure).[111,113−115,145,157]

Diffusion-ordered NMR spectroscopy (DOSY) analyses revealed the complexity of organocuprate aggregate structures beyond the simple CIP−SSIP equilibrium shown in Scheme 3. Thus, DOSY experiments on $\mathrm{Me_2CuLi(\cdot LiX)}$ and $\mathrm{(Me_3SiCH_2)_2CuLi(\cdot LiX)}$ (X = CN, I) in diethyl ether led to a proposal of the presence of oligomeric aggregates such as the structures shown in Chart 4.[155] These model structures consist of homodimeric cores $\mathrm{[R_2CuLi]_2}$, which are bridged by solvent molecules and/or lithium salt molecules. Note that a similar polymeric aggregate structure of a homocuprate $\mathrm{[Li_2Cu_2(CH_2SiMe_3)_4(SMe_2)_2]_\infty}$ (cf. Chart 4a) was determined in crystals. The degree of higher aggregation depends on the steric hindrance, the lithium salt, and the concentration. In particular, the presence of LiCN leads to larger oligomers than occur in its absence, while LiI does not exert significant effects. The proposed major aggregated species of $\mathrm{Me_2CuLi \cdot LiCN}$ consists of two homodimer cores bridged by LiCN units and is about twice the size of $\mathrm{Me_2CuLi \cdot LiI}$, which contains one homodimer core and a LiI unit (Chart 4c).

Chart 4. Structure Models of Higher Aggregates of Gilman Cuprates beyond Dimers



R = $\mathrm{CH_3}$, $\mathrm{CH_2SiMe_3}$; S = solvent molecule; X = I, CN

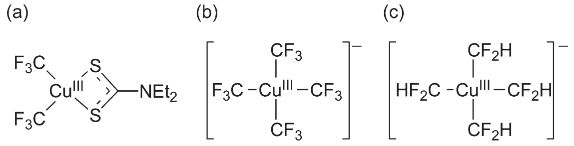
The DOSY studies on $\mathrm{Me_2CuLi \cdot LiI}$ and $\mathrm{Me_2CuLi \cdot LiCN}$ in $\mathrm{Et_2O}$ containing a small amount of THF (0.25−4 equiv) revealed striking effects of the THF molecules on the aggregation levels (and the reactivities, see section 3.3) of the cuprates (Scheme 4).[156] Upon addition of THF, the major aggregate species of $\mathrm{Me_2CuLi \cdot LiI}$ dissociate into the homodimer core and solvated LiI (Scheme 4a), which does not significantly change the size of the cuprate aggregate. On the other hand, THF molecules disaggregate the aggregate species of $\mathrm{Me_2CuLi \cdot LiCN}$ into two homodimer cores (Scheme 4b), which is a significant change in the aggregation level. These studies also revealed the position of the cyanide group of the cyano-Gilman cuprate in solution, which was a subject of long-standing debate.[139]

2.2. Organocopper(III) Complexes

Although tricoordinated organocopper(III) species have been frequently proposed as transient intermediates for a series of nucleophilic organocuprate transformations since the 1970s,[2,5] such species escaped detection for a long time. The neutral triorganocopper(III) complexes are characterized by their T-shaped geometry, as revealed by computational analysis, and are unstable. However, they can be stabilized by addition of a ligand to form a square-planar tetra-coordinated complex.

During the late 1980s to the early 1990s, highly electron-withdrawing polyfluoroalkyl groups such as $\mathrm{CF_3}$ were found to stabilize the Cu(III) oxidation state and make organocopper(III) complexes isolable in the form of tetra-coordinated copper(III) ate complexes (Chart 5). $\mathrm{(CF_3)_2Cu^{III}S_2CNEt_2}$, which was synthesized via oxidation of the cadmium cuprate $\mathrm{[(CF_3)_2Cu][CdI]}$ with *N*,*N*-diethylthiuram disulfide, represents the first example of an isolated organocopper(III) complex (Chart 5a).[158] Tetraorganocuprate(III) complexes such as $\mathrm{[(CF_3)_4Cu^{III}]^-}$ and $\mathrm{[(CF_2H)_4Cu^{III}]^-}$, containing a variety of countercations, have also been synthesized and unambiguously characterized (Chart 5b,c).[159] All of these

Chart 5. Isolated Organocopper(III) Complexes Containing Polyfluoroalkyl Groups



Scheme 4. Proposal of Major Aggregate Species of $\mathrm{Me_2CuLi \cdot LiI}$ (a) and $\mathrm{Me_2CuLi \cdot LiCN}$ (b) in $\mathrm{Et_2O}$ and Their Disaggregation upon Addition of THF

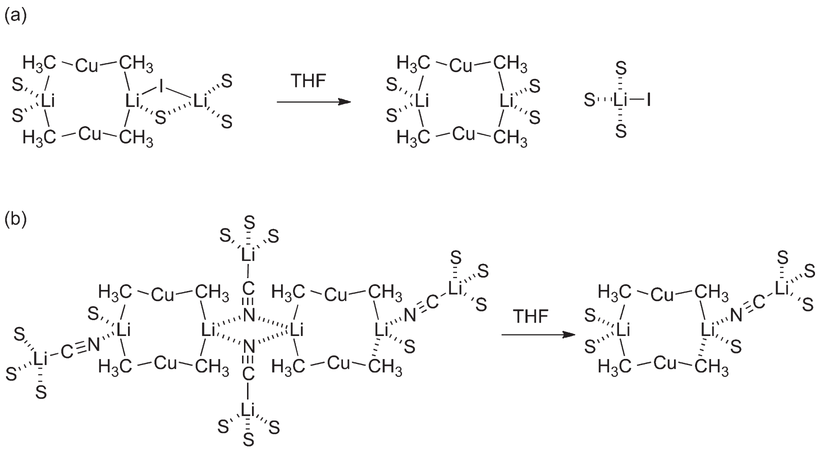


Chart 6. Organocopper(III) Complexes with Macrocyclic Templating Ligands

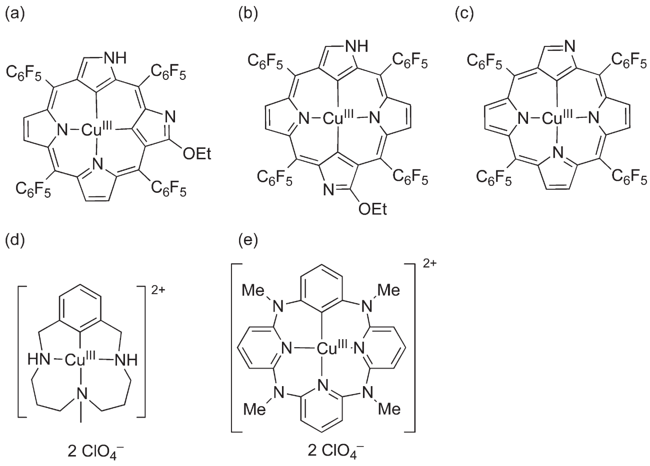
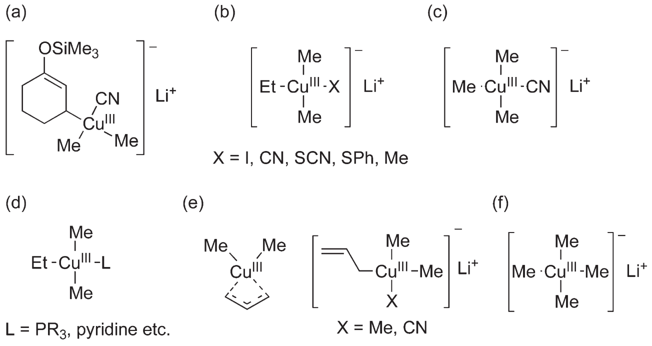


Chart 7. Organocopper(III) Complexes Observed by NMR at Low Temperature



complexes are nearly square planar in geometry, in accordance with the formal d^8 electronic configuration of the copper atom.

The copper(III) species needs a tetra-coordinated geometry, and hence porphyrin or a related macrocyclic compound is an ideal ligand (Chart 6). Representative examples include the Cu(III) complexes derived from *N*-confused porphyrin (Chart 6a−c)[160,161] and triazamacrocyclic arene ligands (Chart 6d,e),[162,163] which were synthesized via aromatic C−H activation with Cu(II) followed by oxidation. The latter complexes have been studied in the context of the reaction mechanism of copper-catalyzed C−N bond formation via Ullmann-type coupling or C−H bond activation.[162c−f]

Theoretical studies in the mid-1990s indicated that a T-shaped trimethylcopper(III) is kinetically unstable and spontaneously undergoes reductive elimination.[164] The trimethylcopper(III) complex can be thermodynamically stabilized by coordination of a fourth ligand, not only a neutral ligand (e.g., Me_2O, Me_2S) or an anion (e.g., Cl^-, CN^-),[165] but interestingly, also by complexation with a Lewis acidic salt (e.g., LiCl, BF_3).[166] Unlike the parent T-shaped copper(III) complexes, the resulting square-planar copper(III) complexes need to overcome a finite activation barrier to undergo reductive elimination and hence can be experimentally detected under appropriate conditions.

Partially stabilized trialkylcopper(III) species that are relevant to synthetic applications have been detected and characterized by NMR with the aid of a judicious choice of the reaction conditions and the instrumental setup, as summarized in Chart 7. In 2007, a trialkylcyanocuprate(III) complex was observed as an intermediate in the conjugate addition of $Me_2CuLi \cdot LiI$ to cyclohexenone in the presence of Me_3SiCN (Chart 7a).[167] The same complex formed in the reaction of $Me_2CuLi \cdot LiCN$ with cyclohexenone in the presence of Me_3SiCl. The structural assignment was supported by a DFT study.[165] In the same year, square-planar copper(III) intermediates relevant to the S_N2 alkylation reaction, that is, *cis*-$[EtMe_2CuX]^-$ (X = I, CN, SCN, SPh, and Me) and $Me_3Cu(CN)^-$, were also observed (Chart 7b,c).[168,169] Neutral trialkylcopper(III) complexes containing a variety of monodentate phosphorus and nitrogen ligands were prepared by ligand exchange and observed at low temperatures (Chart 7d).[170] Furthermore, π- and σ-allylcopper(III) species were detected as intermediates for the allylic substitution reaction (Chart 7e).[171] Even lithium tetramethylcuprate(III) was prepared from a Gilman reagent and 2,3-dichloropropene, which showed high thermal stability (Chart 7f; $t_{1/2}$ = 7 h at 0 °C and 0.75 h at 20 °C).[169c] A complex between a Gilman cuprate and a C═S double bond was also observed, for which a formal Cu(III) oxidation state was indicated.[172]

3. FUNDAMENTAL REACTIVITY OF ORGANOCOPPER COMPOUNDS

This section describes the fundamental reactivities of organocopper compounds that are universally relevant to stoichiometric and catalytic organocopper-mediated C−C bond formations. As mentioned earlier, the nucleophilic organocopper reagents exist in the form of metal organocuprates formulated as R_2CuM (homocuprate) or RCu(X)M (heterocuprate), where R, X, and M stand for a carbanion, a nontransferable (halide, heteroatom, cyanide, etc.) anion, and a Lewis acidic main-group metal cation, respectively. The C−C bond-forming reactions between an organocuprate and an electrophile commonly involve nucleophilic attack of the copper(I) atom on the electrophile (oxidative addition) and reductive elimination of the resulting organocopper(III) intermediate. The oxidative addition step is driven by molecular orbital interactions between the cuprate (R_2Cu^- or $RCu(X)^-$) and the electrophile (sections 3.1 and 3.2) and coordination of the main-group Lewis acid to the electrophile (section 3.3). The reductive elimination step is also important because it is often the rate-determining and/or regio- and stereochemistry-determining step of the reaction (section 3.4). Comparison of organocopper, -silver, and -gold complexes in the context of both the oxidative addition and reductive elimination steps highlights the uniqueness of organocopper reagents (section 3.5).

3.1. Relationship between Geometry and Molecular Orbitals of Diorganocuprate(I)

The correlation between the coordination geometry and the electronic structure of an organocuprate molecule provides the basis for understanding the reactivities of organocuprate reagents (Figure 1).[173] As illustrated in section 2, a diorganocuprate(I) complex is characterized by a linear C−Cu−C coordination geometry. The highest occupied molecular orbital (HOMO) of a linear Me_2Cu^- molecule mainly consists of the copper $3d_{z^2}$ orbital. The $3d_{z^2}$ orbital is highest in energy among the 3d orbitals because of its out-of-phase interaction with the ligand 2p orbitals (Figure 1, left). Importantly, bending of the C−Cu−C geometry not only results in destabilization of the Me_2Cu^- molecule

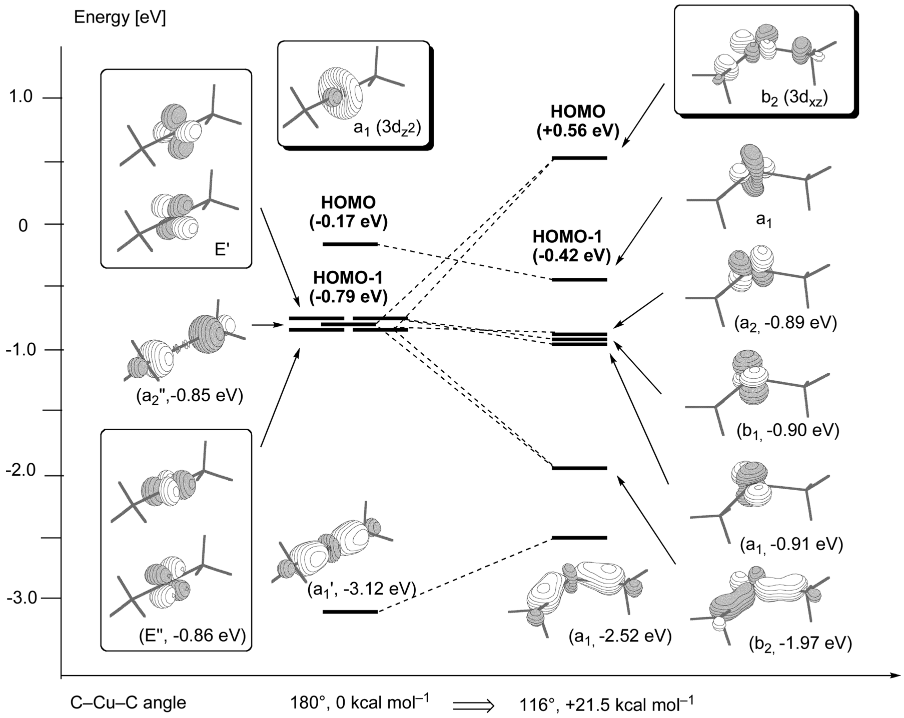


Figure 1. Correlation of the molecular orbital and the C−Cu−C angle of a $(CH_3)_2Cu^-$ molecule (B3LYP/Ahlrichs DZP for Cu, 6-311+G(d,p) for C, H//B3LYP/Ahlrichs SVP for Cu, 6-31G(d) for C, H). Adapted with permission from ref 13c. Copyright 2009 John Wiley & Sons.

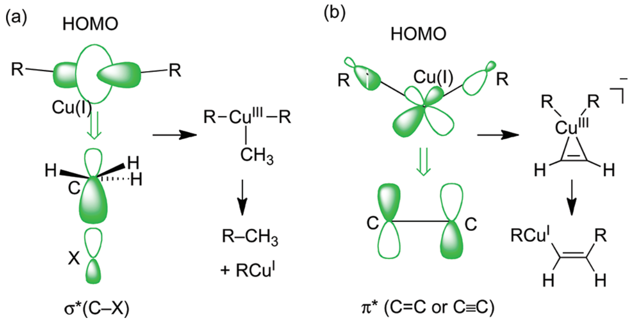
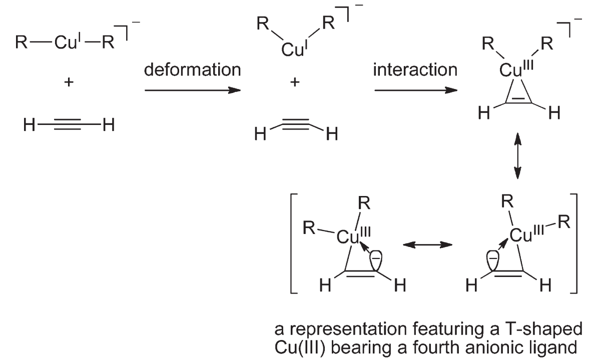


Figure 2. Schematic representations of orbital interactions between R_2Cu^- and electrophiles. (a) Interaction with an alkyl halide. (b) Interaction with an olefin or an acetylene. The back-donative interaction is color coded in green, while red is used to indicate donative interaction (vide infra).

Scheme 5. Deformation/Interaction Scheme to Understand π-Complex Formation



because of deformation (ca. 20 kcal/mol increase in energy at a bond angle of 113°) but also causes mixing of the copper $3d_{xz}$ orbital with the ligand 2p orbitals (Figure 1, right). This orbital mixing raises the energy level of the $3d_{xz}$ orbital and hence makes it the HOMO when the C−Cu−C angle < 150°. Thus, the HOMOs of linear (ground state) and bent Me_2Cu^- molecules are entirely different in terms of orbital symmetry. Note that the 20 kcal/mol energy required to cause all of these events is in the energy range that can be achieved below room temperature. Note also that, if the Me_2Cu^- motif is a part of an aggregate, the deformation energy may be compensated to some extent due to reorganization of the cluster structure.

3.2. Frontier Orbital Interaction with Electrophiles

A back-donative frontier orbital interaction between the HOMO of an organocuprate reagent and the lowest unoccupied molecular orbital (LUMO) of an electrophile is a critical driving force for the oxidative addition of the electrophile to the organocuprate.[13,173,174] For effective interaction, the HOMO and LUMO must have the same orbital symmetry to achieve an in-phase interaction. Below is detailed how an organocuprate molecule undergoes frontier orbital interaction with a series of common electrophiles.

3.2.1. σ^*- and π^*-Systems: S_N2 Alkylation and Carbocupration. The above MO analysis of Me_2Cu^- illustrates a strong correlation between the geometry and the nucleophilic reactivities of an organocuprate(I) anion.[173] In the ground-state (linear) geometry, the R_2Cu^- molecule has a HOMO mainly consisting of the $3d_{z^2}$ orbital, the symmetry of which is suitable for interaction with the σ^* orbital of a C−X (X = halogen or heteroatom) bond (Figure 2a). With this symmetry, however, the HOMO cannot interact with the π^* orbital of C=C double

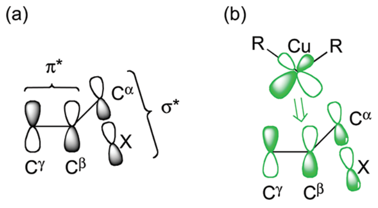


Figure 3. Schematic representations of π^*/σ^* mixed orbital of an allylic electrophile (a) and its interaction with R_2Cu^- (b).

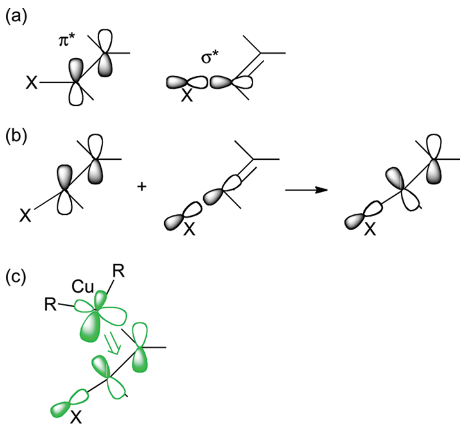


Figure 4. Schematic representations of C═C π^*, C−X σ^*, and their mixed orbitals of an alkenyl electrophile (a, b) and interaction of the mixed orbital with R_2Cu^- (c).

or C≡C triple bonds. Note that thermal vibration can cause bending of the R−Cu−R bond and raise the low-lying $3d_{xz}$ orbital to a new HOMO (Figure 1). This new HOMO has the correct symmetry to achieve an in-phase interaction with the π^* orbital (Figure 2b),[175] a typical case of Dewar−Chatt−Duncanson (DCD) d−π^* back-donation.[97] It must be emphasized, therefore, that the frozen, ground-state geometry of an organocuprate reagent as found by experiments and calculations does not necessarily represent a reactive form of the reagent but provides only the foundation for analysis of the reactive species in solution.

The bent R−Cu−R is a common feature of π-complexes between organocuprates and unsaturated molecules. The π-complexation can be analyzed conceptually as a two-step process in a manner described in the energy decomposition analysis by Morokuma and Kitaura (Scheme 5).[176] The first step is bending of the ground-state geometries of both reactants, for example, the organocuprate and acetylene in this example. Second, the bent reactants mutually expose the HOMO (copper) and LUMO (π^*) of appropriate orbital symmetry to form the π-complex. For any reactions that actually take place in experiments, this favorable interaction compensates the energy loss because of the deformation. The deformation/interaction scheme is useful for the analysis of organocopper complexes as well as other organo-transition metal complexes.[177] Parenthetically, we can see the product π-complex as a resonance form of a T-shaped Cu(III) intermediate stabilized by the neighboring vinylic anion.

In summary, the d_{z^2} orbital is ideally disposed for interaction with the σ^* orbital of an alkyl halide, while the d_{xz} orbital is ideally disposed to interact with the π^* orbital and form a typical DCD-donation/back-donation complex. Regardless of the trans-(Figure 2a) or cis-relationship (Figure 2b, Scheme 5) between the two R ligands in the Cu(III) product, the oxidative addition results in formation of a T-shaped organocopper(III) intermediate. The R ligand and the neighboring cis group undergo coupling (reductive elimination) to afford a C−C bond-formation product (vide infra).

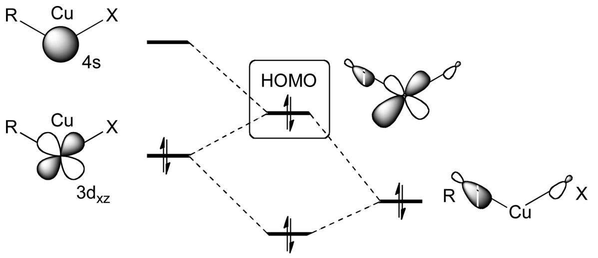


Figure 5. Desymmetrization of the HOMO of a heterocuprate in the bent geometry.

3.2.2. π^*/σ^*-Mixed Systems: Substitution of Allylic and Alkenyl Halides.

The initial interaction of an allylic halide system with an organocuprate is similar to that of an olefin or an alkyne. Thus, when the C═C π^* and C−X σ^* orbitals are aligned with each other, in-phase mixing of the C═C π^* and C−X σ^* orbitals creates a new LUMO (Figure 3a), which is lower in energy than the π^* and σ^* orbitals themselves and is suitable for the intereaction with the $3d_{xz}$ orbital of a bent R_2Cu^- molecule. This frontier molecular orbital (FMO) interaction is the major driving force for the C−X bond cleavage and the reorganization of the π-bond in the allylic substitution reaction (Figure 3b).[178]

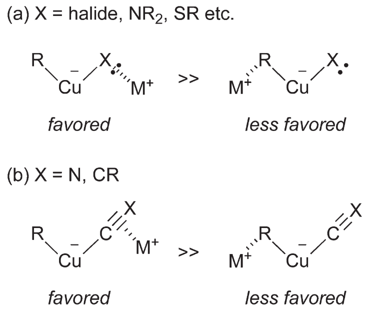
The C═C π^* and C−X σ^* orbitals in an alkenyl halide are orthogonal to each other and hence cannot interact with each other in the ground state (Figure 4a), and the mixing of π^* and σ^* orbitals in a bent conformation plays an important role. When the C−X bond is bent with respect to the π plane, the C═C π^* and C−X σ^* orbitals can mix with each other (Figure 4b). The interaction of the mixed orbital and the $3d_{xz}$ orbital of a bent R_2Cu^- molecule is the major driving force for the cleavage of the C−X bond (Figure 4c).[179] Note that this argument applies to other transition metal-catalyzed alkenyl−X bond cleavages.[92]

3.3. Roles of Nontransferable Ligand, Countercation, and Aggregation Structure

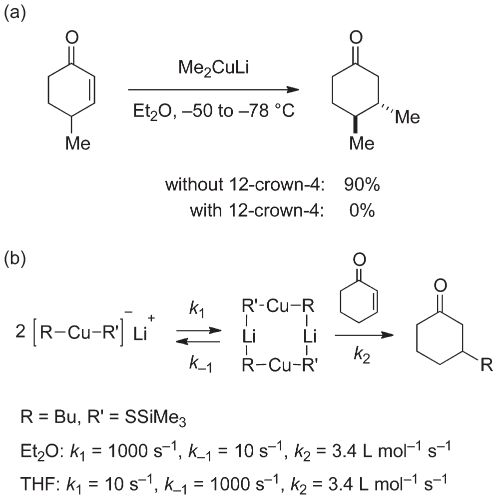
The same FMO interactions described for a homocuprate in the previous section are also applicable to the chemistry of heterocuprates RCu(X)M, although there are three issues that need special attention.[178,180] The first is the lower σ-donor ability of the most nontransferable ligands (X) than alkyl (and alkenyl, aryl, etc.) carbanions (R); the second is the lower symmetry of R−Cu−X compared with R−Cu−R; and the third is the Lewis basicity, which allows strong coordination of the X group with the Lewis acidic countercation M.

The first consequence of the lower σ-donor ability is the lower nucleophilicity. The second and more important consequence is the desymmetrization of the HOMO of $RCu(X)^-$ in the bent geometry, as schematically illustrated in Figure 5. Because R has a higher σ-donor ability than X, the R orbital contributes to a greater extent to the out-of-phase interaction with the $3d_{xz}$ orbital. The empty Cu 4s orbital then mixes with the $3d_{xz}$ orbital so that it weakens the out-of-phase interaction between the $3d_{xz}$ and the R orbitals. Thus, the HOMO becomes more extended in the direction opposite to that of the X ligand. This orbital dissymmetry plays a critical role in the regioselectivity of some

Scheme 6. Interaction of Heterocuprate with Lewis Acidic Countercation



Scheme 7. Effects of Additive and Solvent on Conjugate Addition



without 12-crown-4: 90%
with 12-crown-4: 0%

R = Bu, R' = $SSiMe_3$

Et_2O: $k_1 = 1000\ s^{-1}$, $k_{-1} = 10\ s^{-1}$, $k_2 = 3.4\ L\ mol^{-1}\ s^{-1}$

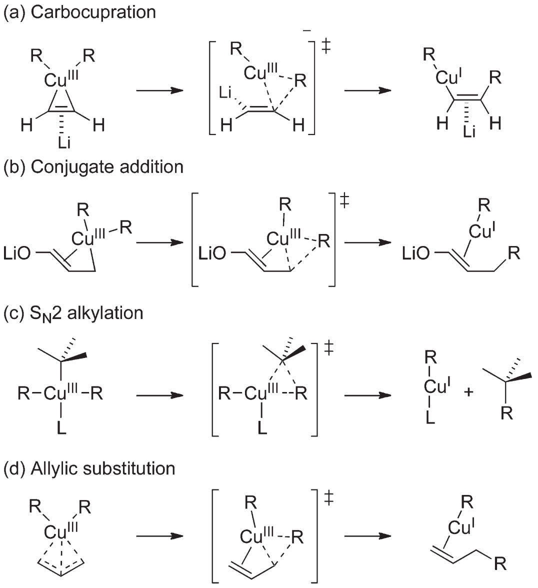
THF: $k_1 = 10\ s^{-1}$, $k_{-1} = 1000\ s^{-1}$, $k_2 = 3.4\ L\ mol^{-1}\ s^{-1}$

reactions, for example, S_N2'-selective allylation with a heterocuprate (see section 5.2).[178]

The ability of nontransferable ligands to strongly coordinate to a main-group metal cation is the final issue. Halides and heteroatom anions have lone pairs suitable for such coordination, while for cyanide and acetylide ligands, π-electrons are available (Scheme 6). Thus, those nontransferable anions, having a better ability to bridge the copper atom and the main-group metal cation, can play decisive roles in the aggregation as well as the regio- and stereoselectivity. The conjugate addition of heterocuprates is an illustrative example where this feature is pronounced (see section 6.3.1).[180]

In addition to the FMO interactions that provide a fundamental driving force for the reaction, the countercations and the aggregation structures of the organocuprate reagents are also critical. For example, a crown ether (12-crown-4) destroys the Lewis acidity of a lithium cation and stops the conjugate addition reaction of a lithium cuprate (Scheme 7a).[181] This retardation effect was also observed for carbocupration[85] and S_N2 alkylation.[182] Similarly, the solvent used for the reaction affects the equilibrium between CIP and SSIP (Scheme 3) and thus affects the reaction rate. As illustrated in Scheme 7b, the conjugate addition reaction in Et_2O is faster than that in THF because of the higher concentration of the reactive CIP species.[108,183,184] Because the sodium cation is not Lewis acidic, sodium organocuprates are too poorly reactive to be used for conjugate addition.[185] The cooperative effects of the Lewis acidic metal cation and the cuprate(I) nucleophilic center will be discussed in more detail in sections 4 and 5.

Scheme 8. Schematic Illustrations of Organocopper(III) Complexes and Their Reductive Elimination Involved in Representative Organocopper Reactions



The reality of the solvent effect appears to be more complex than the simple CIP–SSIP model shown in Scheme 3.[156] The reaction rate of the conjugate addition of $Me_2CuLi\cdot LiI$ to 4,4-dimethyl-cyclohex-2-enone in Et_2O increases upon addition of a small amount of THF (0.25–1 equiv), while further addition decreases the reaction rate. On the other hand, the reaction of $Me_2CuLi\cdot LiCN$, which is faster than that of $Me_2CuLi\cdot LiI$ in pure Et_2O, monotonically slows down upon addition of THF. The different reactivities of the iodo- and cyano-Gilman cuprates have been ascribed to the difference in the aggregate structures in Et_2O and in their disaggregation processes in THF (Scheme 4).

Modulation of reactivity and selectivity of organocopper reagents by introduction of unconventional metal cations has been of great synthetic and mechanistic interest. Acceleration of conjugate addition[42] and epoxide-opening[186] reactions by $BF_3\cdot OEt_2$ are early examples. The origin of the BF_3 effect is discussed in section 6.1. Another notable case is the improved S_N2'-selectivity found in the allylation reactions using organocopper reagents derived from organozinc,[53] -titanium,[56] and -aluminum[187] reagents rather than lithium organocuprates. Higher S_N2'-selectivity is also often achieved in catalytic (asymmetric) allylation reactions using a (chiral) copper catalyst and Grignard, organozinc, and -aluminum reagents.[64,65] These organometallic reagents, being much less nucleophilic than organolithium reagents, are likely to generate heterocuprates (RCu(X)M) rather than homocuprates (R_2CuM) as reactive species (cf. Scheme 2). The S_N2'-selectivity is now considered to originate largely from the dissymmetric HOMO of heterocuprates (Figure 5; see section 5.2).[178]

3.4. Reductive Elimination of Organocopper(III) Intermediates

It is now established that the organocopper(III) complex is an important intermediate that is formed by oxidative addition of an

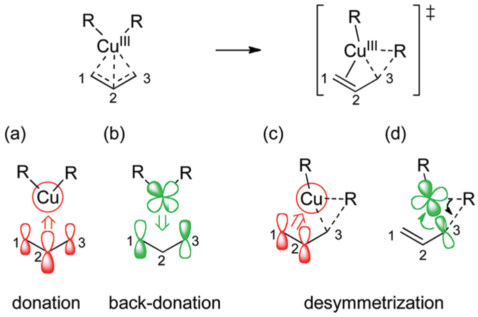


Figure 6. FMO interactions involved in π-allylcopper(III) complex and its reductive elimination. Donation and back-donation interactions are color coded in red and in green, respectively.

electrophilic substrate to an organocuprate(I). Theoretical studies demonstrated that a T-shaped trialkylcopper(III) species is kinetically very unstable and undergoes reductive elimination without an energy barrier but can be stabilized by a donative ligand added to form a stable square-planar complex.[164−166] In agreement with this theoretical prediction, recent experimental and theoretical studies invariably identified a square-planar organocopper(III) complex as a reactive intermediate. Scheme 8 illustrates generic structures of organocopper(III) intermediates involved in representative organocopper reactions, that is, carbocupration (a),[85] conjugate addition (b),[86,89,188] S_N2 alkylation (c),[168−170,182] and allylic substitution (d),[171,178,189] and shows how they undergo reductive elimination to form a new C−C bond. The donor ligand L in the alkylation reaction may be either neutral or anionic.

Molecular orbital interactions involved in an organocopper(III) complex and its reductive elimination transition state (TS) are illustrated for the allylic substitution in Figure 6.[180b,189] The copper−allyl bonding interaction in the π-allylcopper(III) complex consists of allyl-to-copper donation (in-phase π orbital to vacant 4s orbital) and copper-to-allyl back-donation ($3d_{xz}$ orbital to nonbonding π orbital). Toward the reductive elimination TS, the complex desymmetrizes to an enyl [$\sigma + \pi$]-like structure,[190] where the copper atom is σ-bonded to the C3 atom (i.e., back-donation) and coordinated by the C1−C2 π-bond (i.e., donation). Therefore, the reductive elimination is a process in which the copper atom recovers its d-electrons from the Cu−C3 σ-bond while delivering the R ligand to the C3 atom. As such, the formal Cu(III) center becomes reduced to Cu(I).

3.5. Comparison with Organosilver and -Gold Analogues

In contrast to the versatility of copper(I) in organic synthesis, silver(I) and gold(I) located in the same Group 11 have seldom been used as nucleophilic reagents.[191,192] Organosilver(I) compounds are thermally too unstable in solution to be useful.[193] Organoaurate(I) is intrinsically less nucleophilic, and organogold(III) complexes are too stable to undergo reductive elimination as quickly as organocopper(III) species.[194−196] The results of gas-phase experiments have been in line with these trends observed in synthetic studies. Thus, among dimethylcuprate(I),[197] -argentate(I),[198] and -aurate(I),[199] which form through decarboxylation of the corresponding carboxylates and exist as stable species in the gas phase, only dimethylcuprate(I) undergoes a nucleophilic substitution reaction with methyl iodide and allyl iodide.[193d,199,200]

Systematic theoretical studies on organocuprate(I), -argentate(I), -aurate(I), and organocopper(III), -silver(III), and -gold(III) complexes shed light on the origin of the high reactivity of

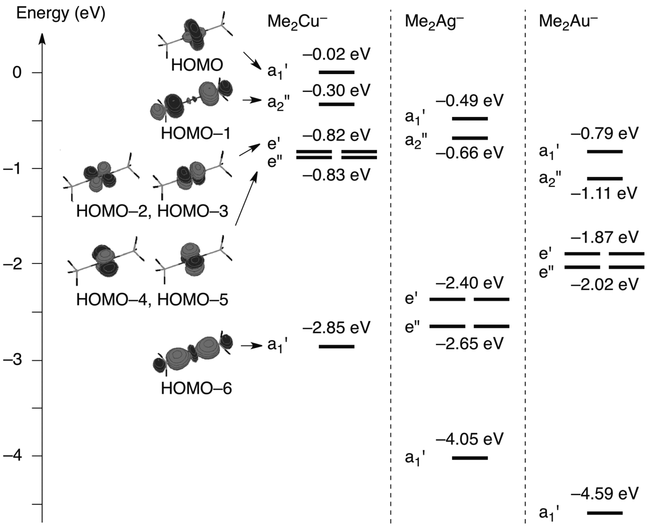
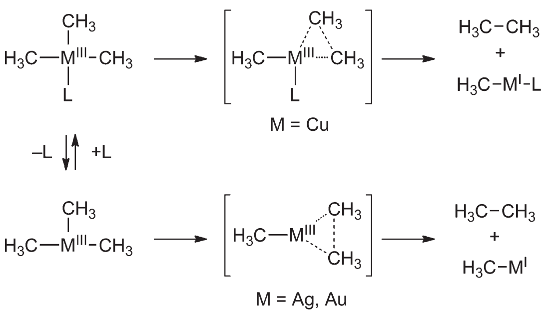


Figure 7. High-lying Kohn−Sham orbitals of $(CH_3)_2Cu^-$, $(CH_3)_2Ag^-$, and $(CH_3)_2Au^-$.

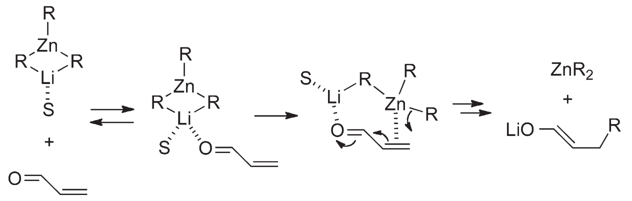
Scheme 9. Reductive Elimination of $(CH_3)_3M^{III}\cdot L$ Complexes (M = Cu, Ag, Au)



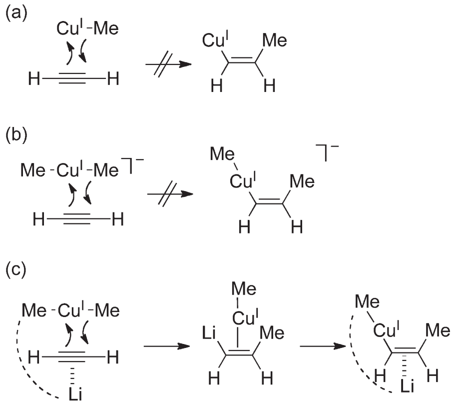
organocuprate reagents as nucleophiles.[94] The high-lying 3d orbitals of copper are responsible for the high nucleophilicity of the copper(I) reagents, while the 4d and 5d orbitals of silver(I) and gold(I) are intrinsically low-lying (Figure 7). The lower energy levels of the 4d and 5d orbitals compared with the 3d orbital arise from the smaller d−d electron repulsions for the diffuse 4d and 5d orbitals than for the contracted 3d orbitals.[201] The difference in the magnitude of d−d repulsions increases from the early to the late transition metals and hence is significant for the Group 11 metals. Note that the 4d and 5d orbitals are rather close in energy. This is due to the relativistic effect raising the energy levels of the 5d orbitals of gold.[202,203]

Another origin of the poor reactivities of organosilver and -gold reagents is the stability of the high-valent intermediates, that is, triorganosilver(III) and -gold(III) complexes. The $R_3Ag(III)$ and $R_3Au(III)$-type complexes undergo reductive elimination less readily than the corresponding Cu(III) complex. Most notably, the reaction pathway for the reductive elimination of a triorganocopper(III) complex is different from that of triorganosilver(III) and -gold(III) complexes (Scheme 9). The reductive elimination of the $R_3Cu(III)\cdot L$ (L = PMe_3) complex occurs with retention of the ligand L. On the other hand, dissociation of the ligand L precedes the reductive elimination of the $R_3Ag(III)\cdot L$ and $R_3Au(III)\cdot L$ complexes, which goes through a Y-shaped TS. This theoretical picture supports an earlier suggestion based on experiments.[195]

Scheme 10. Reaction Pathway of Conjugate Addition of Organozincate to α,β-Unsaturated Carbonyl Compounds



Scheme 11. Three Models of Carbocupration of Acetylene



The higher stability of the gold(III) intermediate partly results from the higher stability of the carbon−gold bond than the carbon−copper bond, which is due to the high relativistic effect in gold.

The difference between organocuprate(I) and organozinc(II) complexes also merits some discussion.[173b] Although isoelectronic to Me_2Cu^-, Me_2Zn has much lower-lying 3d orbitals than Me_2Cu^-. In fact, the energy levels of the zinc 3d orbitals are much lower than the 2p orbital of the methyl ligands. The energy gap is so large that the HOMO of Me_2Zn mainly consists of the methyl 2p orbital. The methyl 2p orbital still represents the HOMO of Me_3Zn^- and Me_4Zn^{2-}, although its energy level increases as the number of the methyl ligands increases.[204,205] In this context, the reactivity of organozincate reagents was also theoretically studied. For instance, while organozincate reagents undergo conjugate addition to α,β-unsaturated carbonyl compounds,[206] the Zn(II) atom acts as a Lewis acid to the C═C bond and the low-lying 3d orbitals of zinc do not play any nucleophilic role in the reaction (Scheme 10).

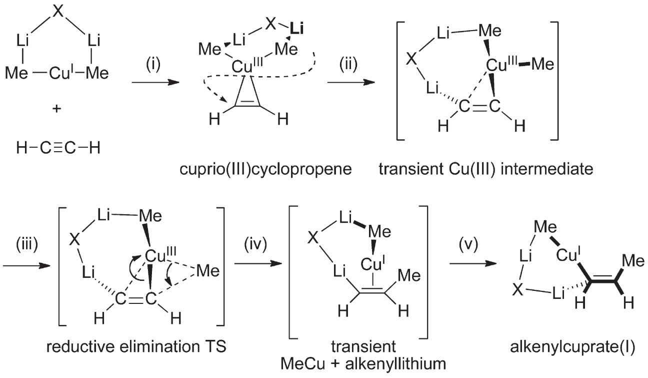
4. ADDITION REACTIONS

Addition reactions across carbon−carbon double and triple bonds represent the archetypal reactivity of organocuprate(I) reagents and therefore are described below in some details. The addition of Me_2CuLi to acetylene is a well-known reaction and may appear to be the simplest model for a mechanistic study. This simplicity was found to be deceptive.

4.1. Carbocupration Reactions of Alkynes

4.1.1. Carbocupration of Acetylene. The addition of an organocuprate across an alkyne, known as "carbocupration", provides a reliable stereoselective route to *cis*-alkenylcopper(I) species, which can participate in further C−C bond formation as an alkenyl nucleophile.[33,207,208] Like other organocuprate reactions, a crown ether dramatically slows down the reaction by strong coordination to the lithium cation.[85] Apparently, the carbocupration reaction is a 1,2-addition reaction of R−Cu(I) across the C≡C triple bond without redox reaction of the copper center.[209,210] However, computational modeling of the addition of MeCu across acetylene (Scheme 11a) results in an unacceptably high activation energy (>40 kcal/mol) because the strong Me−Cu(I) bond (bond dissociation energy = 55 kcal/mol)[211] needs to be directly cleaved.[84a,85] The activation energy becomes much lower (≈20 kcal/mol) with Me_2Cu^- (Scheme 11b) and even lower (≈15 kcal/mol) when a Lewis acidic lithium atom is also allowed to be coordinated on the π-bond not engaged in bonding to the copper atom (Scheme 11c). In the latter case, the reaction course changes because of electron flow from the 3d orbital of the copper atom, and the addition of Me_2Cu^- (but not MeCu) occurs smoothly. Details are discussed below.

Scheme 12. Reaction Pathway for the Carbocupration of Acetylene with $Me_2CuLi\cdot LiX$ (X = a Variety of Anionic Groups)



The presence of a Lewis acidic lithium cation in Scheme 11c is mandatory for the reaction of a lithium organocuprate cluster such as Me_2CuLi dimer or $Me_2CuLi\cdot LiCl$ (Scheme 12).[85] First, the cuprate forms a complex with acetylene through donation/back-donation interactions (step i). The resulting cuprio(III) cyclopropene intermediate, assisted by coordination of the lithium cation to the olefinic π-bond, undergoes reductive elimination to form a C−C bond (steps ii−iv). The first product that forms transiently on the potential surface is a complex of MeCu and vinyllithium, which then undergoes transmetalation (step v) to give the expected vinyl methyl cuprate(I) product. Although the formation of the vinyllithium transient intermediate looks surprising, it is a logical consequence of the reductive elimination reaction (step iv) and serves as an important link to the conjugate addition reaction in which MeCu and lithium enolate forms as the final product.

The DCD character of the cuprio(III)cyclopropene intermediate is evident from its localized molecular orbitals (LMOs), which represent donation of the π-electrons of acetylene to copper (Figure 8a, LMO1) and back-donation of the $3d_{xz}$ electrons of copper to the π^* orbital of acetylene (LMO2). The intrinsically electron-deficient character of sp carbons is responsible for the strong back-donation, which allows the formation of the cuprio(III)cyclopropene. Upon going to the TS (Figure 8b), the whole structure becomes desymmetrized. LMO1 in the π-complex becomes LMO3, responsible for bonding with the lithium atom, and LMO2 becomes LMO4 for bonding with the copper atom. LMO5 represents C−C bond formation between the incoming methyl group and the acetylenic carbon C^2.

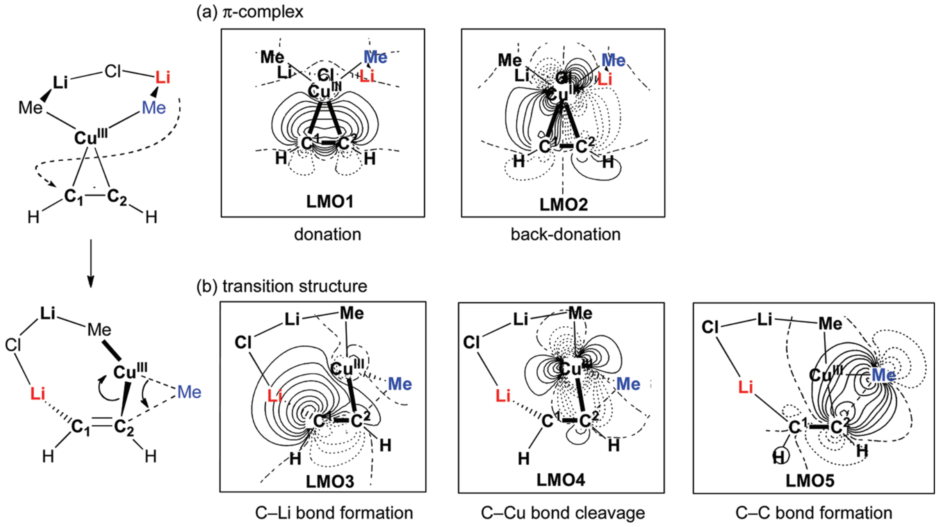
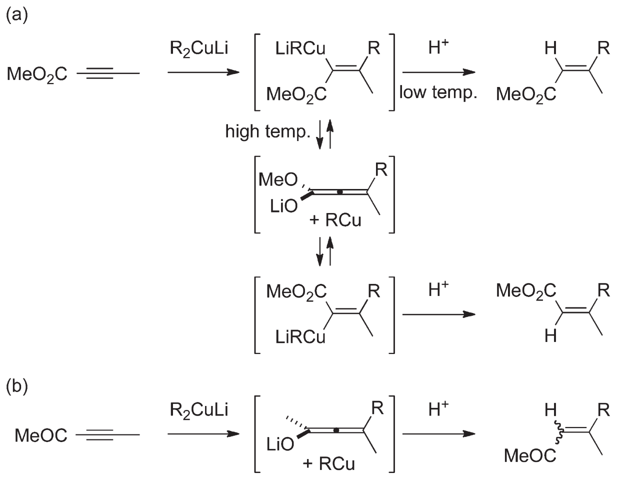
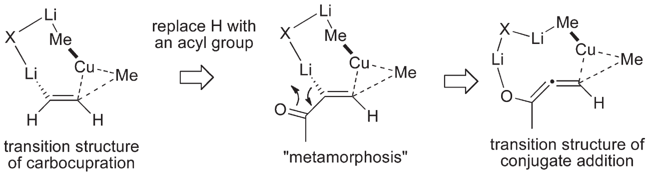


Figure 8. Localized Kohn–Sham orbitals of the complex between Me$_2$CuLi·LiCl and acetylene. Positions of the lithium and chlorine atoms are not indicated for clarity. Migration of the lithium atom indicated by a broken arrow should occur readily in solution.

Scheme 13. Addition of Organocuprate to Acetylenic Ester and Ketone



Scheme 14. Metamorphosis of Carbocupration into Conjugate Addition



Besides simple and heteroatom-substituted alkynes,[208] 1,2-dienes,[212] 1,3-dienes,[213] enynes,[214] and cyclopropenes[215] can participate in the carbocupration reaction without activation by electron-withdrawing substituents. Their reaction mechanisms remain unexplored but are likely to involve oxidative addition/reductive elimination sequences. Simple, unactivated olefins are not electron deficient enough to allow facile back-donation and hence are not reactive.

4.1.2. Addition to Acetylenic Carbonyl Compounds.

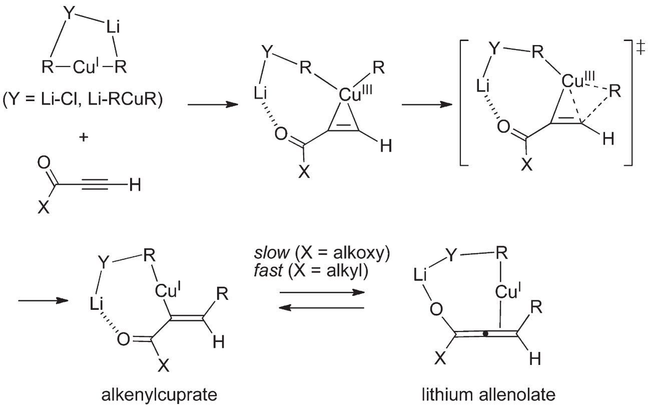
Addition of an organocuprate(I) reagent to an ynoate and an ynone has long been a mystery because of its chameleon reactivity, behaving like a stereoselective *syn*-carbocupration or a nonstereoselective conjugate addition (Scheme 13). Theory puts these two pathways into a single framework, hence revealing a mechanistic link between the two reactions that were once considered to be two different reactions.

Addition of a lithium organocuprate to an acetylenic ester (ynoate) followed by protonation affords an α,β-unsaturated ester with *syn*-stereoselectivity at low temperature (typically −78 °C), while the reaction at higher temperature (e.g., 0 °C) leads to an E/Z mixture (Scheme 13a).[32,216] The stereoselectivity is also affected by other factors, such as the solvent and the composition of the cuprate reagent.[217] Thus, the reaction is considered to proceed through a *syn*-carbocupration pathway, while the resulting alkenylcuprate may undergo E/Z isomerization via an allenolate species. The formation of alkenylcuprates was confirmed by NMR spectroscopy for a few cases.[217] On the other hand, the reaction of an acetylenic ketone (ynone) often gives an E/Z mixture of an α,β-unsaturated ketone in a rather uncontrollable manner (Scheme 13b).[53,218] This suggests a lithium allenolate as the major intermediate, which may be derived from an alkenylcuprate initially formed via carbocupration. The allenolate intermediate was also confirmed experimentally for some cases.[217,218a]

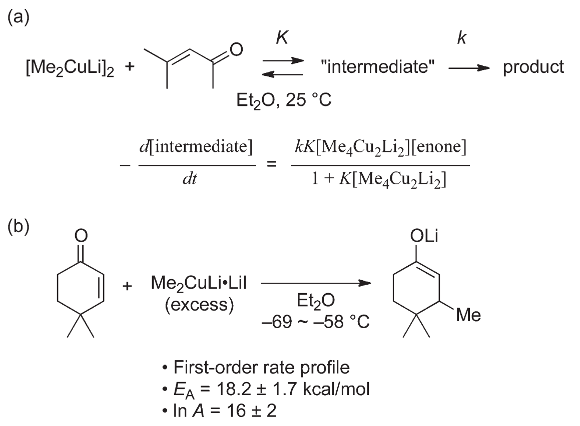
Scheme 13 suggests a strong connection between the carbocupration and the conjugate addition, which leads to a small thought experiment that can be easily tested in silico (Scheme 14). What would happen if one replaces an acetylenic hydrogen atom in the transition structure of the carbocupration? Would this operation generate an α-lithio ketone that should undergo metamorphosis to create the TS of the conjugate addition? A brief computational optimization readily proves that this is indeed the case.

Theoretical analysis of the whole reaction pathway provided a unified mechanistic picture for the above transformations (Scheme 15).[219] The reactions were found to be *syn*-selective carbocupration reactions, and the loss of the stereoselectivity through formation of a lithium allenolate species occurs readily in the ynone reaction, while it is slow in the ynoate reaction. The alkenylcopper product in the ynoate reaction is not only

Scheme 15. Reaction Pathways of Organocuprate Addition to Alkynyl Carbonyl Compounds



Scheme 16. Kinetic Studies on Cuprate Conjugate Addition

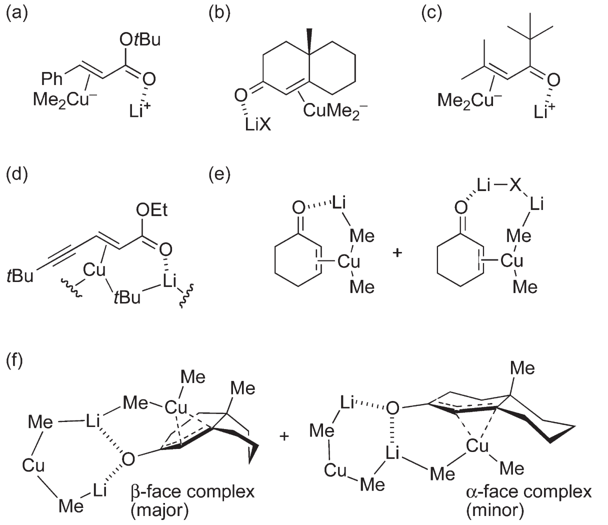


thermodynamically more stable than the allenolate, but the activation energy to the latter is quite high because of the kinetic stability of the C−Cu(I) bond. On the other hand, in the ynone reaction, the allenolate is thermodynamically as stable as the alkenylcuprate and the barrier connecting the two is small. The computational results account for the experimental observations very well. Note that the regioselectivity of carbocupration of a heteroatom-substituted alkyne is generally controlled by electrostatic interaction in the TS, where the mode of polarization of the acetylenic triple bond plays a decisive role.[82a,208] For example, an alkynyl ether affords a branched adduct because of mesomeric electron donation of the oxygen group,[220] while an inductive effect of a silicon substituent gives rise to linear selectivity.[221]

4.2. Conjugate Addition Reactions

4.2.1. Conjugate Addition to Enones. The conjugate addition reaction of organocuprates to enones and related α,β-unsaturated carbonyl compounds is undoubtedly the most versatile organocopper reaction and among the most useful C−C bond-forming reactions in organic synthesis. The mechanism of this reaction, among many organocuprate reactions, has been most extensively studied. The first kinetic study on the cuprate conjugate addition was performed on the reaction of Me_2CuLi and mesityl oxide in Et_2O, which exhibited first-order dependence on the enone concentration and more complex dependence on the cuprate dimer concentration (Scheme 16a).[222]

Chart 8. Representative π-Complexes between Cuprates and α,β-Unsaturated Carbonyl Compounds Proposed on the Basis of NMR Studies

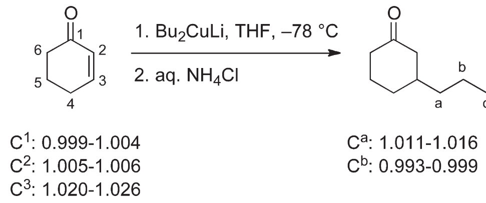


The observed kinetics suggests a mechanism involving reversible formation of a cuprate−enone complex followed by unimolecular conversion of the intermediate to the product. The experiments were performed at a synthetically unusual temperature (25 °C) at which the cuprate undergoes thermal decomposition. Kinetics experiments under synthetically more relevant conditions (−69 to −58 °C) were later performed on the reaction of 4,4-dimethylcyclohexen-2-one and $Me_2CuLi\cdot LiI$ in Et_2O (Scheme 16b).[223] In the presence of an excess amount of the cuprate (≥2 equiv), the reaction rate exhibited first-order behavior (i.e., not affected by the cuprate concentration), indicating the intramolecular nature of the rate-determining step. The activation energy was determined to be ca. 18 kcal/mol. The magnitude of the preexponential term (ln A = 16) also supports the intramolecular nature of the reaction.[224]

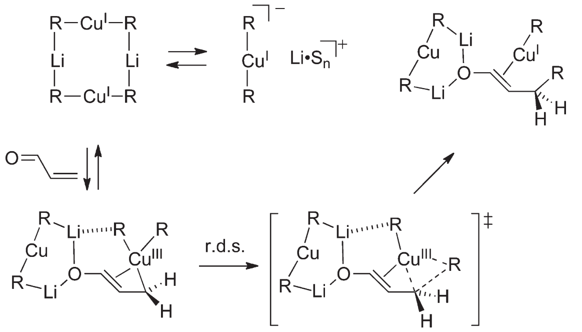
Several NMR studies on the intermediate complexes between organocuprates and α,β-unsaturated carbonyl compounds have been reported (Chart 8).[188,225−234] The common structural feature reported in these studies is a loosening of the C═C bond in the π-complex, which was ascribed to π-complexation with the copper atom. Coordination of the carbonyl oxygen to the lithium atom was also indicated. While complexation of both the copper and lithium atoms was indicated, details of the aggregation structures of the cuprate−enone (enoate) complexes remained unclear with a few exceptions. Studies on the π-complexation between $Me_2CuLi\cdot LiX$ (X = I, CN) and 2-cyclohexenone in THF by the rapid-injection NMR technique led to a proposal of two types of cuprate−enone π-complexes (Chart 8e).[230] In another example, the aggregation structure of the complex between $Me_2CuLi(\cdot LiX)$ and 10-methyl-$\Delta^{1,9}$-2-octalone in Et_2O was studied in great detail (Chart 8f; see also Chart 8b).[188,226] Thus, the presence of major (β-face) and minor (α-face) complexes was found, while the product analysis indicated exclusive methyl delivery from the β-face.[235] Importantly, this observation was achieved in Et_2O, which is synthetically the most common solvent for standard conjugate addition, while most of the other NMR studies were performed in THF.

Kinetic isotope effects (KIEs) provided valuable mechanistic information on the rate-determining step of the reaction.

Scheme 17. ^{13}C KIEs for Conjugate Addition of Bu_2CuLi to 2-Cyclohexenone



Scheme 18. General Reaction Pathway of Organocuprate Conjugate Addition (S = Ethereal Solvent)[a]



[a] Coordinating solvent molecules on lithium atoms are omitted for clarity.

The reaction of Bu_2CuLi and 2-cyclohexanone exhibited significant ^{13}C KIEs on the β-carbon atom (C^3) of the enone and the α-carbon (C^a) of the incoming butyl group, while KIEs on the rest of the carbon atoms were much smaller or negligible (Scheme 17).[236] This result strongly supports that the C—C bond-forming reductive elimination of an organocopper(III) intermediate is the rate-determining step of the reaction.

A general mechanistic picture of the reaction consistent with the accumulated experimental observations has been established through a series of theoretical studies (Scheme 18).[86,89] While the reaction involves complicated equilibrium processes of the cuprate cluster (e.g., aggregation/disaggregation, structural reorganization, and complexation/decomplexation), the most important steps are oxidative addition of an enone to the cuprate to form a β-cuprio(III)enolate, and its reductive elimination to afford the conjugate adduct. The latter step requires the highest activation energy and hence is the rate- and stereochemistry-determining step. Snapshots of reductive elimination process in conjugate addition of Me_2CuLi to methyl vinyl ketone are shown in Figure 9 (see the Supporting Information for a movie).

From a molecular orbital point of view, the conjugate addition reaction represents a typical transition metal/olefin reaction. One can draw a pair of symmetrical donation and back-donation schemes for Me_2Cu^- and ethylene (Figure 10a), which however does not happen because ethylene is not electron deficient enough to accept the d-electrons from copper. α,β-Unsaturated ketones on the other hand do form π-complexes, in which the donation/back-donation scheme is unsymmetrical, as shown in Figure 10b. One can view this π-complex also as a T-shaped Cu(III) complex containing an enolate moiety as a fourth ligand in a square-planar coordination sphere. Thus, the cuprate—enone π-complex (Chart 8) and the β-cuprio(III)enolate are different representations of the same species. For the reductive elimination to take place, the Cu(III) center has to recover its d-electrons specifically from the Cu—C(β) bond, because the two electrons localized in this bond have largely originated from the copper atom (Figure 10c). This process generates a vacant orbital on the C(β) atom, which is ready to accept the incoming R ligand to form the C—C bond. A similar reasoning was already advanced in Figure 8 for carbocupration.

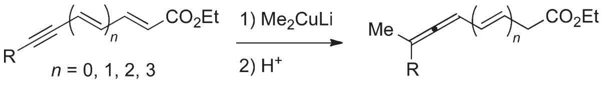
Besides the d—π* interaction, the lithium atom in the organocuprate cluster also plays an important role in facilitating the oxidative addition of the cuprate. As mentioned in section 3.3, the importance of the lithium atoms and the cluster structure has been demonstrated experimentally.[108,181] Note that evaluation of the solvation of lithium atoms is critical for the theoretical prediction of activation energies and KIEs (see Figure 11).[89]

Given the accepted wisdom that a Cu(I) center prefers to form a π-complex with a C═C bond rather than with a C═O bond, the exclusive selectivity of an organocuprate for 1,4-addition over 1,2-addition appears obvious. Theoretical calculations on the reaction of an organocuprate cluster and acrolein support this conjecture, showing that the 1,4-addition pathway is overwhelmingly favored over the 1,2-addition pathway because of the much greater stability of the olefin π-complex (β-cuprio(III)enolate) than the carbonyl π-complex (Scheme 19).[237]

A mechanism that involves single-electron transfer (SET) from Cu(I) to the enone substrate was proposed in the 1970s based on some experimental observations,[238] for example, *E*/*Z* isomerization of the olefin moiety,[239] correlation of the rate of conjugate addition with the reduction potential of the enone,[240] and ring-opening of a β-cyclopropyl α,β-unsaturated ketone.[241] However, this proposal is no longer considered seriously with a few exceptions[230b,242] because the observations can be accommodated with the inner-sphere mechanisms discussed above,[48,222,228,243,244] and because direct evidence for the generation of radical intermediates from a cuprate and an enone has scarcely been obtained.[245,246] The SET mechanism may, however, be involved in the reaction of exceptionally electrophilic substrates, for example, fullerenes,[78] fluorenone,[20] doubly activated olefins,[247] and bromonaphthoquinone.[248]

4.2.2. Remote Conjugate Addition to Polyconjugated Carbonyl Compounds.

The reaction of an organocuprate reagent with a carbonyl compound connected to an extended conjugation system may occur at a variety of positions. In many cases, the regioselectivity is poor, unpredictable, or highly dependent on the reaction conditions.[48b,249] An exceptional substrate is a polyenynyl compound, in which the conjugation is terminated by a carbon—carbon triple bond. The conjugate addition results in selective or exclusive C—C bond formation at the terminal carbon and hence serves as a useful method for the synthesis of allenes (eq 1), and poses an interesting mechanistic question.[7,250–252]



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Experimental studies provided important pieces of information on the mechanism of the 1,6-addition reaction of organocuprates (Scheme 20). First, NMR studies indicated the presence of a cuprate—substrate complex, where the lithium and the copper atoms interact with the carbonyl oxygen and the nearby C═C double bond, respectively,[227] which is a rather usual

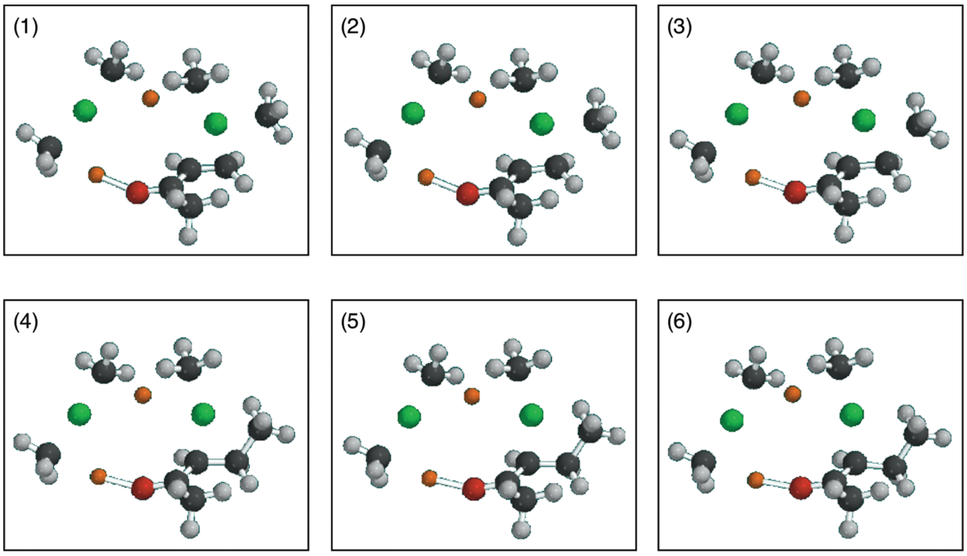


Figure 9. Snapshots of reductive elimination process in the conjugate addition of Me_2CuLi dimer to methyl vinyl ketone as studied by the intrinsic reaction coordinate analysis. Color code: green, copper; orange, lithium; gray, carbon; white, hydrogen; red, oxygen.

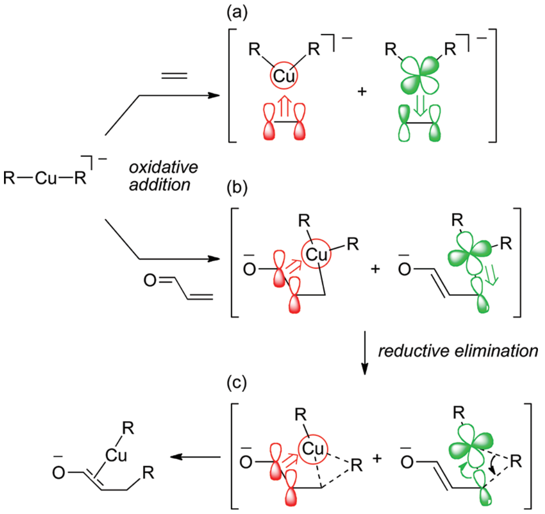


Figure 10. Schematic representations of FMO interactions in (a) cuprate−olefin complex, (b) cuprate−enone complex, and (c) its reductive elimination TS.

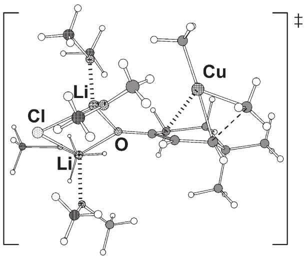
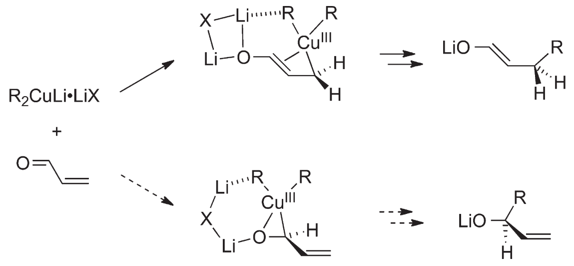


Figure 11. Transition state of the reaction of 4,4-dimethylcyclohex-2-en-1-one with $Me_2CuLi\cdot LiCl$ solvated with four molecules of dimethyl ether. Adapted with permission from ref 13c. Copyright 2009 John Wiley & Sons.

behavior (cf. Chart 8). An allenylcopper(III) complex was proposed as a putative intermediate prior to C−C bond

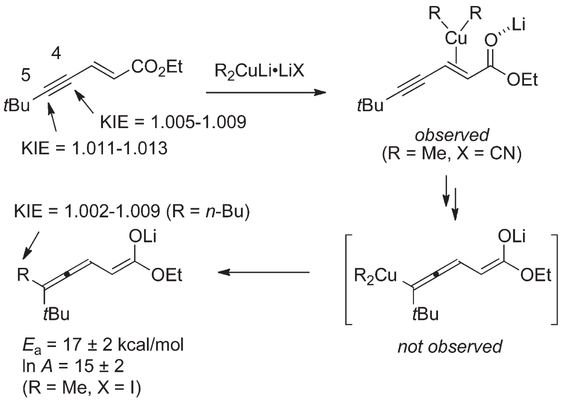
Scheme 19. Preferred 1,4-Addition over 1,2-Addition of Organocuprate to Acrolein



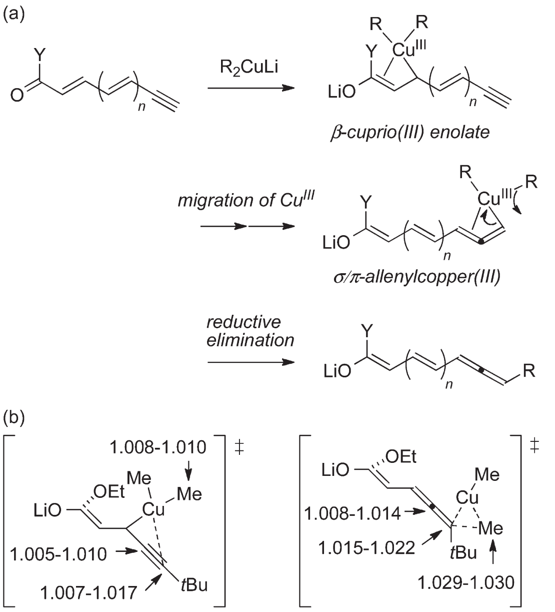
formation but could not be experimentally observed. Second, kinetic experiments showed first-order rate dependence on the cuprate−substrate complex and gave an activation energy of ca. 17 kcal/mol.[223] The magnitude of the preexponential factor of the Arrhenius plot also supported the intramolecular nature of the reaction. Third, ^{13}C KIEs were observed on the C4 and C5 atoms of the Michael acceptor and the incoming alkyl carbon,[253] while their magnitude was much smaller than in the cases of ordinary 1,4-addition (and other reactions) where C−C bond formation is the rate-determining step. KIEs on the rest of the carbon atoms were rather negligible.

A general mechanistic framework for the remote conjugate addition, which is consistent with the above experimental data, was established by theoretical studies (Scheme 21a).[253,254] The interaction of a cuprate with the substrate initially generates a β-cuprio(III)enolate. Good agreement of the experimental and computational ^{13}C NMR data suggests that this β-cuprio(III)enolate is the cuprate−substrate complex observed in the experiment. This intermediate undergoes sequential migration of the Cu(III) center via σ/π-allylcopper(III) intermediates with modest activation energies until the metal atom reaches the terminal alkyne group. The resulting σ/π-allenylcopper(III) intermediate is kinetically unstable because of the structural strain and undergoes rapid reductive elimination to yield the allene product. The calculated ^{13}C KIEs for the Cu-migration TS compare favorably with the experimental values

Scheme 20. Experimental Mechanistic Studies on 1,6-Addition to Ethyl 6,6-Dimethylhept-2-en-4-ynoate



Scheme 21. General Reaction Pathway of Remote Conjugate Addition of Organocuprate (a) and TSs and Calculated ^{13}C KIEs for Cu-Migration and Reductive Elimination Steps

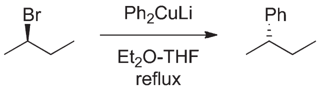


(Scheme 21b; see also Scheme 20), while the ^{13}C KIEs calculated for the bond-forming carbon atoms are too large. Therefore, the rate-determining step of the reaction is probably the Cu-migration step rather than the final reductive elimination step.

5. SUBSTITUTION REACTIONS

5.1. S_N2 Alkylation Reactions

S_N2 alkylation of alkyl halides, tosylates, epoxides, and aziridines is an important class of reaction. Several pieces of mechanistic information have been obtained from experiments. The S_N2 alkylation reactions of secondary alkyl bromide and tosylate with Ph_2CuLi take place with inversion of the configuration of the electrophilic carbon center (eqs 2 and 3),[24,255] while the reaction of a secondary alkyl iodide leads to a racemic product (eq 4).[43c] The reaction rates for substitution of alkyl halide and tosylate with R_2CuLi are both first order with respect to both the R_2CuLi dimer and the electrophile.[148,255] H/D and ^{12}C/^{13}C KIEs for the reaction of $Me_2CuLi \cdot LiI \cdot PBu_3$ and methyl iodide and tosylate were studied, which suggested that the rate-determining step of the reaction is the displacement of the leaving group.[256] The importance of the Lewis acidity of the lithium cation was illustrated by observations such as the lack of reactivity of RCu and $RCu \cdot PBu_3$ toward epoxides[257] and the retardation of the S_N2 alkylation by a crown ether.[182] Exclusive formation of a cross-coupling product (R−R′) from R_2CuLi and R′−X is also an important mechanistic feature of the reaction.[195]



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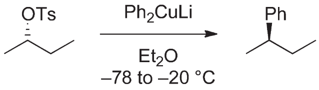

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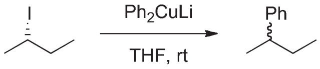
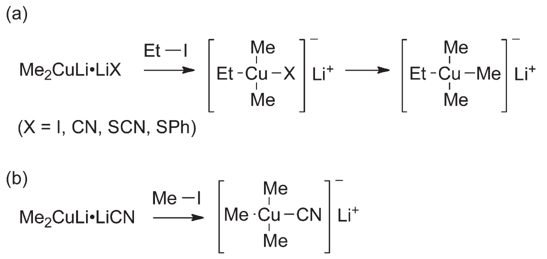


(4)

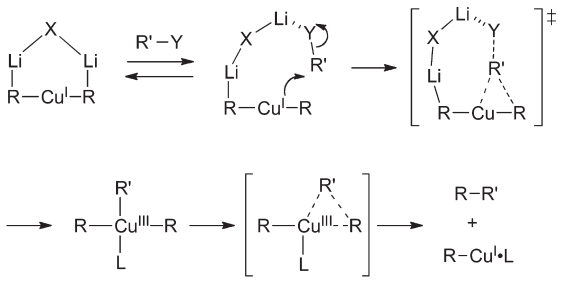
The formation of a square-planar Cu(III) intermediate in the S_N2 alkylation was confirmed by the NMR spectroscopic observation of tri- and tetra-alkylcopper(III) species at −100 °C (Scheme 22).[168,169] The formation of *trans*-$[EtMe_2CuX]^-$ species was observed in the reaction of EtI with a series of Gilman cuprates $R_2CuLi \cdot LiX$ (X = I, CN, SCN, SPh). In the presence of excess cuprate, these species are converted to a more stable tetraalkylcuprate(III) species, that is, $[EtMe_3Cu]^-$. Trimethylcyanocuprate(III) was also observed in the reaction of MeI with $Me_2CuLi \cdot LiCN$. The *trans* relationship of the R ligands of the cuprate reagent is retained during the oxidative addition, and hence the resulting Cu(III) complex features *cis*-orientation of the R and R′ (from electrophile) ligands. This coordination geometry accounts for the exclusive formation of a cross-coupling product (R−R′) upon reductive elimination, while some of the copper(III) species show configurational instability and hence give a homocoupling product.[168,258] Note that a dialkylaurate(I) reagent and an alkyl iodide react in a similar fashion to produce a square-planar trialkylgold(III) complex $R_2R'Au^{III} \cdot L$, which is, in contrast to the Cu(III) analogue, thermally stable (see section 3.5).[194−196]

Theoretical studies on the reactions of alkyl halides (CH_3I and CH_3Br) with lithium organocuprate clusters revealed mechanistic details of this class of organocuprate reactions that agree well with the experiments (Scheme 23).[182] Thus, the two major elementary steps of the reaction are the rate-determining displacement of the leaving group (i.e., oxidative addition) by a nucleophilic copper(I) atom and subsequent reductive elimination of the resulting trialkylcopper(III) intermediate. The oxidative addition is driven by the efficient overlap of the copper $3d_{z^2}$ orbital of the linear R_2Cu^- geometry and the C−Y σ^* orbital (Figure 12; see also Figure 2a). The presence of the lithium atom in the cuprate assists the C−Y bond cleavage by coordinating to the leaving Y atom. Such a push−pull mode of substrate activation is a common feature in nucleophilic organocopper reactions. The calculated KIE values for the reaction of CH_3I showed good agreement with the experimental data.

Scheme 22. Observation of Square-Planar Tri- and Tetraalkylcopper(III) Species



Scheme 23. Reaction Pathway of Substitution of Alkyl Electrophile (R′—Y) with Organocuprate



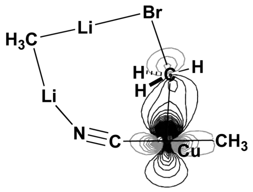


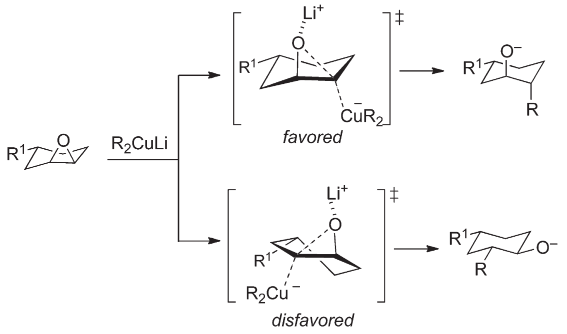
Figure 12. Localized Kohn—Sham orbital in the S_N2 reaction between a cyanocuprate $MeCu(CN)Li{\cdot}LiMe$ and MeBr. For the cyanocuprate, see section 6.3.2. Adapted with permission from ref 13c. Copyright 2009 John Wiley & Sons.

The rate-determining displacement of the leaving group leads to the formation of a T-shaped trialkylcopper(III) intermediate, which is coordinated by a fourth ligand (L) in a square-planar geometry. The fourth ligand, depending on the reaction conditions (cuprate composition, additive, solvent), may be anionic (e.g., halide, cyanide, thiolate, alkyl) or neutral (e.g., ethereal solvent, phosphine). The linear geometry of the R_2Cu^- moiety in the oxidative addition step is reflected in the copper(III) complex, which is characterized by the trans-orientation of the two R groups and the cis-orientation of the R and R′ groups. Thus, reductive elimination of the copper(III) complex exclusively affords the cross-coupling product.

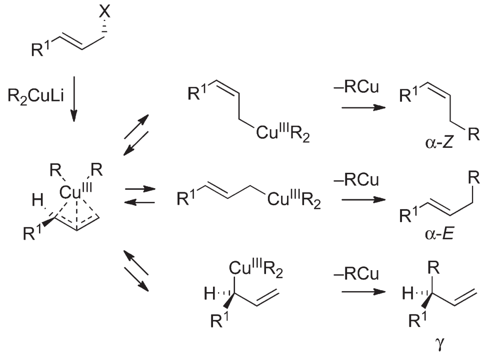
Note that a SET mechanism was proposed for some cases, where stereorandomization of the electrophilic carbon center was observed (e.g., secondary alkyl iodide; see eq 4).[43c,259,260] However, the scope of the SET mechanism is considered to be limited; it should operate only when the electrophile is prone to generate an alkyl radical.

A similar reaction pathway was revealed for the ring-opening alkylation of an epoxide with a Gilman reagent.[182b] The configuration of the electrophilic carbon center is significantly inverted in the TS. This stereochemical feature is responsible for the trans-diaxial opening of cyclohexene oxide derivatives that has been widely observed (Scheme 24),[261] and this TS leading to the trans-diaxial product takes a chairlike conformation, while the diequatorial TS is characterized by a less stable twisted boat conformation. The effect of BF_3, a commonly used Lewis acid to accelerate the epoxide-opening reaction,[186] is discussed in Section 6.1.

Scheme 24. Opening of Cyclohexene Oxide with R_2CuLi

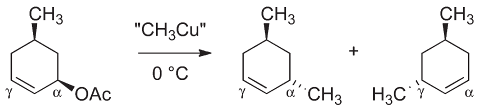


Scheme 25. Conventional Mechanism of Allylic Substitution with Lithium Diorganocuprate



5.2. Allylic Substitution Reactions

Regio- and stereoselective substitution of allylic electrophiles such as halides and esters with an organocopper reagent provides an invaluable synthetic tool. The reaction is mechanistically much more complicated than the substitution reaction of an alkyl halide because the C—C bond formation can take place a priori at the position α or γ to the leaving group, and on the face *anti* or *syn* to the leaving group. An illustrative example of this complexity is shown in eq 5. Thus, the reaction of a dialkylcuprate with *cis*-5-methyl-2-cyclohexenyl acetate takes place with *anti*-stereoselectivity but not regioselectively,[262] whereas a heterocuprate MeCu(CN)Li undergoes the reaction in an *anti*- and γ-selective (i.e., *anti*-S_N2') manner.[263] General trends of stereo- and regioselectivity in allylic substitution may be summarized as follows. (1) *anti*-Selectivity is generally observed, while *syn*-S_N2' selectivity is achieved only with a substrate containing a leaving group that can coordinate to the copper atom.[68,264−266] (2) The regioselectivity for a Gilman cuprate (R_2CuLi) is dependent on the substrate rather than the reaction conditions. (3) The regioselectivity and the S_N2' selectivity in particular often depend on the choice of the reagents and the reaction conditions.[41,53,96,267−269] No rational explanation existed until a theoretical study suggested a rationale on the basis of the molecular orbital analysis.



(5)

$CH_3Cu(CN)Li$	4	:	96
$(CH_3)_2CuLi$	50	:	50

An empirical mechanistic analysis on the basis of experimental regio- and stereoselectivities used to assume the following processes: (1) Displacement of the leaving group by the cuprate in an *anti* fashion to generate a π-allylcopper(III) intermediate; (2) equilibration of the π-allylcopper(III) intermediate with σ-allylcopper(III) intermediates; and (3) reductive elimination of the σ-allylcopper(III) intermediates to afford the allylation products (Scheme 25).[96,262b,267,270] The presence of π- and σ-allylcopper(III) intermediates and the equilibrium between them were indirectly suggested from the product ratio in the reaction of a diallylcuprate reagent and an allyl ester[271] and directly shown by a low-temperature NMR study (Chart 7e).[171] Nonetheless, these studies did not provide insights into the origin of the regio- and stereoselectivities.

Scheme 26 summarizes the nonregiospecific reaction pathway of the substitution reaction of a homocuprate and allyl acetate, as revealed by the theoretical studies.[178] First, the homocuprate reversibly forms a square-planar olefin π-complex, which then irreversibly releases an acetate anion in an *anti* fashion with the assistance of the lithium cation (oxidative addition), providing a symmetrical π-allylcopper(III) complex (Scheme 26a). The *anti*-elimination pathway is preferred to the *syn*-elimination pathway because it enjoys effective overlap of the copper $3d_{xz}$ orbital and the C=C π^*/C−O σ^* mixed orbital (see section 3.2.2), although the *syn*-elimination may be favored if the copper reagent is coordinated to the leaving group.

The π-allylcopper(III) complex equilibriates with a less stable σ-allylcopper(III) complex with the assistance of a fourth ligand (e.g., solvent molecule, Scheme 26b).[189] Both the π-allyl and σ-allylcopper(III) species can undergo reductive elimination, while the reaction of the former is kinetically favorable. The TS of the reductive elimination of the π-allylcopper(III) species is structurally similar to an enyl $[\sigma + \pi]$ complex.[190] The molecular orbital interactions involved in the π-allylcopper(III) complex and its reductive elimination were discussed earlier in section 3.4.

The above mechanism accounts for the lack of regiospecificity in the reaction of a homocuprate and a symmetrically substituted allylic electrophile (cf. eq 5). If the allylic electrophile is substituted differently at the α- and/or γ-positions, the regioselectivity is determined in the reductive elimination step.[189] A systematic study on substituted π-allylcopper(III) complexes showed that reductive elimination at the unsubstituted position (C^3) is generally preferred and that the rate of reductive elimination increases with an electron-donating substituent (Scheme 27). The calculated activation energy for reductive elimination at each allylic terminus correlates well with the Hammett σ_p^+ constant, indicating the significance of the resonance effect. Note the similarity between the π-allylcopper(III) complex containing an electron-donating substituent (e.g., $OSiMe_3$, OMe) and the β-cuprio enolate intermediate of the conjugate addition reaction (Scheme 18).

A heterocuprate such as a cyanocuprate can undergo oxidative addition of allyl acetate by two diastereomeric pathways. Theoretical studies indicated that the γ-selectivity observed in the experiment (eq 5) originates from the FMO interaction in this step (Scheme 28).[178] As discussed earlier, the HOMO of a bent $RCu(CN)^-$ fragment is more extended in the direction opposite to the CN ligand because of its lower σ-donor ability (Figure 5). On the other hand, the LUMO of allyl acetate is more extended on the γ position, as shown by a simple MO diagram (Scheme 28b). Hence, the TS with the R ligand on the γ side enjoys better FMO interaction than its diastereomer (Scheme 28c), leading to an enyl $[\sigma + \pi]$-type allylcopper(III) complex in which the copper atom is σ-bonded to the γ carbon. The allylcopper(III) complex is configurationally stable and thus undergoes reductive elimination exclusively at the γ position. Note that the lower σ-donor ability of the CN and related ligands makes the corresponding heterocuprates less nucleophilic and hence less reactive toward oxidative addition. On the other hand, such ligands accelerate the reductive elimination step by destabilizing the corresponding allylcopper(III) intermediates.[178,180b]

An interesting reaction of a dialkylcuprate (R_2CuM) and perfluoroallyl iodide that exclusively afforded a homocoupling product R−R has been reported (Scheme 29).[272] This unusual selectivity can be ascribed to the reluctance of the highly electron-withdrawing perfluoroallyl group to take part in reductive elimination of a copper(III) intermediate, $Me_2(C_3F_5)C$, a well-known effect of highly electron-deficient groups in organotransition metal chemistry.[97]

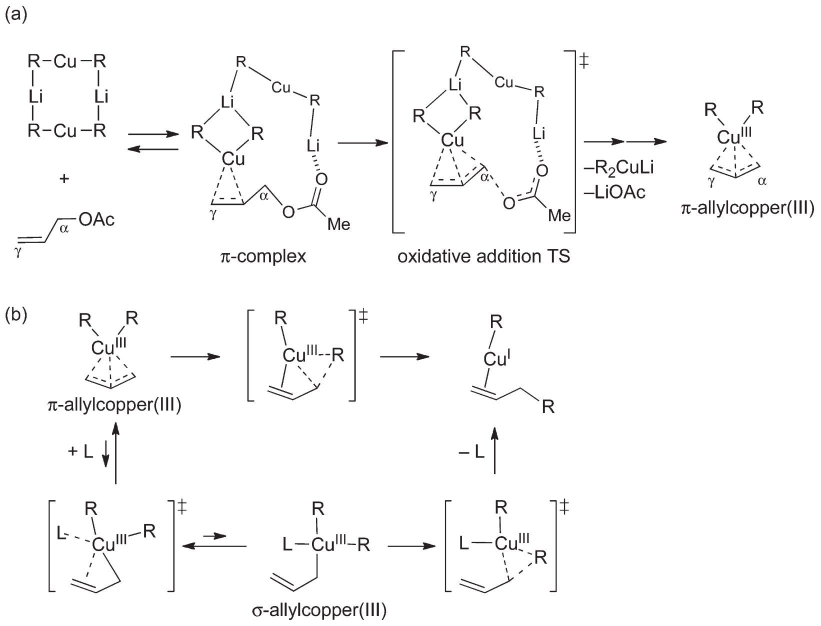
5.3. Substitution on sp^2 Carbon Atoms

5.3.1. Substitution on Alkenyl Halides.

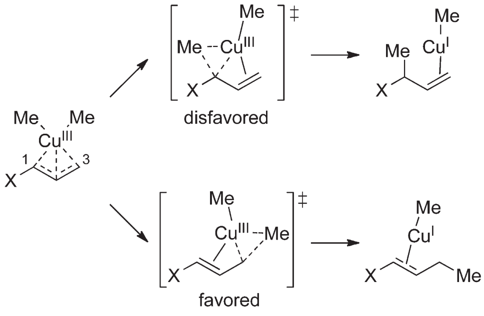
Nucleophilic substitution on an alkenyl or acyl sp^2-carbon atom has great historical value because it paved the way to the palladium-catalyzed cross-coupling between main-group organometallics and sp^2 halide electrophiles.[273] The substitution reaction of an alkenyl halide initially reported in 1967 changed the accepted wisdom that a nucleophilic substitution on an unactivated sp^2 carbon is synthetically impractical.[21a] This report preceded, by several years, the discoveries of cross-coupling reactions of sp^2 electrophiles with iron,[274] nickel,[275] and palladium catalysts.[276] The reaction features the retention of the double bond geometry,[277] and a mechanism widely accepted until recently involves insertion of the Cu(I) atom into the sp^2 carbon−halogen bond (oxidative addition) followed by reductive elimination of the resulting alkenylcopper(III) intermediate (Scheme 30).[278]

The accumulated theoretical knowledge on the reaction of a polymetallic organocuprate cluster suggested significant modification of this accepted mechanism and led to a new mechanism outlined in Scheme 31.[179] First, the cuprate forms a π-complex with the alkenyl bromide, and significant charge transfer from the cuprate to the substrate occurs at this stage. It is therefore necessary to view the π-complex as a cuprio(III)cyclopropane, and the C−Br bond cleavage can readily occur through two pathways, one denoted as a three-centered pathway and the other as an eliminative pathway, as illustrated in Scheme 31. The former pathway involves insertion of the copper atom into the C−Br bond followed by reductive elimination of the resulting alkenylcopper(III) intermediate, while in the latter pathway, Li-assisted elimination of the bromide anion and C−C bond formation occur concomitantly. Theoretical study and ^{13}C KIE

Scheme 26. Non-regioselective Reaction Pathway for Substitution of Allyl Acetate with R$_2$CuLi Dimer



Scheme 27. Reductive Elimination of Unsymmetrically Substituted π-Allylcopper(III) Complex

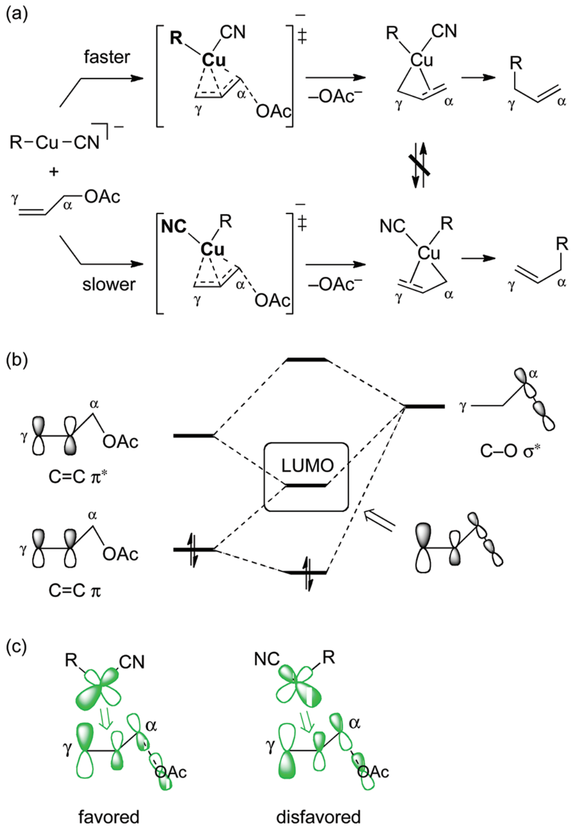


X = OSiMe$_3$, OMe, Me, Ph, CO$_2$Me, NO$_2$

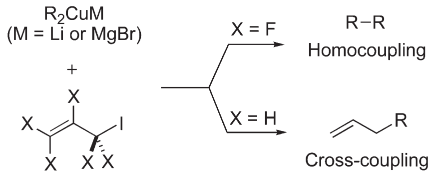
experiments suggested that the eliminative pathway is a favored pathway (Scheme 32). Back-donation from the Cu 3d$_{xz}$ orbital to the C=C π^*/C−Br σ^* mixed orbital is the driving force of the C−Br bond cleavage (section 3.2.2).

The theoretical study on the cuprate reaction revealed several important mechanistic issues in the oxidative addition of an alkenyl or aryl electrophile to a d^{10} transition metal complex, namely, (1) formation of a π-complex prior to C−X bond cleavage;[93,279] (2) intrinsic mechanistic dichotomy (three-centered vs eliminative) of C−X bond cleavage;[280] and (3) assistance of C−X bond cleavage by a Lewis acid. This mechanistic framework offers a useful guideline for the design of catalytic processes involving oxidative addition as a critical elementary step and led to a successful computational design of a highly active nickel catalyst featuring a hydroxyphosphine ligand. This ligand allowed smooth cross-coupling of unreactive aryl electrophiles with Grignard reagents (Scheme 33).[92] Mechanistic studies on this system indicated that the C−X bond activation was achieved efficiently through cooperative action of nucleophilic nickel(0) and Lewis acidic magnesium(II) centers.

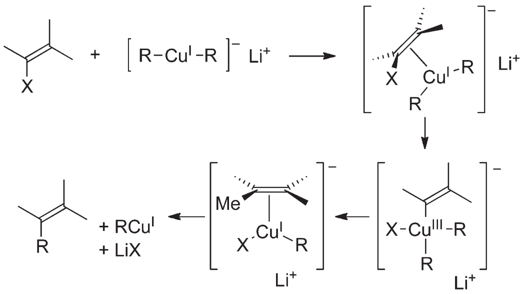
Scheme 28. Stereospecific Reaction Pathways of Substitution of Allyl Acetate with Cyanocuprate and Schematic Representations of FMO Interaction Involved



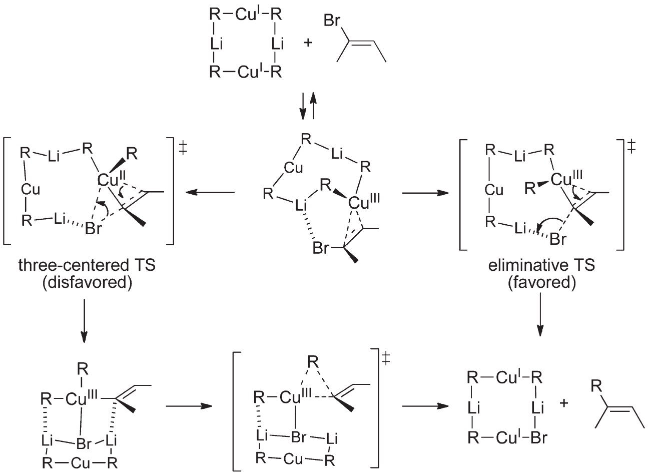
5.3.2. Substitution on Acyl Electrophiles. The substitution reaction of an acid chloride with an organocuprate reagent, Scheme 29. Reaction of Organocuprate with Allyl- and Pentafluoroallyl Iodide



Scheme 30. Conventional Mechanism of Substitution Reaction of Alkenyl Halide with Organocuprate



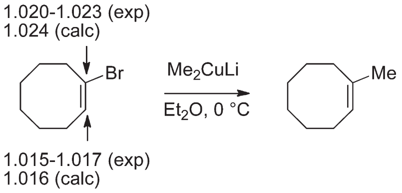
Scheme 31. Reaction Pathways for Substitution of Alkenyl Bromide with R$_2$CuLi Dimer



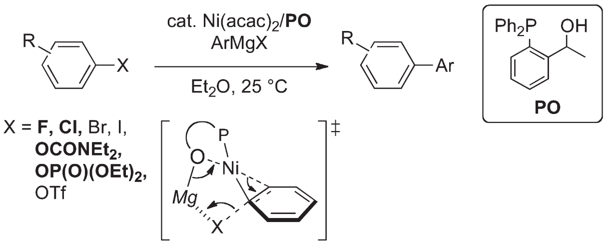
developed in the early 1970s, offers a versatile method for the synthesis of ketones owing to its compatibility with a series of functional groups, including ketones, nitriles, and esters.[30] The substitution of a thioester, reported shortly after the acid chloride reaction, further expanded the scope of the organocuprate reaction.[31] While catalytic cross-coupling reactions of acyl electrophiles have emerged,[281] the stoichiometric reactions remain useful for their high reliability.[282]

The reaction pathway of the substitution of an acyl electrophile with an organocuprate depends on the nature of the leaving group (Scheme 34).[283] Because a thiolate anion has a high affinity to a copper atom, the reaction of a thioester involves insertion of the copper atom into the C–S bond. On the other hand, an acid chloride reacts via an eliminative pathway (cf. Scheme 31) because the chloride anion can enjoy better electrostatic interaction with the lithium cation.

Scheme 32. Experimental and Computational ^{13}C KIEs for the Reaction of 1-Bromocyclooctene and Me$_2$CuLi (the Computational Data Obtained on the Basis of the Eliminative Pathway in Scheme *31*)



Scheme 33. Nickel/Hydoxyphosphine-Catalyzed Cross-Coupling of Unreactive Aryl Electrophiles with Grignard Reagents



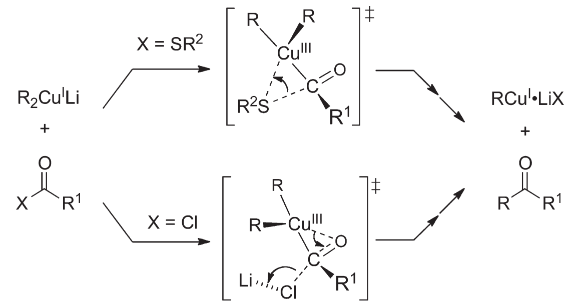
6. REACTIVITY OF MODIFIED ORGANOCOPPER REAGENTS

Besides the standard Gilman cuprates, a wide variety of modified organocuprate reagents have served as useful reagents for C–C bond formation. The modifiers, typically Lewis acidic or basic additives, are employed for acceleration and/or regio-, stereo-, and chemoselectivity control of the reaction. In this section, mechanisms behind some representative cases including the BF$_3$ effect, Me$_3$SiCl effect, dummy ligand effect, and cyano-Gilman cuprate are discussed (sections 6.1–6.3). An organocopper species generated in a copper-catalyzed (asymmetric) reaction of an organometallic reagent (e.g., Mg, Zn, Al) can also be regarded as a modified organocuprate reagent. Thus, the mechanisms for copper-catalyzed asymmetric C–C bond-forming reactions will be discussed in section 6.4. In addition, the mechanisms of miscellaneous reactions involving organocopper intermediates and Cu(I)/Cu(III) redox processes will also be briefly discussed (section 6.5).

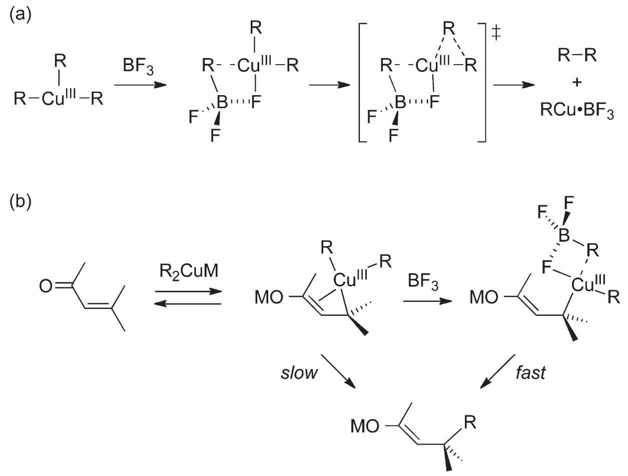
6.1. Lewis Acid-Modified Organocopper Reagents

A Lewis acidic additive such as BF$_3$ dramatically increases the reaction rate and changes the selectivity of conjugate addition of an organocopper reagent to an unsaturated carbonyl compound, as discovered by Yamamoto in the late 1970s.[41,42] Structural analysis of the BF$_3$-complexed organocopper reagent did not allow rationalization of the effect.[284] Because the rate-determining step of the conjugate addition is the reductive elimination of the copper(III) intermediate, one possible effect of BF$_3$ is the acceleration of this step (see section 4.2.1). A theoretical model study of the interaction between Me$_3$Cu(III) and BF$_3$ revealed a strong two-point interaction.[166] The electronegative fluoride

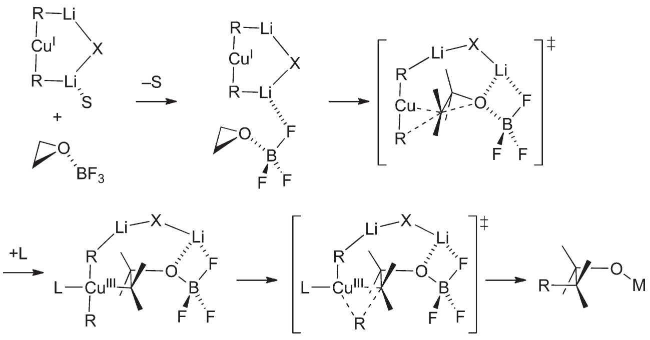
Scheme 34. Substitution Reaction of Organocuprate and Acyl Electrophile



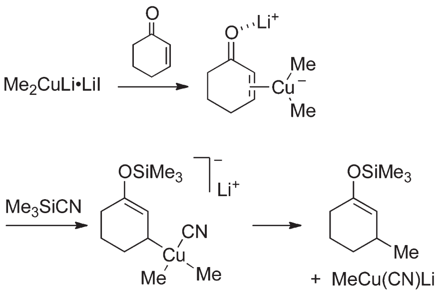
Scheme 35. Complexation of $R_3Cu(III)$ Species with BF_3, and Proposed Mechanism for Rate Acceleration of Conjugate Addition by BF_3



Scheme 36. Mechanism of Acceleration of Epoxide Alkylation by BF_3



Scheme 37. Conjugate Addition of $Me_2CuLi \cdot LiI$ to 2-Cyclohexenone in the Presence of Me_3SiCN

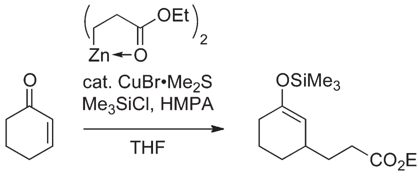


ligand coordinates to the Lewis acidic Cu(III) center, while the Lewis acidic boron atom interacts with one of the methyl ligands (Scheme 35a). The interaction is so strong that the resulting complex is better described as $R_2FCu(III) \cdot BF_2R$ rather than $R_3Cu(III) \cdot BF_3$. This complex is kinetically unstable toward reductive elimination, because of the low electron density of the copper atom. Overall, BF_3 thermodynamically traps the $R_3Cu(III)$ species and makes it kinetically labile, which may account for the accelerated conjugate addition (Scheme 35b). Naturally, the role of BF_3 to activate the carbonyl group to facilitate the oxidative addition cannot be entirely discounted.

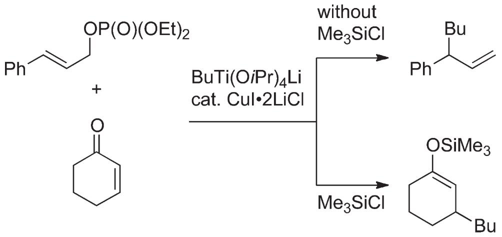
BF_3 may act directly on the electrophile and accelerate the ring-opening alkylation of an epoxide,[186] in which the displacement of the oxygen atom with Cu is the rate-determining step (see section 5.1).[182b] A plausible pathway for BF_3 participation in the reaction is shown in Scheme 36. The cooperative interaction of BF_3 fluorine and boron atoms with the cuprate and epoxide is responsible for the acceleration of the C−O bond cleavage.

6.2. Me_3SiCl-Modified Organocopper Reagents

Since the independent discoveries by Nakamura/Kuwajima,[45] Corey,[48] and Alexakis,[49] chlorotrimethylsilane (Me_3SiCl) has been a standard reagent for acceleration of conjugate addition reactions. The effect was first reported for copper-catalyzed conjugate additions of zinc homoenolates (eq 6)[45] and was followed by applications to Grignard-based organocopper reagents[46,47] and stoichiometric lithium organocuprates.[48−52] Acceleration of conjugate additions and modification of their stereoselectivities by means of silylating agents is now well established. Me_3SiCl was also used to switch the chemoselectivity of organocuprate reactions. The competitive reaction of an allyl phosphate and an enone with the standard copper reagent is dominated by the allylic substitution, whereas the addition of Me_3SiCl completely alters the chemoselectivity (eq 7).[56b]



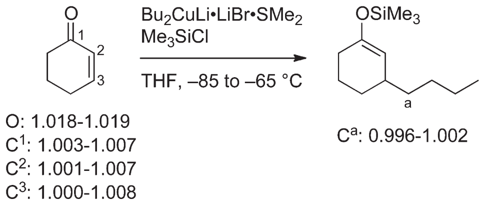
(6)



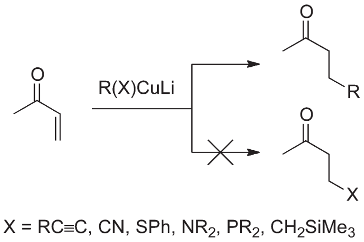
(7)

The mechanistic origin of this acceleration effect has been the subject of considerable debate.[48,285−287] A recent experimental study suggested that the reaction involves silylation of an organocopper−enone π-complex (β-cuprioenolate; see section 4.2.1).

Scheme 38. ^{13}C and ^{17}O KIEs for Me_3SiCl-Assisted Conjugate Addition of Dibutylcuprate to 2-Cyclohexenone



Scheme 39. Selective Ligand Transfer in Conjugate Addition of Mixed Organocuprate



Thus, an intermediate in the silylative conjugate addition reaction was spectroscopically observed at −100 °C (Scheme 37).[167] First, the Gilman cuprate $Me_2CuLi \cdot LiI$ and 2-cyclohexenone form a well-known type of π-complex. Upon the addition of Me_3SiCN, the π-complex is converted to a square-planar trialkylcyanocuprate(III) species with concomitant silylation of the oxygen atom. When warmed to −80 °C, the Cu(III) complex containing a silyl enol ether moiety undergoes reductive elimination to give the conjugate addition product. The same Cu(III) complex is obtained from 2-cyclohexenone and a reagent consisiting of $Me_2CuLi \cdot LiCN$ and Me_3SiCl.

A few other mechanistic studies have been reported. A positive correlation between the silylating ability of the reagent and the magnitude of rate acceleration was demonstrated, which strongly suggests that the rate-determining step of the reaction is the silylation step rather than the C−C bond-forming step.[288] Studies of KIEs also supported this conjecture (Scheme 38).[289] Thus, the reaction of a dibutylcuprate and 2-cyclohexenone in the presence of Me_3SiCl exhibited a significant ^{17}O KIE, while ^{13}C KIEs, particularly those at the C^3 and C^a atoms, were much smaller than observed in the ordinary conjugate addition (Scheme 17). Further studies are, however, still needed to address mechanistic details.

6.3. Ligand-Modified Organocopper Reagents

6.3.1. Dummy Ligand Effect. A homocuprate reagent R_2CuLi can transfer only one of the two R groups to the electrophilic substrate, and the other one is lost as an unreactive RCu species. This intrinsic reactivity is particularly problematic when the R group is precious. To solve this problem, a mixed organocuprate R(X)CuLi, in which the X group acts as a nontransferable dummy ligand, was first introduced by Corey in 1972 (X = alkynyl; Scheme 39).[34] The selectivity of intramolecular ligand transfer of mixed organocuprates was systematically studied,[35] which suggested that the general order of ligand transferability is *n*-Bu ≈ *sec*-Bu > *t*-Bu ≫ Ph > alkynyl[35a] and alkenyl > Me ≫ alkynyl.[35b,c] Together with these studies, synthetically useful mixed organocuprates containing a series of dummy ligands including alkynyl,[35a,36] cyano,[37] phenylthio,[38] alkoxy,[39] dialkylamino,[40] phosphido,[40] and trimethylsilylmethyl[290] groups have been developed. The dummy ligand approach also led to the invention of chiral mixed organocuprates, which serve as reagents for enantioselective conjugate addition.[291]

A systematic theoretical study on the reactivity of heterocuprates in the context of allylic substitution and conjugate addition reactions revealed several factors that control transferability of ligands on cuprates (Schemes 40 and 41).[180] Analysis of the reductive elimination of Me(X)Cu(η^3-allyl) demonstrated that the Me−allyl bond formation is preferred to X−allyl bond formation for the common dummy ligands, that is, X = C≡CH, CN, SMe, and CH_2SiMe_3 (Scheme 40a). In contrast, reductive elimination of an alkenyl group is much easier than that of a methyl group. The ligand transfer selectivity for X = C≡CH, CN, and SMe is ascribed to the weaker σ-donation ability of these ligands compared with that of the Me ligand. Thus, the stronger trans influence of the Me ligand than of the X ligand results in the enyl [$\sigma + \pi$] geometry of the allylcopper(III) complex, which is more amenable to Me−allyl reductive elimination (Scheme 40b; see also Figure 5). On the other hand, when X = CH_2SiMe_3 or alkenyl, the allylcopper(III) complex takes a symmetric π-allyl geometry. The slow transfer of the CH_2SiMe_3 ligand is ascribed to the destabilizing 4-electron interaction between the Cu 3d$_{xy}$ orbital and the Si−C σ orbital, while the fast transfer of the alkenyl group is due to participation of the C=C π orbital (Scheme 41c,d).

A further model study on the reductive elimination of β-cuprio(III)enolates derived from heterocuprates provided additional reasons for the ligand transfer selectivity in conjugate addition (Scheme 41). Thus, the Cu(III) complex leading to the alkyl ligand transfer is more stabilized than its isomer leading to the X ligand (alkynyl, cyano, alkylthio) transfer because of stronger electrostatic interaction of the X ligand with the lithium cation than of the alkyl ligand (Scheme 41a,b; see also Scheme 6). Thus, the ligand transfer selectivity for such dummy ligands is thermodynamically controlled. As described for the allylic substitution reaction in section 5.2, dummy ligands play decisive roles not only in the group-transfer selectivity but also in the regio- and stereoselectivity of the reaction.

6.3.2. Cyano-Gilman Cuprates. In 1981, Lipshutz and coworkers introduced a cyano-Gilman cuprate $R_2CuLi \cdot LiCN$, a reagent formed by addition of 2 equiv of RLi to CuCN, to organocopper chemistry.[43,44] This reagent exhibits higher reactivity than the corresponding Gilman cuprate R_2CuLi in certain reactions, for example, substitution reactions of secondary alkyl halides. The cyano-Gilman cuprate also shows some unusual reactivity (e.g., deprotonation of an acetylenic proton, 1,2-addition to a carbonyl group) that is not observed with the Gilman cuprate, suggesting that a minute amount of alkyllithium is generated in equilibrium with the major R_2Cu^- species.[292] Structural studies on the Gilman and cyano-Gilman cuprates showed that both reagents share the same dimeric core structure $[R_2CuLi]_2$ but differ in their propensity to form higher aggregate structures (see section 2),[154−156] yet such structural features were not proven to have direct connection to their reactivities.

Theoretical studies suggested a possible origin of the higher reactivity of the cyano-Gilman cuprate in S_N2 alkylation (Scheme 42).[292] Computational comparison of the reactivity of a homodimer $[Me_2CuLi]_2$, a LiCN-bridged species $Me_2CuLi \cdot LiCN$,[157] and a MeLi-bridged species MeCu(CN)Li·LiMe toward methyl bromide revealed that the latter two species undergo nucleophilic displacement of MeBr with much lower activation energies than for the homodimer. In particular, MeCu(CN)Li·LiMe, while much less thermodynamically stable, was suggested to be as reactive as $Me_2CuLi·LiCN$. The kinetic importance of the thermodynamically less stable isomer was also suggested for the conjugate addition reaction.[293] The study suggested that a minor constituent of organocopper(I) aggregates can be the true reactive species in some cases.[294]

6.4. Catalytic (Asymmetric) Organocopper Reactions

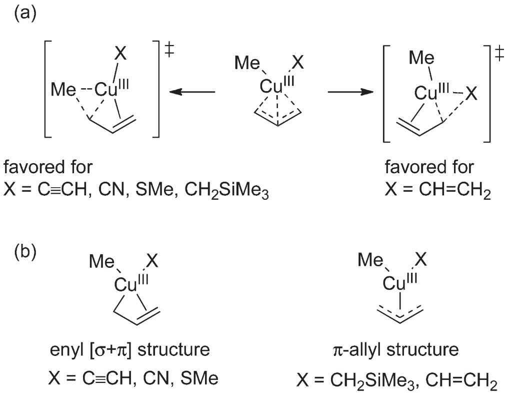
While Grignard reagents readily undergo 1,2-addition to carbonyl compounds, organozinc reagents are rather unreactive nucleophiles by themselves. Both of them undergo conjugate addition and allylic substitution in the presence of a small amount of an inorganic copper salt through in situ generation of a highly reactive organocopper(I) species. In the presence of an optically active ligand, the reaction serves as a useful method for asymmetric synthesis. Their reaction mechanisms have long remained obscure, while a few specific systems of conjugate addition[64b,295,296] and allylic substitution reactions[96] and the structures of precatalytic copper−ligand complexes[297−300] have been experimentally studied. Nonetheless, it is widely believed that the stoichiometric and catalytic reactions share the same mechanistic principles. Therefore, catalytic cycles consisting of transmetalation, oxidative addition, and reductive elimination are considered to be plausible for copper-catalyzed conjugate addition[64b,295d,296,301] and allylic substitution (Scheme 43; see also Scheme 2),[96] while little consensus has been reached on the rate-limiting step of the catalytic cycles.[295c,d,296] It is generally believed that the reactions operate on the Cu(I)/Cu(III) catalytic cycle even when a copper(II) salt is used as a precatalyst.

As discussed earlier with Scheme 2, the transmetalation step is considered to give a monoorganocuprate $[RCuX(L^*)]^-$ when organozinc and -aluminum reagents are used or when Grignard reagents are used in low concentration or in the presence of an external ligand (L*) such as phosphines and *N*-heterocyclic carbenes.[96,296] On the other hand, a homocuprate R_2Cu^- may be generated when an excess amount of a Grignard reagent is used without an external ligand, as suggested from the similar reactivity and selectivity observed for such catalytic reactions and reactions of a Gilman homocuprate.[96a]

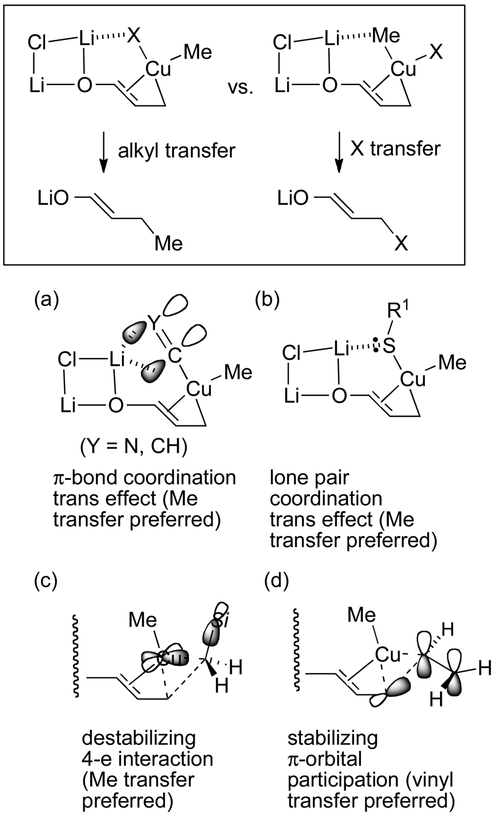
In light of the chemistry of stoichiometric reactions (vide supra), the oxidative addition step must be reversible for the conjugate addition (Scheme 43a) and irreversible for the allylic substitution (Scheme 43b). This difference may affect the selectivity of the reactions. For instance, the stereochemistry-determining step for the conjugate addition is probably the reductive elimination step, while the regio- and stereochemistry of the allylic substitution may be determined in the oxidative addition step. Thus, the S_N2'-selectivity generally observed in catalytic allylic substitution[64a,b,65] would originate from the electronic effect of a heterocuprate species, as discussed in section 5.2. Note that the conjugate addition is often accompanied by isomerization of the double bond geometry of an enone/enoate substrate,[295e,296] which is consistent with the reversibility of the oxidative addition step forming a Cu(III) intermediate.

In analogy to the reaction mechanism of a lithium organocuprate, aggregation of nucleophilic copper and Lewis acidic main-group metal atoms has been considered essential for the reactivity and selectivity of catalytic organocopper species. For example, a mechanistic study on asymmetric conjugate addition of a Grignard reagent catalyzed by a chiral copper−diphosphine complex suggested that the reactive species is a bromide-bridged Cu(I)/Mg(II) bimetallic complex (Scheme 44).[296] This complex has been proposed to undergo oxidative addition of an enone (enoate) through cooperative actions of the Cu(I) and Mg(II) centers, which is followed by rate-limiting reductive elimination.

Scheme 40. Reductive Elimination of Me(X)Cu(η^3-allyl)

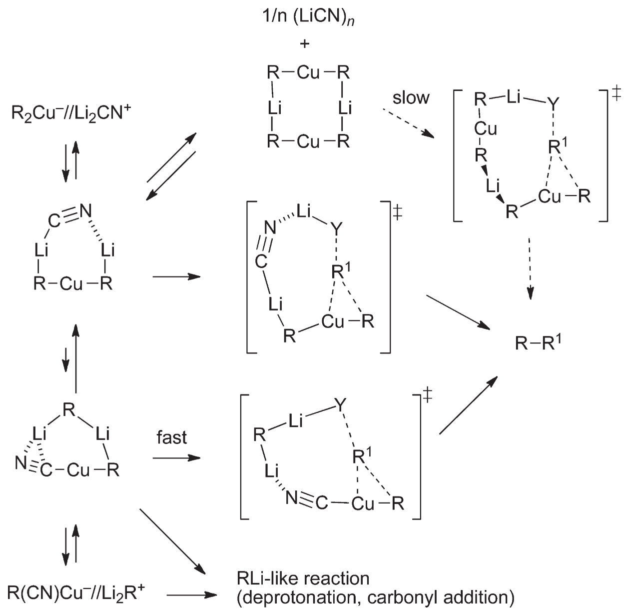


Scheme 41. Ligand Transfer Selectivity in Conjugate Addition and its Rationale

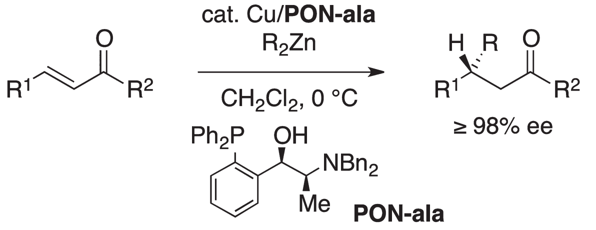


The concept of bimetallic cooperativity of copper and Lewis acidic main-group metals helps the design of enantioselective

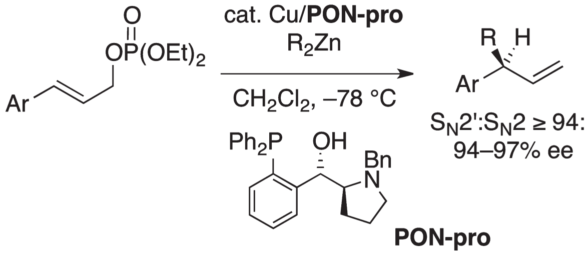
Scheme 42. A Suggested Reaction Pathway for Alkylation of the Lipshutz Cuprate



copper catalysis. For example, chiral aminohydroxyphosphine (PON) ligands, which can chelate both nucleophilic copper(I) and Lewis acidic zinc(II) atoms, show excellent enantioselectivities in conjugate addition and allylic substitution reactions (eqs 8 and 9).[302] Computational modeling of the plausible stereochemistry-determining TSs suggested cooperation of the copper and zinc centers in both the substrate activation and the stereochemical control (Chart 9).

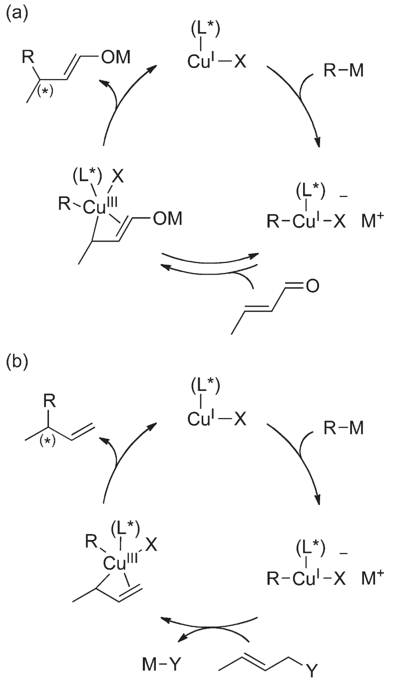


(8)



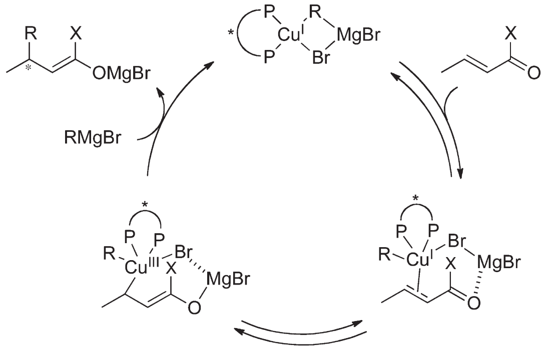
(9)

Scheme 43. Possible Catalytic Cycles for Copper-Catalyzed (Asymmetric) Conjugate Addition (a) and Allylic Substitution (b)[a]



[a] R = alkyl, alkenyl, or aryl ligand; X = nontransferable anion (e.g., halide, heteroatom anion, cyanide); L* = (chiral) ligand; M = main-group metal (e.g., Mg, Zn, Al).

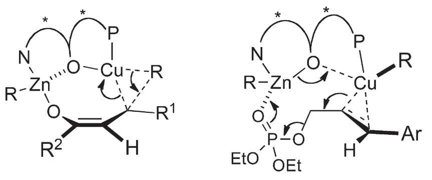
Scheme 44. Proposed Catalytic Cycle for Conjugate Addition of Grignard Reagent Catalyzed by Chiral Copper−Diphosphine Complex



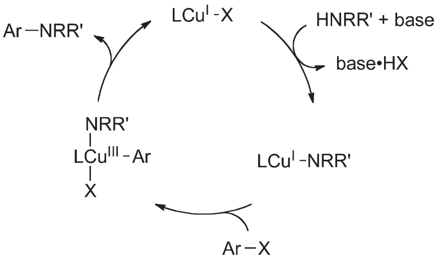
6.5. Other Reactions Involving the Cu(I)/Cu(III) Redox Process

As has been discussed throughout this review, Cu(I)/Cu(III) redox is a common key process involved in organocuprate reactions, where copper 3d orbitals play a critical role. A few other copper-mediated/catalyzed reactions have been proposed to involve a similar redox process on the basis of experimental and theoretical studies. A representative example of such reactions is the Ullmann-type coupling reaction of an aryl halide and a heteroatom nucleophile (eq 10), in particular, copper-catalyzed C−N bond formation.[303−305] Lines of evidence including kinetic data, characterization of relevant Cu(III) complexes, and computational analysis have indicated a catalytic cycle involving a Cu(I)/Cu(III) redox process, as simplistically illustrated in Scheme 45.[162,306,307] Thus, the reaction involves three important elementary steps, that is, (1) formation of a copper(I) amide species from a copper(I) halide, an amine, and a base; (2) oxidative addition of an aryl halide to the copper(I) amide to give a copper(III) species; and (3) C−N reductive elimination to give the product and regenerate the copper(I) halide.

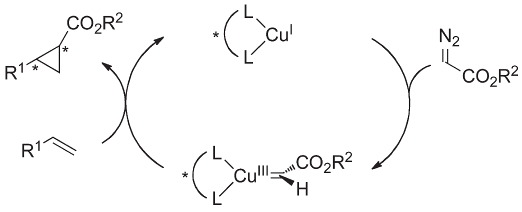
Chart 9. TS Models for Cu/PON-Catalyzed Conjugate Addition (left) and Allylic Substitution (right) of Organozinc Reagent



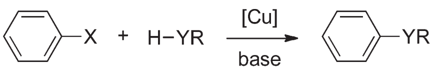
Scheme 45. General Catalytic Cycle for Copper-Catalyzed Ullmann-type C−N Bond Formation



Scheme 46. General Catalytic Cycle for Copper-Catalyzed Cyclopropanation



One can find a parallelism between this catalytic cycle and the catalytic cycles for conjugate addition and allylic substitution (see Scheme 43). However, in light of the diversity of catalytic systems and nucleophiles for the Ullmann-type reaction, the generality of the Cu(I)/Cu(III) mechanism is not clear.[308] An alternative mechanism involving a SET process is also possible.[309]



(10)

X = I, Br
Y = NR', O, S etc.

Another important reaction involving Cu(I)/Cu(III) redox reactions is a copper-catalyzed olefin cyclopropanation reaction via a copper carbenoid species (eq 11).[310] With a chiral copper(I) catalyst, the reaction serves as a useful method for the enantioselective synthesis of cyclopropanes. Considerable success has been achieved with chiral anionic or neutral bidentate ligands such as salicylaldimine, semicorrine, and bisoxazoline. Scheme 46 shows a generally accepted mechanism, which is drawn for the reaction employing an anionic bidentate ligand L_2. Thus, the reaction involves two major steps, that is, formation of a copper−carbene complex from a copper(I) catalyst and a diazo compound, and transfer of the carbene ligand to an olefin. The copper carbene complex features a rather short copper−carbene bond, as demonstrated by experiments[311] and computation,[312] which indicates significant back-donation of the copper 3d electrons to the vacant p orbital of the carbene ligand. Thus, the formal oxidation state of the complex may be regarded as Cu(III).

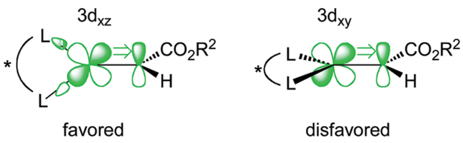
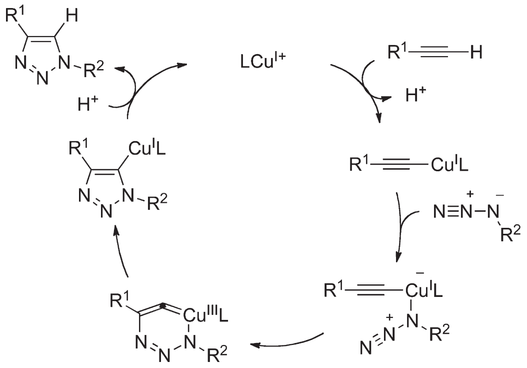
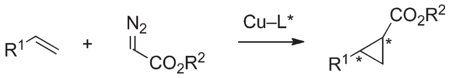


Figure 13. MO-based rationale for the geometry of the copper−carbene complex.

Scheme 47. Proposed Mechanism for Copper-Catalyzed Alkyne/Azide Cycloaddition





(11)

The geometry of the copper carbene complex deserves further comments from a molecular orbital point of view. Thus, experimental and theoretical studies invariably showed that the carbene ligand is perpendicular to the plane made by the copper atom and the bidentate ligand.[311,312] This geometry can be rationalized with the aid of FMO analysis, discussed earlier in section 2. With its bent geometry, the HOMO of the L_2Cu fragment mainly consists of the Cu $3d_{xz}$ orbital. Thus, back-donation from copper to the carbene p orbital is achieved most effectively when the carbene ligand is perpendicular to the L_2Cu fragment (Figure 13).[312e]

Copper-catalyzed alkyne/azide [3 + 2] cycloaddition, known as a "click" reaction,[313] has also been proposed to involve a Cu(I)/Cu(III) redox process on the basis of theoretical and experimental studies (Scheme 47).[314] The proposed catalytic cycle is initiated by the formation of a copper(I) acetylide from a copper(I) catalyst and a terminal alkyne. Coordination of an azide to the copper(I) acetylide followed by cyclization affords a highly strained, cyclic copper(III) vinylidene species, which readily decomposes into a triazolylcopper(I) complex. Protonation of the Cu−C bond affords the cycloadduct and regenerates the catalyst. Copper(I) acetylide and copper(III) vinylidene species might also be involved in other copper-catalyzed reactions of acetylene, for example, dimerization of acetylene known as the Nieuwland reaction.[315]

7. CONCLUDING REMARKS

Nucleophilic organocopper(I) reagents and catalysts have long been used as the most synthetically useful and versatile species in transition metal-mediated/catalyzed organic synthesis. Mechanisms of organocopper(I)-mediated C−C bond-forming reactions commonly involve three elementary steps: namely, transmetalation with main-group organometallics; oxidative addition of an electrophile to Cu(I); and reductive elimination of the resulting organocopper(III) species. The high synthetic versatility of organocopper reagents originates from several electronic and structural features. The polarizable and high-energy 3d orbitals of the copper atom in the Cu(I), d^{10} electronic configuration enable efficient inner-sphere charge transfer upon interaction with an electrophile, which leads to the formation of an organocopper(III) intermediate. The instability of the Cu(III), d^8 electronic configuration, then results in facile C−C bond-forming reductive elimination. The ability of organocuprates to form a variety of aggregate structures with Lewis acids and Lewis bases is also critical for the reaction to be successful. Lewis acidic metal atoms (including countercations) not only activate the electrophile and thereby facilitate the oxidative addition, but also may bind to the organocopper(III) intermediate to promote the reductive elimination. Lewis basic anions and ligands connect the nucleophilic copper atom and Lewis acidic cations so that various events take place within such a supramolecular complex. Such complexes are often important for regio- and stereoselectivity of C−C bond formation.

A review in *Organic Reactions* published in 1992 listed three mechanistic possibilities of conjugate addition of a cuprate to an α,β-unsaturated ketone, namely, single-electron transfer, carbocupration, and nucleophilic copper mechanisms.[5] After extensive experimental studies in the past 20 years supported by the computer-assisted theoretical analysis, it is now established beyond any doubt that the nucleophilic copper mechanism is the one operating in a majority of the reactions. Given the ever-increasing diversity of organocopper reactions,[64−77] we hope that the fundamental mechanistic frameworks discussed in this review will help understanding of new reactivity of organocopper reactions and designing of new reactions mediated or catalyzed by copper and other late transition metals. Finally, the expected scarcity of chemical elements in future society and the need to utilize base metals instead of precious metals[15] will cause researchers in the catalysis field to focus again on the value of organocopper chemistry in the coming decades.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Cartesian coordinates of representative optimized structures in the organocuprate reaction mechanisms, and a movie of the reductive elimination process in the conjugate addition reaction (cf. Figure 9). This material is available free of charge via the Internet at http://pubs.acs.org.

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Eiichi Nakamura received his Ph.D. from Tokyo Institute of Technology. He first took an academic position at this Institute and in 1995 moved to the University of Tokyo. He has been honored with the Chemical Society of Japan Award (2003), the Humboldt Research Award (2006), the Medal with Purple Ribbon from the Japanese Government (2009), and Arthur C. Cope Scholar Award of the American Chemical Society (2010). He is an Elected Fellow of the American Association for the Advancement of Science (1998), a Fellow of the Royal Society of Chemistry (2005), an Honorary Foreign Member of the American Academy of Arts and Sciences (2008), and an Honorary Member of the Israel Chemical Society (2009). His interests cover the fields of physical organic, synthetic, organometallic, bioorganic, computational/theoretical chemistry, and electron microscopy, all of which focus on reactive intermediates.

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