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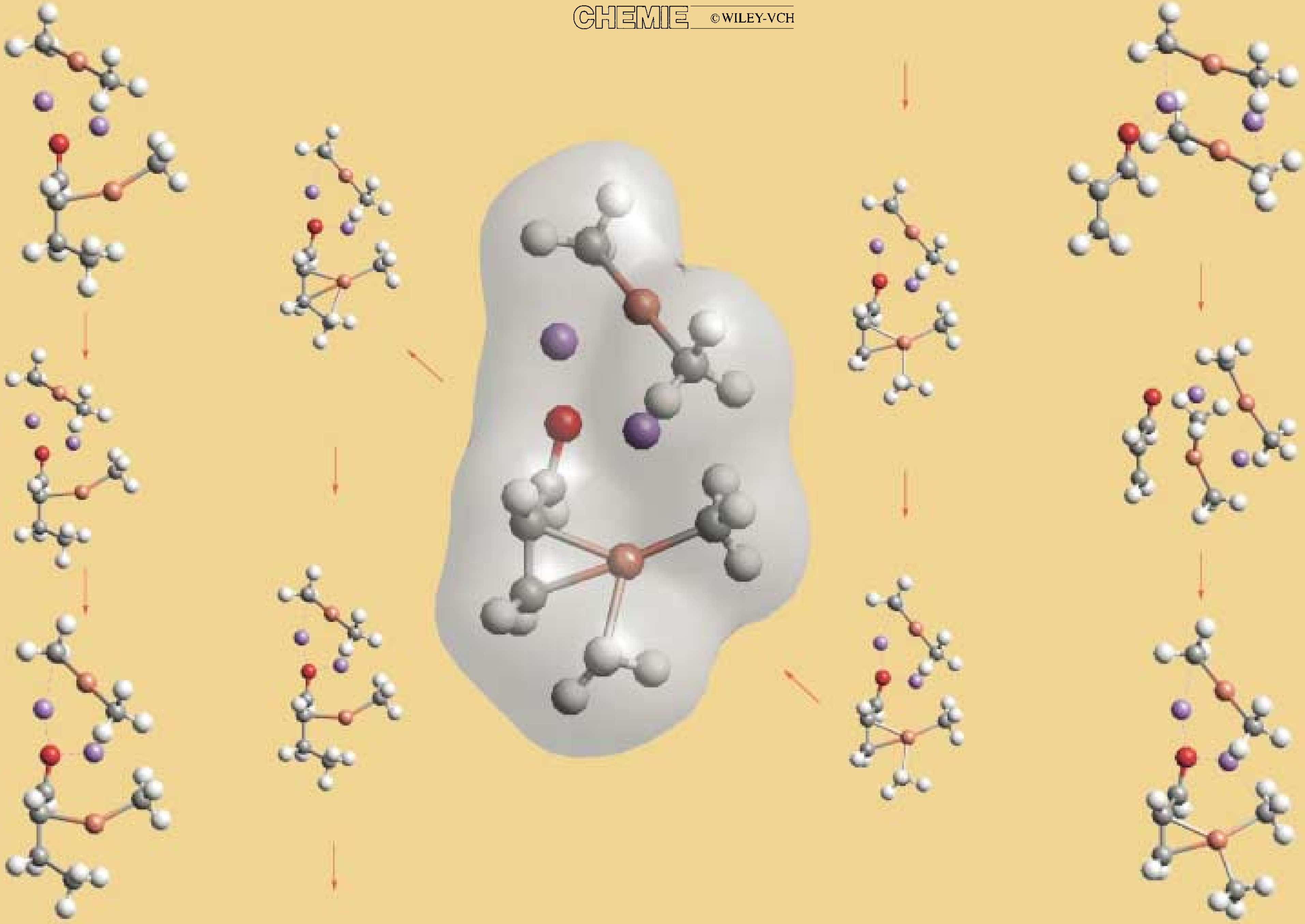


Wherefore Art Thou Copper? Structures and Reaction Mechanisms of Organocuprate Clusters in Organic Chemistry

Eiichi Nakamura* and Seiji Mori

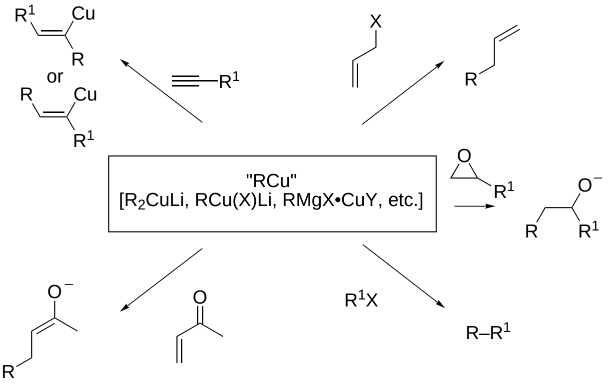
Organocopper reagents provide the most general synthetic tools in organic chemistry for nucleophilic delivery of hard carbanions to electrophilic carbon centers. A number of structural and mechanistic studies have been reported and have led to a wide variety of mechanistic proposals, some of which might even be contradictory to others. With the recent advent of physical and theoretical methodologies, the accumulated knowledge on organocopper chemistry is being put together into a few major mechanistic principles. This review will summarize first the general structural features of organocopper compounds and the previous mechanistic arguments, and then describe the most recent mechanistic pictures obtained through high-level quantum mechanical calculations for three typical organocuprate reactions, carbocupration, conjugate addition, and S_N2 alkylation. The unified view on the nucleophilic reactivities of metal organocuprate clusters thus obtained has indicated that organocuprate chemistry represents an intricate example of molecular recognition and supramolecular chemistry, which chemists have long exploited without knowing it. Reasoning about the uniqueness of the copper atom among neighboring metal elements in the periodic table will be presented.

Keywords: catalysis · conjugate additions · copper · density functional calculations · supramolecular chemistry

1. Introduction

The desire to learn about the nature of elements has been and will remain a main concern of chemists. In this review, we will consider what properties of copper make organocopper chemistry so useful in organic chemistry.

Lying on the border between the transition metals and the main group elements, copper occupies a unique position in the periodic table. The key roles of copper have been widely recognized in various areas including superconductivity,[1] biological oxygenation,[2] and organic synthesis.[3–6] The most important utility of copper in organic chemistry is in the form of nucleophilic organocopper(I) reagents, which are used either in a catalytic or a stoichiometric manner. Generally formulated as R_2CuM with a variety of metal and organic groups (M and R, respectively), metal organocuprates and related species are uniquely effective synthetic reagents for nucleophilic delivery of hard anionic nucleophiles such as alkyl, vinyl, and aryl anions (Scheme 1). Conjugate addition,[7] carbocupration,[8] alkylation,[9] and allylation[10] represent the reactions that can be achieved readily with organocuprate reagents but not with other organometallics (Scheme 1). Half a century after Kharasch and Tawney's initial discovery,[11] organocopper reagents are still the most useful synthetic reagents among transition metal organometallics.[12] The chemistry of organocopper reagents has been reviewed many times with emphasis on synthetic utility and sometimes on structural properties,[13] but rarely on reaction mechanisms.[14]



Scheme 1. Nucleophilic reactivities of organocopper reagents RCu. R = sp^2, sp^3 carbon anionic centers; X, Y = halogen, etc.

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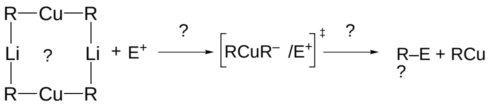
[*] Prof. Dr. E. Nakamura, Dr. S. Mori
Department of Chemistry
The University of Tokyo
Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81)3-5800-6889
E-mail: nakamura@chem.s.u-tokyo.ac.jp

In spite of the long history and popularity of copper, there remains the fundamental question: what properties of copper make organocopper reagents so useful? In a similar manner to Juliet on the balcony, we may say to ourselves "O Copper, O Copper, wherefore art thou Copper?" Information on the nature of reactive species in solution and their reactivities has been fragmentary and incomplete. The most widely accepted "resting state" of the metal organocuprate(I) species in solution is represented by the eight-centered dimer $(R_2CuLi)_2$ shown in Equation (1), but there has been little consensus on the "reactive conformation of a true reactive species". To make matters worse, the structures of the final copper-containing products are generally unknown. Those exploring the frontiers of organocopper chemistry in industry and academia have desperately required a better mechanistic understanding.



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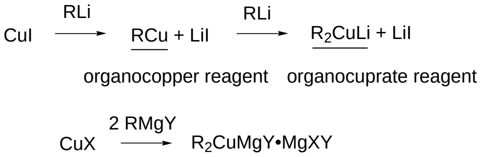
Two sources of mechanistic information have surfaced in the past several years, new analytical and theoretical methods. As recently demonstrated by Nakamura, Morokuma, and co-workers, theoretical analysis of the reactions of large lithium organocuprate clusters with realistic electrophiles has become possible with explicit consideration of solvent molecules and bulk solvent polarity.[15–23] In this review, the current status of understanding of organocuprate mechanisms will be summarized by focusing on lithium dialkylcuprate(I) clusters in the context of the following topics: (1) structures of the clusters in crystals, in solution, and as studied by theoretical methods, (2) conventional mechanistic schemes for organocuprate reactions, and (3) reaction pathways of large lithium dialkylcuprate(I) clusters as analyzed through a combination of theoretical and experimental data. We will suggest an answer to part of the question "Wherefore art thou copper?"

1.1. Historical Background and Recent Progress

The initial implication of the forthcoming golden age of organocopper chemistry was in 1941, when Kharasch and Tawney[11] reported the 1,4-addition reaction of a Grignard reagent to an α,β-unsaturated ketone in the presence of a small amount of a Cu^I salt.[24] Gilman et al. reported in 1952 that addition of one equivalent of MeLi to a Cu^I salt results in the formation of yellow precipitates, which then afford a colorless solution upon addition of another equivalent of MeLi (Scheme 2).[25] In 1966 Costa et al. isolated a complex between phenylcopper(I) and magnesium, as well as crystals of a lithium diphenylcuprate(I) complex.[26] Although the organocopper reagents derived from Grignard reagents are widely used and may be described as R_2CuMgX, it is still uncertain to what extent this reflects the reality in solution.



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

organocopper reagent organocuprate reagent

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

Scheme 2. Preparation of organocopper reagents.

The organic chemistry of organocuprates started its rapid development in 1966, when House et al. showed that the reactive species of conjugate addition is the lithium diorganocuprate(I) called the "Gilman reagent".[27] Foundations for subsequent vigorous synthetic development were laid by Corey and Posner,[28] and other important initial developments, such as substitution reactions on sp^2 carbons or in an allylic system[10, 29–31] and the carbocupration of acetylene[32] were reported before the mid 1970s.

The nature of the Gilman reagent now needs some careful definition. While numerous reports (in particular, old ones) describe the Gilman reagent as R_2CuLi, a vast majority of

Eiichi Nakamura received his PhD in Chemistry from Tokyo Institute of Technology in 1978. Following postdoctoral study in the Department of Chemistry at Columbia University, he joined the faculty of his alma mater in 1980 and was promoted to the rank of full professor in 1993. In 1995, he moved to the Department of Chemistry of the University of Tokyo. His interest in the dynamism of action of organic molecules forms the basis for his research activities which range through organic synthesis, chemical theory, and biology.

E. Nakamura

S. Mori

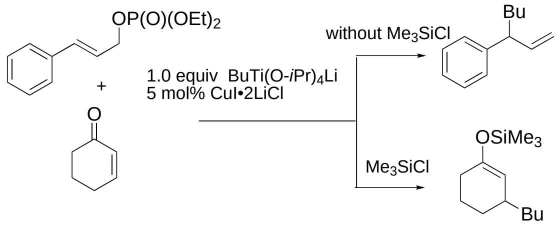
Seiji Mori was born in 1968 in Tokyo. He studied at the Tokyo Institute of Technology, and was awarded his BSc in 1993 and MSc in 1995. In 1998, he recieved his PhD degree at the University of Tokyo under the guidance of Professor Eiichi Nakamura. He became a fellow of Japan Society for the Promotion of Science in 1997, worked at Emory University in USA, and is currently an assistant professor at Ibaraki University in Japan. His research interests center on the theoretical studies of organic and organometallic reactions.

them actually used an LiX cluster $R_2CuLi\cdot LiX$, prepared by an in situ reaction between RLi and CuX (X = Br, I, or CN, sometimes with a ligand such as Me_2S and PR_3). Although R_2CuLi and $R_2CuLi\cdot LiX$ may show largely the same reactivities, Lipshutz et al.[33] showed by analyses of reactivities and spectroscopic properties that they are indeed different species. Even a small difference of solvent may affect the composition of the reagent and hence the reactivities. Due to such complexity, it is now customary to show all ingredients upon describing a reagent (for example, $R_2CuLi\cdot LiI\cdot Me_2S/BF_3\cdot Et_2O$ in THF/hexane).

Shortly after the opening of the "Lewis acid age" with the discovery of the Mukaiyama aldol reaction in 1973,[34] Yamamoto and Marayama's reports on the "$RCu\cdot BF_3$" reagent[35] introduced the new concept of Lewis acid assistance in organocopper chemistry.[36] Although the identity of $RCu\cdot BF_3$ is still elusive,[37] the BF_3 activation was applied to numerous synthetic works, as illustrated in Scheme 3 by a diastereoselective addition of a homoenolate species in a total synthesis.[38]

Since the initial discovery by Nakamura and Kuwajima in 1984,[39] Me_3SiCl has become a standard reagent for acceleration of conjugate addition. This effect was reported first for the copper-catalyzed conjugate addition of the zinc homoenolate of propionic acid esters, as shown in Scheme 3, then for Grignard-based catalytic reagents[40, 41] and stoichiometric lithium diorganocuprate(I)s.[42–46]

The zinc homoenolate started the chemistry of metal homoenolates.[47–49] The synthetic scope of such a "nucleophile-bearing electrophile" was further exploited by Tamaru, Yoshida,and co-workers first,[50] and then extensively by Knochel et al., and others.[51–53] Dominated by lithium- and magnesium-based systems until the mid 1980s, organocopper chemistry now routinely utilizes much milder organometallic nucleophiles, such as organozinc, -titanium,[54] -zirconium,[55, 56] and -aluminum reagents.[57] With the aid of proper activators, these mildly reactive reagents show selectivities unavailable with the conventional reagents, as illustrated in Equation (2) for Me_3SiCl-dependent chemoselectivity.[58]



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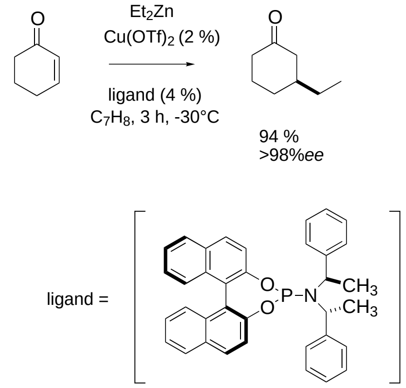
Organocopper chemistry is still rapidly expanding its synthetic scope. The scope of carbocupration, previously limited to acetylenes, has been extended to olefins.[59–62] Enantioselective conjugate addition[63] has become truly useful through the use of dialkylzinc, a cationic copper catalyst, and a chiral ligand [Eq. (3)].[64] Magnesium-based reagents have found use in quantitative fivefold arylation of C_{60}[65] [Eq. (4)] and threefold arylation of C_{70};[66] this paves the way to new classes of cyclopentadienyl and indenyl ligands with unusual chemical properties.[67]



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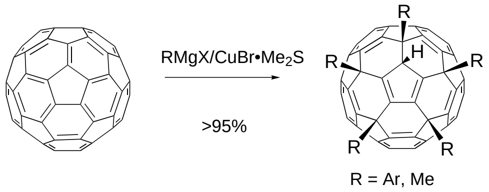

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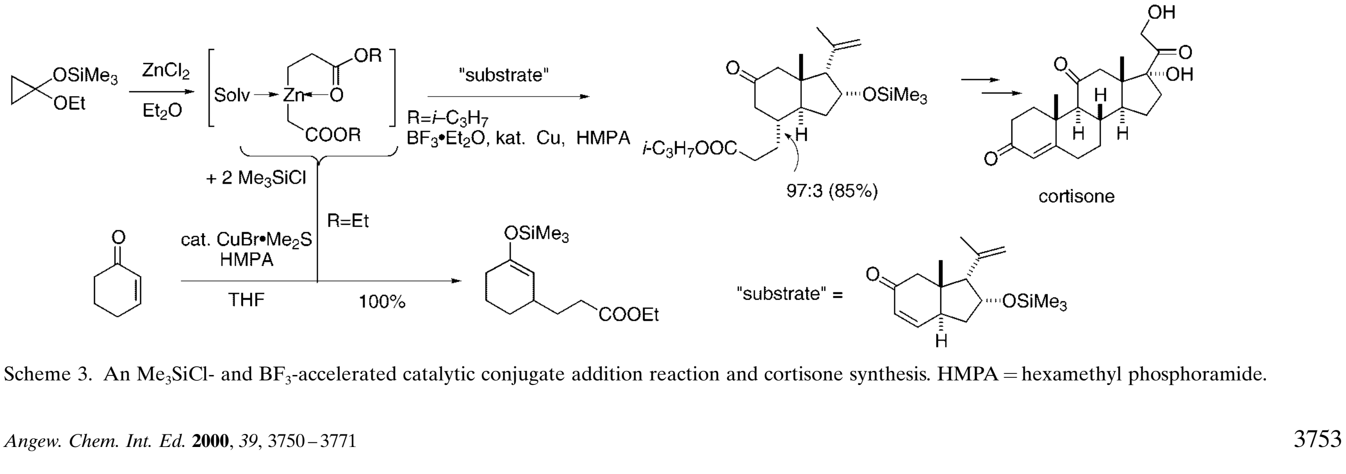
1.2. Controversial Mechanistic Issues

With the lack of detailed mechanistic information, various fundamental mechanistic issues have remained the subject of controversy. They are outlined in this section and some will be discussed later in more detail.



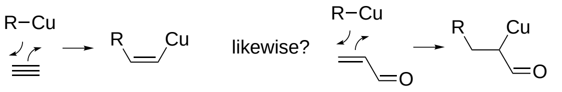
Scheme 3. An Me_3SiCl- and BF_3-accelerated catalytic conjugate addition reaction and cortisone synthesis. HMPA = hexamethyl phosphoramide.

1.2.1. The Single Electron Transfer Controversy

House proposed in the 1970s[68] that conjugate addition of organocuprate starts with single-electron transfer (SET) from the reagent to the enone substrate, and this hypothesis became widely believed for some time. After many years of studies, however, the evidence obtained for SET has proven to be too weak to substantiate this once-favored mechanism.

1.2.2. The 1,2-Addition Mechanism in Conjugate Addition

Conjugate addition and carbocupration were once suggested to take place through direct 1,2-addition of R–Cu across a C–C multiple bond [Eq. (5)].[69] As detailed in Section 4, recent theoretical studies have shown that the two reactions do take place in the same manner but not through this mechanism.



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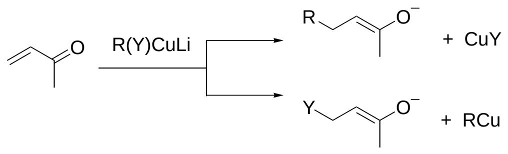
1.2.3. The Dummy Ligand

A synthetic problem associated with the use of homoorganocuprates $[R_2Cu]^-$ is that the reagent can transfer only one of the two precious R ligands to the target electrophile (E^+, for example, an α,β-unsaturated carbonyl compound) and one R ligand is lost as an unreactive RCu species. The introduction, in 1972, of mixed organocuprates $[R(Y)Cu]^-$,[70] in which the Y group acts as a nontransferable dummy ligand, provided the first general solution to this problem [Eq. (6)]. Typical dummy ligands include alkynyl,[71] cyano,[72] phenylsulfanyl,[73] dialkylamino, and phosphanyl groups.[73, 74] The selectivity of ligand transfer has been thought to arise during the process of ligand–ligand coupling in an intermediate bearing three ligands, R, Y, and E. A widely accepted hypothesis has been that a Y group forming a stronger Cu–Y bond acts as a better dummy ligand (because it resists transfer). While this hypothesis has been successfully applied to the design of dummy ligands, recent theoretical studies by Nakamura and Yamanaka revealed an entirely different controlling factor in the dummy ligand chemistry (see Section 4.2).[22]



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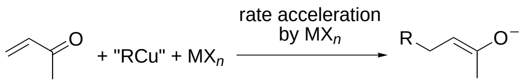
1.2.4. Lewis Acid Effects of the Countercation

It has been shown for all major categories of lithium organocuprate reactions[15, 17, 75] that addition of a crown ether significantly retards the desired reactions. In addition, sodium organocuprates are much inferior to lithium organocuprates for conjugate addition.[76] On the other hand, $BF_3 \cdot Et_2O$ accelerates conjugate addition[35] and alkylation of epoxides.[77] In the allylation chemistry, zinc-,[49] titanium-,[54] and aluminum-[78] based organocopper reagents show much higher S_N2' selectivity than lithium organocuprate. The Lewis acidity of the countercation to the organocuprate is undoubtedly important, but the mechanistic role still needs further studies [Eq. (7)].[18, 23]



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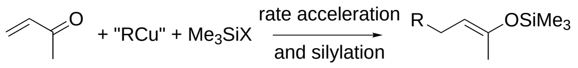
1.2.5. Me$_3$SiCl Acceleration

Acceleration and change of selectivity of conjugate additions by a silylating agent are now well established [Eq. (8)].[46] Me_3SiCl also affects the stereoselectivity of carbonyl 1,2-addition.[79] Considerable mechanistic discussions have occurred in the literature.[80] One argument assumes simple Lewis acid activation of the starting enone with Me_3SiCl,[81] which is supported neither by experiments nor by theory.[82] To the contrary, the lithium cation in the organocuprate reagent has been shown to coordinate to Me_3SiCl (on the chlorine atom).[80a] Chloride coordination to copper was suggested by theory[80b] on the basis of seemingly erroneous experimental data.[83] Another theorem, combined with an inner-sphere electron-transfer hypothesis, assumes in situ trapping of an enolate-like intermediate by the silylating agent, which makes the process irreversible.[42] The positive correlation between the silylation power of the reagent and the magnitude of rate acceleration[83, 84] suggests that the rate-determining step of the reaction is the silylation step rather than the C–C bond-forming step. Mechanistic data such as reaction rate, stereochemistry, and theoretical analysis are still lacking, however.



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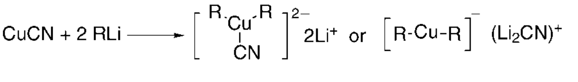
1.2.6. The Higher Order Organocuprate Controversy

Organocopper(I) species bearing three anionic groups, $[R_3Cu]^{2-}$, are called "higher order" organocuprates.[27] To allow differentiation, conventional organocuprate(I) species $[R_2Cu]^-$ may be called "lower order organocuprates". It has been the subject of controversy whether or not there exists, as a stable species, a higher order lithium cyanocuprate "$R_2Cu(CN)Li_2$" that bears two carbanionic residues and a cyanide anion on the copper [Eq. (9)]. The controversy generated numerous mechanistic and structural studies on organocuprates in general.


$$CuCN + 2\,RLi \longrightarrow \left[R_2Cu(CN) \right]^{2-} 2Li^+ \text{ or } \left[R\text{-}Cu\text{-}R \right]^- (Li_2CN)^+ \quad (9)$$

It was reported in the 1970s that a higher order organocuprate reagent, which was prepared by the use of more than two equivalents of an alkyllithium reagent for a copper(I) salt, is more reactive[27, 85, 86] and more selective than ordinary organocuprates.[87] Ashby and Watkins showed by NMR spectroscopy and cryoscopy that species form which may be considered as higher order organocuprates.[88] Bertz and Dabbagh demonstrated for the first time the presence of a tricoordinated Cu^I complex ($[R_3Cu_2]^-$) by solution NMR spectroscopic studies,[89] and Olmstead and Power[90]demonstrated the existence of a tricoordinated organocuprate $[Li_3Cu_2Ph_5(SMe_2)_4]$ in crystals.[91]

Lipshutz et al. reported that reagents formed by addition of two equivalents of RLi to CuCN are higher yielding than the corresponding Gilman organocuprates (R_2CuLi) or lower order cyanocuprates (RCu(CN)Li), and described it as $R_2Cu(CN)Li_2$ to imply a tricoordinated structure.[72b, 92] With the aid of ^{13}C, ^{6}Li, and ^{15}N NMR data,[93, 94] Bertz et al. pointed out that cyanide is not attached to copper(I) in the Lipshutz mix, and started the controversy.[95] Physical measurements by Penner-Hahn and co-workers[96, 97] and Lipshutz et al.,[98] and theoretical studies by the groups of Snyder,[99] and Penner-Hahn and Frenking[97] contributed much to the discussion. All of the recent crystallographic data for the cyanocuprates of "higher order stoichiometry" reported by Boche et al.[100] and van Koten and co-workers[101] indicated that the cyanide anion is coordinated to lithium and not to copper. Consensus after many years of studies is therefore that three-coordinated $[R_2Cu(CN)]^{2-}$ is not a stable structure in ethereal solution.[94, 102–104] In spite of this conclusion, the Lipshutz mix still remains as the reagent of choice in many synthetic transformations,[105] and the presence of a tricoordinated cuprate(I) dianion was indicated by $^{13}C-^{13}CN$ carbon coupling for the cyanostannylvinylcuprate(I) dianion in a mixture of THF/HMPA.[106] In addition, the cyanide anion finds its way to copper at the end of the reaction and forms RCu(CN)Li, although it is not known when the cyanide–copper coordination starts. The true role of the cyano group in the reactions of higher order cyanocuprates still remains obscure.[103]

1.2.7. Other Issues

While a large number of studies have reported on conjugate addition and S_N2 alkylation reactions, mechanisms of many important organocopper reactions have not been discussed. These reactions involve substitution on sp^2 carbons,[28] acylation with acyl halide,[107] carbonyl addition, oxidative coupling,[108] nucleophilic opening of electrophilic cyclopropanes,[109] and the Kocienski reaction.[110] The chemistry of organocopper(II) species has rarely been studied experimentally[111–113] or theoretically.

2. Structures of Organocopper Compounds

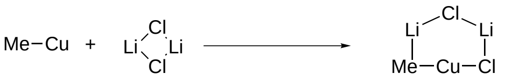
Organocopper compounds can be classified into four basic types, RCu^I, R_2Cu^ILi, $R_3Cu^ILi_2$, and R_3Cu^{III}. As represented by polymeric MeCu, the RCu reagents are unreactive and not very useful synthetic reagents. R_2CuM (M = Li, MgX, etc.) and $R_3Cu^ILi_2$ generated in situ are the most useful sources of carbon nucleophiles and hence have been studied most extensively. The structure of the R_3Cu^{III} species, which has long been discussed in the literature without rigorous proof of its existence, was recently determined. A summary of the structures of organocopper reagents will be given below. Discussions will be limited to those pertinent to the understanding of organocuprate reaction mechanisms, as more extensive structural reviews[13] have already been published. Several representative crystal structures are shown in Figure 1, and will be discussed in the following sections.

2.1. Mono- and Dicoordinated Organocopper(I) Compounds

2.1.1. Neutral Organocopper(I) Compounds: RCu

Though MeCu itself is polymeric in ethereal solution, RCu may form a monomeric cluster such as $[MeCu(PPh_3)_3]$ in the presence of a ligand having high affinity to copper (such as phosphane; Figure 1 a).[114] A strong neutral donor ligand (like PPh_3) may increase the reactivity of a neutral organocopper reagent.[115] Neutral organocopper(I) compounds have also been characterized as eight-centered cyclic tetramers, for example, $[(2\text{-}Me_2NC_6H_4)Cu]_4$,[116] $[(Me_3SiCH_2)Cu]_4$,[117] and $[PhCu]_4 \cdot 2\,Me_2S$[118] (Figure 1 b). We see here that a copper atom in a neutral RCu compound may accept a solvent molecule as a ligand. It is a general characteristic of neutral RCu aggregates that we find a three-center two-electron bonding pattern and the copper atoms solvated with a heteroatom ligand.

Since the method commonly used for generation of RCu species produces an extra alkali metal salt in solution (Scheme 2), the reagent commonly described as a neutral RCu reagent may react as a halocuprate complex. In fact, density functional calculations indicate that conversion of free monomeric MeCu into a six-centered cluster MeCu · 2 LiCl is an energetically favorable process [Eq. (10)].[17] In addition,



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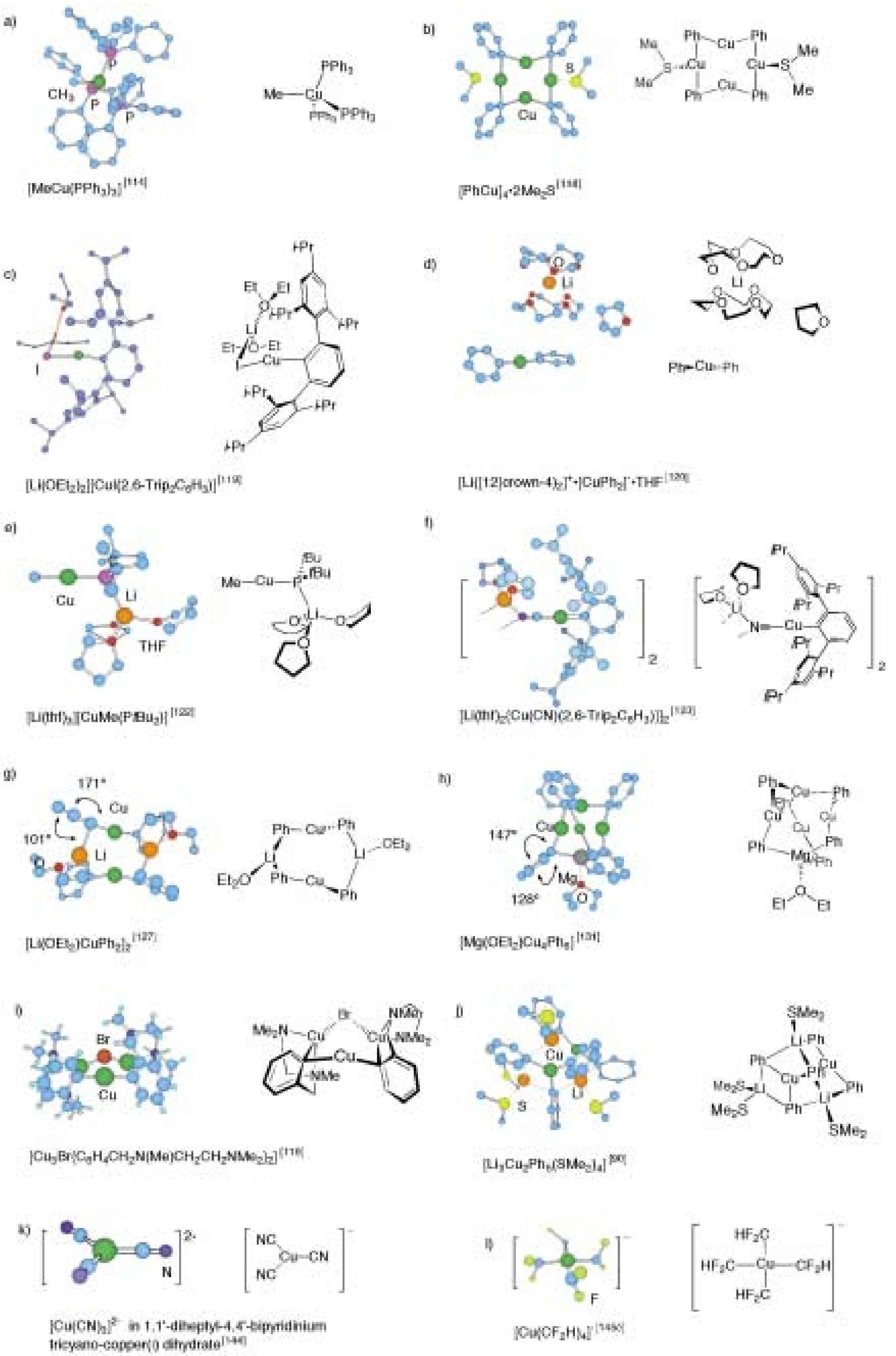
the crystal structure of a mixed alkylhalocuprate bearing an R−Cu−X moiety was reported recently (Figure 1 c).[119] The particular compound reported was isolated as a monomeric species owing to the bulkiness of the organic group.

2.1.2. Linear Free Organocuprates: $[R_2Cu]^-$

The most basic structural property of diorganocuprate(I) is their linear R−Cu−R arrangement. It is clearly seen in $[Li([12]\text{-crown-}4)_2]^+[CuPh_2]^- \cdot THF$, prepared by mixing Ph_2CuLi and the crown ether (Figure 1 d).[120] A linear organocuprate structure of $[Me_2Cu]^-$[120] was also identified in crystals. Note that these solvent-separated ion pairs are unreactive in many standard organocopper reactions, the



a) $[MeCu(PPh_3)_3]$[114]

b) $[PhCu]_4 \cdot 2Me_2S$[118]

c) $[Li(OEt_2)_2][CuI(2,6\text{-}Trip_2C_6H_3)]$[119]

d) $[Li([12]crown\text{-}4)_2]^+ \cdot [CuPh_2]^- \cdot THF$[120]

e) $[Li(thf)_3][CuMe(PtBu_2)]$[122]

f) $[Li(thf)_2\{Cu(CN)(2,6\text{-}Trip_2C_6H_3)\}]_2$[123]

g) $[Li(OEt_2)CuPh_2]_2$[127]

h) $[Mg(OEt_2)Cu_4Ph_6]$[131]

i) $[Cu_3Br(C_6H_4CH_2N(Me)CH_2CH_2NMe_2)_2]$[118]

j) $[Li_3Cu_2Ph_5(SMe_2)_4]$[90]

k) $[Cu(CN)_3]^{2-}$ in 1,1'-diheptyl-4,4'-bipyridinium tricyano-copper(I) dihydrate[144]

l) $[Cu(CF_2H)_4]^-$[145]

Figure 1. Crystal structures of representative organocopper compounds. Hydrogen atoms are omitted for clarity. In (g) and (h) the dihedral angles are given. Trip = 2,4,6-iPr$_3$C$_6$H$_2$.

reasons for which have recently been elucidated by the studies of Nakamura, Morokuma and co-workers.[15]

2.1.3. *Minimum Lithium Organocuprate Clusters: R_2CuLi*

Coordination of a lithium cation to the linear R–Cu–R anion creates R–Cu–R–Li, which may be called a minimum lithium diorganocuprate(I) cluster. For the partial charges on the two ends to be neutralized, the minimum cluster dimerizes, polymerizes, or attracts an ambiphilic LiX unit to form a closed cluster, $R_2CuLi \cdot LiX$.[121] Due to the high energy cost of bending the R–Cu–R bond,[21] the four-centered cyclic structure (often found for alkyllithium compounds) does not form.

Monomeric $[Li(thf)_3][CuMe(PtBu_2)]$ (Figure 1 e)[122] has been observed in crystals obtained from a reagent mixture that shows the typical reactivity of an organocuprate bearing a dummy ligand. In the structure of linear dimers of lower order cyanocuprates ArCu(CN)Li (Figure 1 f),[123] we also see strong Li–N association. Such a dimeric unit structure may be found in a polymeric complex.[100]

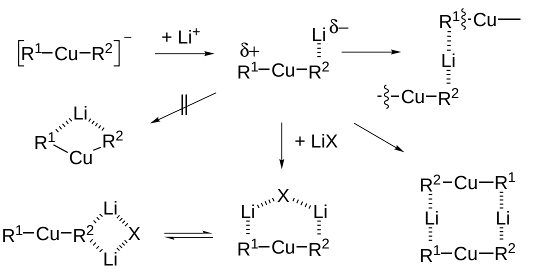
2.1.4. *Closed Clusters: $R_2CuLi \cdot LiX$ and $(R_2CuLi)_2$*

The neutral closed cluster is widely detected in crystals and in solution, and accepted as the typical resting state of lithium organocuprates in ethereal solution. Eight-centered dimers of R_2CuLi were suggested first by van Koten and Noltes on the basis of NMR spectroscopic and cryoscopic analyses of lithium diarylcuprate(I) compounds in benzene.[124] The dimeric structure was further indicated in NMR spectroscopy, cryoscopic, and X-ray scattering experiments by Pearson and Gregory.[125] Following the first crystal structure determination of a R_2CuLi by van Koten et al.,[126] Weiss and Lorenzen, and Olmstead and Power determined various dimeric structures $[\{[Li(OEt_2)]CuPh_2\}_2]$ (Figure 1 g),[127] $[Li_2(SMe_2)_3Cu_2Ph_4]$,[118] and $[\{[Li(SMe_2)]Cu(Me_3SiCH_2)_2\}_2]$.[128] These structures have their lithium cation tricoordinated (two R groups and one solvent molecule). The R groups (aryl and alkyl) are pentacoordinated with a stronger bond to copper and a weaker electrostatic bond to lithium. As seen from the metal–C_{ipso}–C_{ortho}–C_{meta} angles in lithium diphenylcuprate (Figure 1 g), the copper atom is σ-bonded and the lithium atom is π-coordinated to the *ipso* phenyl carbon atom. In a dialkylcuprate(I), the copper atom is covalently bound to a nearly tetrahedral sp^3 carbon, which is electrostatically associated with a lithium atom. Unlike the copper atom in neutral RCu complexes (see Section 2.1.1.), the negatively charged copper atom is not Lewis acidic and does not accept an extra ligand (solvent).[129, 130]

A structure of an organomagnesium-based organocopper(I) compound is known and has a magnesium-bridged structure (Figure 1 h).[131] As seen from the dihedral angle in Figure 1 h, the Lewis acidic magnesium atom is more tightly bound to the phenyl group than than the lithium in the lithium organocuprate. Organocuprates bearing more Lewis acidic metals such as zinc(II) and titanium(IV) cations have not yet been characterized.[132]

While no crystal structures have been determined for $R_2CuLi \cdot LiX$ (X = halogen), the presence of $(Li_nX_{n+1})^-$ units in organocuprate clusters has been suggested through studies using electrospray ionization mass spectrometry.[133] The six-centered structure of a neutral arylcopper complex (Figure 1 i)[116] offers a good model, and is similar to the structure of $Me_2CuLi \cdot LiCl$ or $Me_2CuLi \cdot LiI$ determined by calculations.

In the hypothetical structural conversion shown in Scheme 4, we may start with a free dialkylcuprate(I) anion $[R^1R^2Cu]^-$ and go through a minimum cluster R^1R^2CuLi to either polymers, eight-centered dimers, or mixed cyclic clusters. The linear R^1–Cu–R^2 structure will be retained throughout the conversion. The stable linear C–Cu–C geometry is due to bonding participation of the copper d_{z^2} orbital.[21]



Scheme 4. Various structural possibilities of cuprates. Solid lines indicate (largely) covalent bonds and dashed lines indicate (largely) electrostatic bonds between a metal cation and an organic or heteroatomic anion. (Such distinctions will not be generally made in the remaining schemes in this review.) X = RCuR, halogen, CN, etc.

2.1.5. *Dynamic Equilibria in Solution*

Although the crystal structures offer important reference points, they do not reflect the reactive conformations of these species in solution. Recent experimental studies revealed a wealth of information on the time-averaged, as well as dynamic, structures in solution.

The Me_2CuLi dimer is the species studied most carefully. Its molecular weight indicates a (time-averaged) dimeric structure in diethyl ether and Me_2S, and X-ray scattering studies support this conclusion by showing the Cu–Cu distance in solution as 2.6–2.8 Å,[125, 130] which is close to the value in crystals. The extended X-ray absorption fine structure (EXAFS) spectra in solution indicate dicoordination of the copper atom with a C–Cu bond length of 1.94–1.96 Å.[130, 134] All these data are consistent with the persistence of the eight-centered structure both in crystals and in solution.

Cryoscopic measurement of the reagent $Me_2CuLi \cdot LiI$ in THF indicated persistence of this stoichiometry,[135] whose stable structure was shown by theory to be the six-centered structure shown in Scheme 4. Supporting such a structure, EXAFS spectroscopic studies on $Me_2CuLi \cdot LiCN$ and $Me_2CuLi \cdot LiI$ in THF indicated a single Cu atom in a cluster.[96a, 130, 136] According to NMR spectroscopy studies in diethyl ether,[137] the cuprate may exist as an equilibrium mixture of the Me_2CuLi dimer and the LiX cluster.

Recent NMR studies by Berger and co-workers on the cuprates Me_2CuLi, $Me_2CuLi \cdot LiMe$, and $Me_2CuLi \cdot LiCN$ in THF revealed the dynamic properties of the clusters in solution.[104] The lithium atom exists in the time-averaged vicinity of the methyl group in the $[Me_2Cu]^-$ moiety, but rapidly exchanges with other lithium atoms. Hence, a predominant and thermodynamically stable cyclic cluster undergoes fast and reversible cleavage of the Me–Li electrostatic bond (Scheme 5). The spectroscopic observations are consistent with the experimental and theoretical thermodynamic considerations. Dissociation of the $(Me_2CuLi)_2$ dimer to the monomer is enthalpically highly disfavored by gas-phase calculations,[138] and must also be entropically disfavored due to solvent participation,[139, 140] as is known experimentally for alkyllithium oligomers (see Equation (11); the dissociation process is accompanied by a loss of 18.8 cal mol^{-1} K^{-1}[140]).

$$(BuLi)_4{\bullet}4THF \quad + \quad 4\,THF \quad \rightleftharpoons \quad 2[(BuLi)_2(thf)_4] \qquad (11)$$

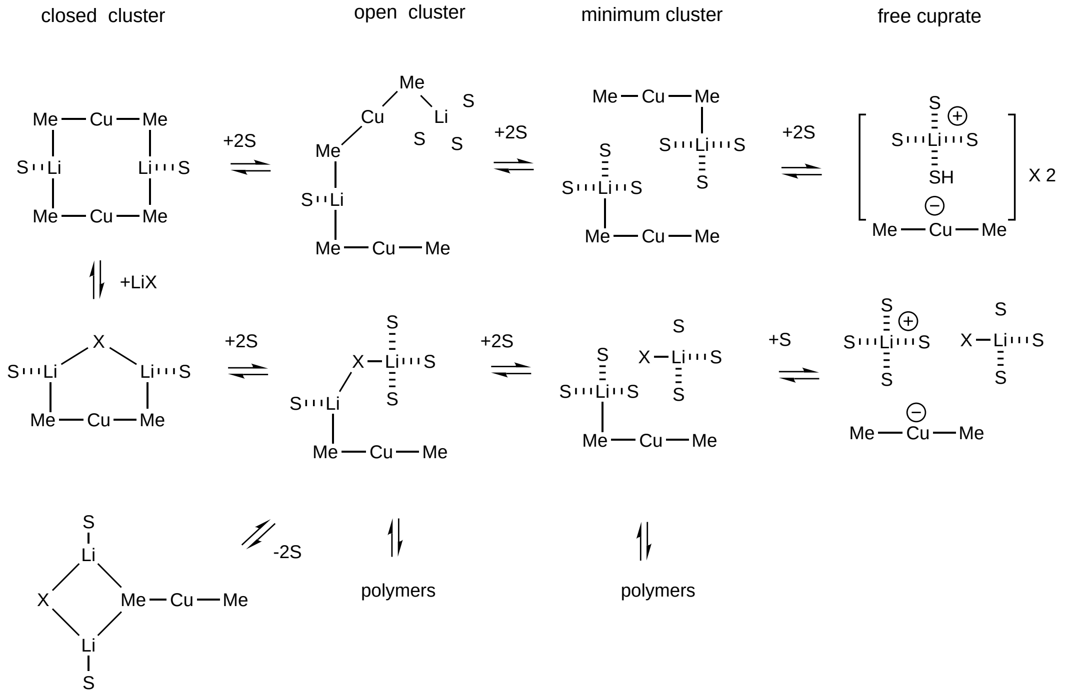
The presence of lithium halide is known to affect reactivities and selectivities,[33] but only to an energy scale of a few kcal mol^{-1} of activation energy. This may be partly due to accelerated cluster reorganization or to coordination of lithium halide to a Cu^{III} intermediate, which is formed during nucleophilic reactions. In the light of contrasting reports (one reports slower conjugate addition in THF than in diethyl ether,[141] another reports a faster reaction in toluene,[142] and the further one reports that 1,4-addition in toluene can be promoted over 1,2-addition in the presence of Me_2S[143]), solvent effects are a difficult subject to deal with.

Putting together the body of current data, one can draw a series of mobile equilibria, as shown in Scheme 5, for $(Me_2CuLi)_2$ and $Me_2CuLi \cdot LiX$; they will dissociate sequentially into free $[Me_2Cu]^-$ with Gibbs free energy loss in ethereal solution. $Me_2CuLi \cdot LiX$ equilibrates with the dimer through exchange of an Me_2CuLi unit with LiX. Oligomers and polymers may also form. As will be discussed in Section 4, the "open cluster" (among other clusters) serves as a gateway channel to organocuprate reactions.

2.2. Tricoordinated Copper Compounds: $[R_3Cu^I]^{2-}$ and R_3Cu^{III}

2.2.1. Higher Order Organocuprates

$[Li_3Cu_2Ph_5(SMe_2)_4]$ (shown in Figure 1j)[90, 91] is the only crystal structure known for the controversial[89] nucleophilic higher order organocuprates. This complex forms only from a dimethylsulfide solution, and not from diethyl ether or THF. Therefore it is not clear if the higher order organocuprates can also exist in ethereal solution. Solution NMR studies[104] indicated that Me_3CuLi_2 dissociates into Me_2CuLi and MeLi through rapid exchange of lithium atoms. As to the controversial higher order cyanocuprates, no such tricoordinated copper(I) species have been experimentally or theoretically identified, except a case reported for $[Cu(CN)_3]^{2-}$(Figure 1k),[144] where the two negative charges are stabilized by the presence of three cyano groups. Other than this tricyano structure, all known organocuprates of a higher order cyanocuprate stoichiometry have usual dicoordinated copper centers.[100, 101, 123]



Scheme 5. Rapid cluster equilibration for $(Me_2CuLi)_2$ and $Me_2CuLi \cdot LiX$. Dashed lines indicate coordination between a metal cation and a neutral solvent molecule or ligand; S = solvent; X = halogen, CN, RO, etc.

2.2.2. Organocopper(III) Species

Although trialkylcopper(III) species have appeared in numerous mechanistic discussions since the 1970s, it is only since the late 1980s that crystal structures substantiated the presence of such species. We now have three crystal structures of discrete organocopper(III) species.[145] As illustrated for $[Cu(CF_2H)_4]^-$ in Figure 11,[145c] all of them are nearly square planar in geometry in consonance with the formal d^8 electronic system of the copper atom, and they can be regarded as T-shaped neutral Cu^{III} species bearing a fourth ligand. Recent theoretical analysis on the stability of Me_3Cu^{III} [146–149] supported the stabilizing effects of a donor ligand.

2.3. Theoretical Analysis of Organocopper Structures

Although a variety of structural data were already accumulated by the beginning of the 1990s, connecting this mass of structural data into molecular level mechanisms has been a difficult task. With the advent of theory and computers, quantum mechanical calculations are now playing the key role. The development of post Hartree–Fock (HF) and density functional calculations, which was honored by the 1998 Nobel Prize, has made a strong impact on the study of organocopper chemistry.

Pioneering theoretical works by Poirier et al.,[150] Ziegler et al.,[151] Morokuma et al.,[152, 153] Bauschlicher et al.,[154] Frenking et al.,[155] and Baerends et al.[156] often used monomeric MeCu. Studies by Hwang and Power, Snyder et al., Sosa et al., and Frenking and co-workers demonstrated the importance of electron-correlated calculations in the structural studies of organocuprate clusters.[119, 121a, 157, 158] The electron-correlated methods (MP2, B3LYP, and higher levels) are mandatory for description of the intermediates and transition states in the reactions of lithium organocuprate clusters. Good description of the high-lying copper 3d orbitals is necessary. The HF calculations give very low-lying d_{xz} orbitals, and understandably fail in adequate description of π-backdonation ability of the cuprates.[19] As is the case for R_2Zn, neutral RCu has 3d orbitals that are too low-lying to be nucleophilic, and it behaves rather as a Lewis acid.[19] Relativistic effects on copper are small on structures and energetics.[15] The high activation energies of MeCu addition reactions obtained in earlier studies[115, 156, 157] are due to lack of d-orbital participation.

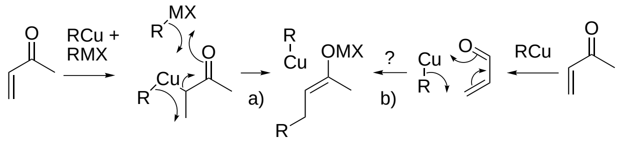
3. Experimental Studies on Organocuprate Reaction Mechanisms

Mechanistic studies on organocuprate reactions have been hampered by the complexity of the cluster structures. Crystallographic and spectroscopic structural analyses have provided information only for discrete data points. Various contradicting mechanistic proposals have made obscure the mechanistic pictures of organocuprate chemistry. Nonetheless, a certain mechanistic consensus has been achieved, and is summarized in the following sections. Three important categories of organocuprate reactions, conjugate addition, carbocupration reactions, and alkylation reactions, have been most extensively studied.

3.1. Conjugate Addition

3.1.1. The Four- and Six-Centered Mechanisms

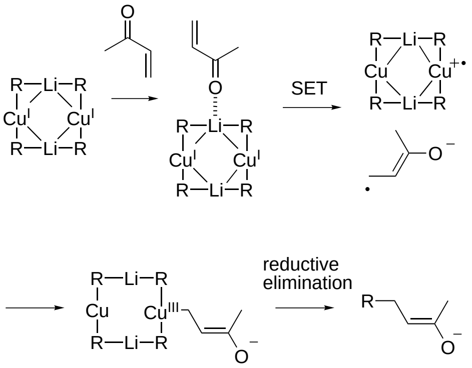
Four-centered addition of RCu to an enone was discussed in the 1960s.[162] There have been discussions about a six-centered transition state until recently,[152] but this does not explain however the formation of an *E*/*Z* mixture of enolate stereoisomers.[159, 160] These mechanisms (Scheme 6) must now be considered obsolete.



Scheme 6. a) 1,2-Addition and b) 1,4-addition mechanisms.

3.1.2. The Single Electron Transfer Theorem

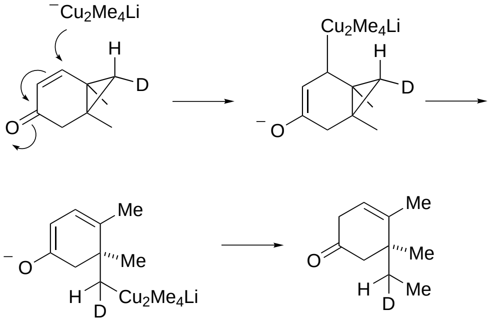
House and co-workers pioneered the synthetic and mechanistic studies of organocuprate reactions in the 1970s. In their papers a mechanism was proposed that assumes a single electron transfer (SET) from the dimer which would lead to a Cu^{III} intermediate (Scheme 7).[68, 161] The SET/Cu^{III} theorem had a strong impact for many years. However, most of the experimental facts, once considered to support the SET process, are not accepted as evidence of SET now. Only the Cu^{III} hypothesis has survived the test of the time.



Scheme 7. The House mechanism of 1,4-addition.

1) *E*/*Z* Isomerization of the olefinic part in an enone was once taken as evidence for reversible electron transfer. It was later reported that the isomerization takes place even in the presence of LiI, a usual component of the Gilman cluster reagent (that is, $Me_2CuLi \cdot LiI$).[163] Such isomerization is also possible by reversible generation of an advanced d →π* copper/enone complex along the reaction pathway,[42, 164] and, thus, does not represent strong evidence of SET.

2) Qualitative correlation of the apparent rate of 1,4-addition with the reduction potential of the enone[161] was later proven by quantitative kinetic studies by Krauss and Smith to be only superficial.[165]
3) β-Cyclopropyl α,β-unsaturated ketones, such as the one shown in Equation (12), often give a ring-opened product, which was taken as strong evidence for radical anion formation by SET.[166] An elegant study by Casey and Cesa with deuterium-labeled substrate indicated stereospecificity of the cyclopropane ring opening that denies the radical mechanism [Eq. (12)].[167] On the basis of a series of control experiments, Bertz et al. reinterpreted the results in terms of Cu^{III} intermediates formed by two-electron transfer.[168]



(12)

4) Electron spin resonance (ESR) and chemically induced dynamic nuclear polarization (CIDNP) spectroscopic studies for detecting the radical intermediates failed.[169] Conjugate addition of a vinylcuprate reagent to enone takes place with retention of the vinyl geometry, indicating that a vinyl radical intermediate is not involved.[170, 171] Kinetic isotope effects and substituent effects on organocuprate addition to benzophenone indicate that the C–C bond formation is rate-determining, which is not consistent with the involvement of a radical ion pair intermediate.[172]

The SET processes do not occur among moderately electrophilic olefinic acceptors, but are likely to be involved with highly electrophilic substrates. A recent example is the polyaddition of an organocuprate to fullerenes (see Section 1.1; [Eq. (4)]). A fluorenone ketyl radical has been detected in an organocuprate reaction of fluorenone.[159] Doubly activated olefins[173, 174] and bromonaphthoquinone[175, 176] are also likely to react by SET.

3.1.3. Kinetics and the Spectroscopic Analysis of Intermediates

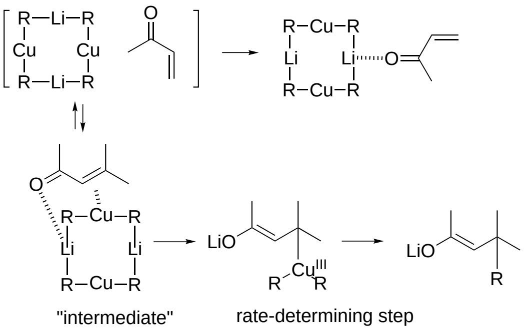
Conjugate addition to α,β-unsaturated ketones and esters are the most important organocuprate reactions. Important kinetic studies by Krauss and Smith for Me_2CuLi and a variety of ketones revealed the kinetic expressions shown in Equation (13), which are first order for both the organocuprate dimer and the enone.[165]

$$(Me_2CuLi)_2 + \text{enone} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{"intermediate"} \xrightarrow{k_2} \text{product} \qquad (13)$$

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

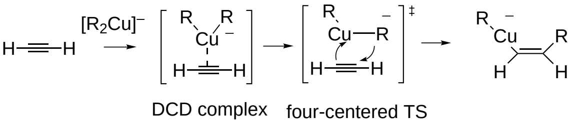
$$-\frac{d[\text{intermediate}]}{dt} = \frac{kK[(Me_4Cu_2Li_2]}{1 + K[Me_4Cu_2Li_2]}[\text{enone}]$$

This rate expression is consistent with the reaction scheme shown in Equation (14) which was prepared on the basis of the Krauss and Smith paper. Thus, the first-formed organocuprate dimer/enone complex with lithium–carbonyl and copper–olefin coordinations[177] forms the product via the intermediate(s). A lithium–carbonyl complex also forms but is a dead-end intermediate. Although the detailed structures of the intermediates remained obscure for a long time, the essence of this scheme has been supported by subsequent NMR spectroscopic studies and recent theoretical studies. The key "intermediate" is now considered to be an organocopper(III) species formed by two-electron inner-sphere electron transfer [Eq. (14)].[16, 20]



(14)

Corey and Boaz proposed explicitly a Dewar–Chatt–Duncanson (DCD) complex for such a Cu^{III}/olefin complex (see [Eq. (15)]).[42] X-ray absorption near-edge structure



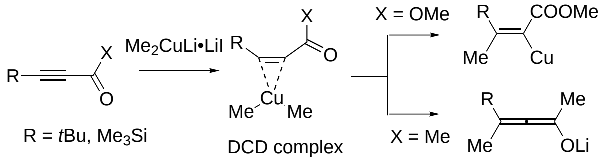
(15)

(XANES) investigation of a complex between a *trans*-cinnamate and $Me_2CuLi \cdot LiI$ in THF indicated elongation of the C–Cu bond and increase of the coordination number of the copper atom. NMR spectroscopic studies on the organic part of the complexes by Ullenius and co-workers,[178] Krause et al.,[179] and others[180] indicated loosening of the olefinic bond. Very recently, Krause et al. determined, for the first time, the kinetic activation energies ($E_a = 17-18\ \text{kcal mol}^{-1}$) of some conjugate addition reactions.[181]

3.2. Carbocupration of Acetylenes and Olefins

Carbocupration of acetylene smoothly takes place in a *cis* fashion to provide a reliable synthetic route to vinyl copper species [Eq. (15)].[32] Magnesium and zinc, which are more Lewis acidic than lithium, are better countercations for this reaction, and strong coordination of a lithium dialkylcuprate(I) with a crown ether dramatically slows down the reaction.[15] This reaction was generally considered to proceed through a four-centered mechanism, and, hence, to be mechanistically different from the conjugate addition.

In the addition of Me_2CuLi reagents to electron-deficient acetylenes,[182–184] DCD-type complexes have been identified by NMR spectroscopy.[185] As shown in Equation (16), ynoates afford vinylcopper intermediates, and ynones instead afford allenolates.[186] The origin of this diversity remains unclear. A related carbocupration mechanism was also proposed for the reaction with allenylphosphane oxide.[69] Carbocupration of olefins is known for dienes[187] and cyclopropenes[60] but the mechanisms also remain unknown.

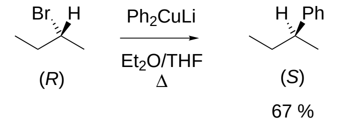


(16)

3.3. The S_N2 Substitution Reaction on sp^3 Carbons

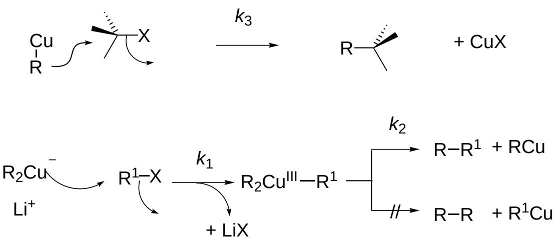
The S_N2 substitution reaction of an alkyl halide with a hard nucleophile such as an alkyl anion can be most readily achieved with the aid of organocopper chemistry.[188] The S_N2 reaction with epoxides and aziridines is also synthetically useful.[189] The accelerating effects of $BF_3 \cdot Et_2O$ in the latter reaction imply the importance of substrate activation.[190]

The alkylation of an alkyl bromide, tosylate, or epoxide with organocuprates takes places with 100% inversion of the configuration at the electrophilic carbon as shown in Equation (17).[29, 191] The magnitudes of primary and secondary kinetic isotope effects in the reaction of $Me_2CuLi \cdot LiI \cdot PBu_3$ with CH_3I strongly suggested that the rate-determining step of the reaction is the S_N2-displacement stage.[192] The reaction with alkyl halide, aryl halide, and alkyl tosylate of R_2CuLi has been shown to be first order to the concentration of the $(R_2CuLi)_2$ dimer and the alkylating reagent.[125, 197] RCu and $RCu(PBu_3)$ do not react with epoxides,[189] and alkylation reactions of R_2CuLi do not take place in the presence of a crown ether, indicating the importance of a Lewis acidic LiX compound associated with the organocuprate moiety.



(17)

Two mechanistic possibilities have been suggested for the substitution reactions (Scheme 8).[5] The first assumes simple S_N2 substitution by the R anion group. The second one assumes rate-determining displacement of the leaving group with copper bearing a formal negative charge, and subsequent formation of a trialkylcopper(III) intermediate.[146] The latter then undergoes reductive elimination to give the cross-coupling product. Although the second mechanism may look pleasing enough for a copper specialist, it leaves unanswered a few important questions, namely: the role of the lithium cation, the relative magnitude of k_1 and k_2, and, among others, the reason why exclusive production of a cross-coupled product $R{-}R^1$ is always observed from the symmetrical $R_2(R^1)Cu^{III}$ intermediate.



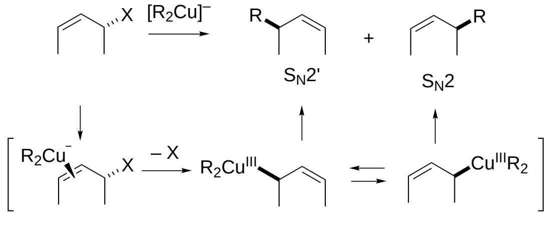
Scheme 8. Two proposed mechanisms for alkylation reactions.

The proposed participation of a Cu^{III} intermediate is based on analogy to the chemistry of lithium diorganoaurate(I) compounds, R_2Au^ILi.[193–196] Crystallographic data of Cu^{III} species[145] further supported the similarity between Au^{III} and Cu^{III}.[197]

The SET mechanism has also been discussed for the alkylation of secondary alkyl iodides, where the substitution reaction takes place stereorandomly.[29, 191b] The reaction of triphenylmethylbromide and Me_2CuLi generated an ESR-active triphenylmethyl radical; this may, however, be regarded as a special case.[198] Intramolecular cyclization of an olefinic iodide in the presence of an organocopper reagent has been taken as possible but not conclusive evidence of SET.[199]

3.4. The S_N2'-Allylation Reaction

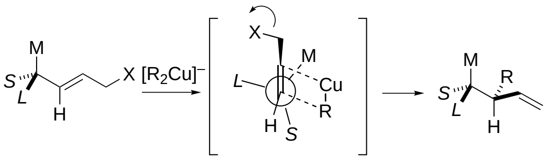
Organocuprates react rapidly with allylic halides (or acetates),[31, 200] propargyl halides (or acetates),[201] and vinyloxiranes,[30] often with S_N2' regioselectivity (Scheme 9). The reaction takes place with *anti* stereochemistry with respect to the leaving group, while *syn* substitution occurs when an allylic carbamate is employed as the substrate.[202]



Scheme 9. An *anti*-S_N2' allylation reaction with a competing S_N2 reaction pathway. X = OAc, halogen, $OP(O)Y_2$.

The reaction of R_2CuLi tends to give a mixture of S_N2 and S_N2' products, which has been suggested to be due to the involvement of the regioisomeric σ-allylic Cu^{III} species shown in brackets in Scheme 9.[200] Studies on substitutent effects in competitive reactions suggested that the rate-determining stage might involve a two-electron transfer from copper to the allylic substrate.[214] The S_N2 selectivity of the reaction of $Bu_2Cu(X) \cdot 2MgBr$ is higher with X = I, OTs than with X = Cl, Br, and is also higher in ether than in THF.[203] A combination of an organocopper compound and a Lewis acid, such as $RCu \cdot BF_3$, $R_2CuLi \cdot ZnCl_2$,[49] $R_2CuLi \cdot Ti^{IV}$,[54] or $R_2CuLi \cdot AlCl_3$,[78] greatly enhances the S_N2' selectivity. NMR spectroscopic studies on $R_2CuLi \cdot ZnCl_2$ and $R_2CuLi \cdot Ti^{IV}$ only showed rapid transmetalation from Cu to Zn or Ti, giving us little information on a putative Cu/Zn or Cu/Ti mixed reagent.[53, 57]

Scant information is available for the transition state. The stereoselectivity of the S_N2' reaction of δ-substituted allylic halides suggested that the transition state for the delivery of an R group from copper has a four-centered character, as shown in Equation (18) (S, M, L = small, medium, and large substituents, respectively.[54, 129, 204] This conjecture was supported by theoretical comparison of the transition state geometries of olefin carbolithiation with acetylene carbocupration (compare with Scheme 10).[16, 205]



(18)

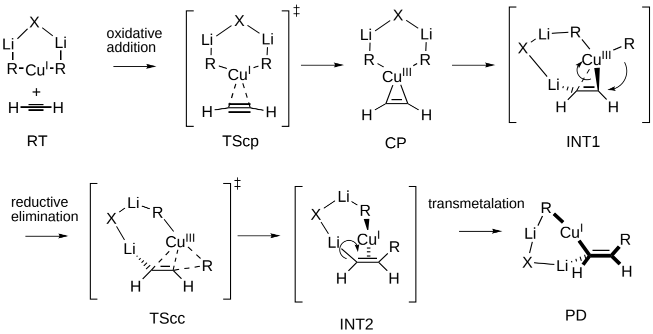
4. Theory-Based Molecular Pictures of Organocuprate Reactions

As summarized in the foregoing sections, numerous experimental studies indicated active participation of large organocopper clusters. They typically bear nucleophilic alkyl residues, copper(I) atoms, and countercations (typically lithium). The Nakamura – Morokuma theoretical analysis has provided answers to a fair number of questions among the numerous problems in organocuprate chemistry. Three representative reactions, carbocupration, conjugate addition, and S_N2 alkylation reaction, have been examined so far in detail to obtain molecular pictures on the cluster participation and the Cu^I/Cu^{III} redox chemistry in these reactions.

4.1. The Reaction Pathway of Acetylene Carbocupration

Carbocupration of acetylene was studied systematically for five model species, MeCu, $[Me_2Cu]^-$, Me_2CuLi, $Me_2CuLi \cdot LiCl$, and $(Me_2CuLi)_2$,[15] all of which were invoked once in a while in the discussions of organocuprate mechanisms. A few general conclusions have been made for the reactivities of these reagents with π acceptors. (1) As its d orbital is very low lying (and hence not available for redox chemistry),[21] MeCu can only undergo addition by a four-centered mechanism [Eq. (5)]. (2) This four-centered path requires high energy, since the covalent Me–Cu bond with an energy of 55 kcal mol^{-1}[206] must be cleaved. The neutral RCu species is, therefore, not a reactive nucleophile. (An ancillary result of this analysis suggests that the conventional "RCu" reagent must be a certain kind of $RCu \cdot X^-$ cluster, where X^- may be a halide anion.) (3) Being electron-rich (and having high-lying d orbitals), lithium organocuprates, such as $(R_2CuLi)_2$, bind tightly to acetylene through two-electron donation from the copper atom (see CP in Scheme 10 and Figure 2). (4) In such complex formation, a cluster structure larger than the parent species R_2CuLi is certainly necessary to achieve cooperation of lithium and copper.

The reaction pathway may be viewed as a "trap-and-bite" mechanism: The structures are shown in Scheme 10 and Figure 2, and the approximate energetics in Figure 3. The cluster opens up and traps the acetylene (INT1), transfers electrons, and then "bites" the substrate to form a C–C bond (TScc). The important events include: formation of a DCD complex CP via a low energy transition state TScp,[21] inner-



Scheme 10. The "trap and bite" pathway of carbocupration. X = RCuR, halogen, etc.

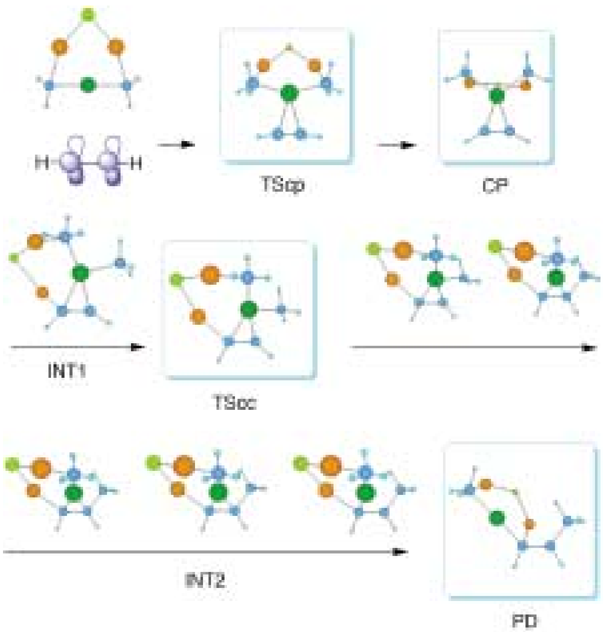


Figure 2. "Snapshots" of intermediates on the potential surface of acetylene carbocupration with $Me_2CuLi \cdot LiCl$. Color code: Cu = dark green, Li = orange, Cl = light green, C = large blue, H = small blue spheres.

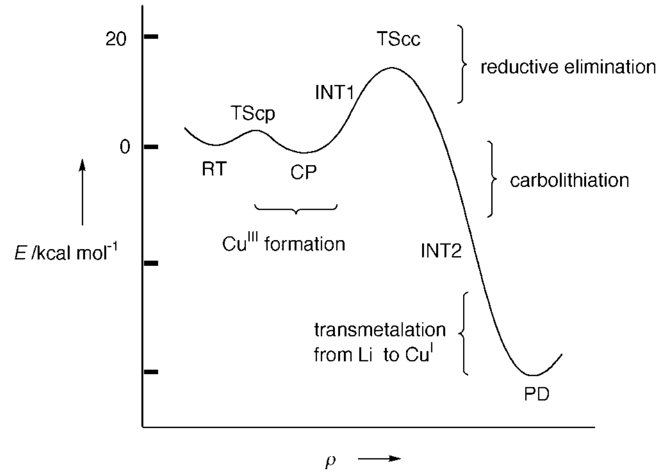


Figure 3. Approximate energy profile of acetylene carbocupration. The energies are relative to the energies of the reactants. E = relative energies, ρ = reaction coordinates. (In physical and theoretical chemistry all species on the potential surface are termed intermediates.)

sphere electron transfer to form a transient intermediate INT1, C–C bond formation through the rate-determining stage (TScc), and intra-cluster transmetalation from lithium to copper(I) (INT2). The DCD character of CP is shown by the localized molecular orbitals (LMOs, Figure 4) and was also

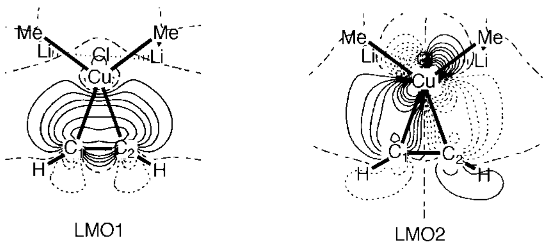


Figure 4. Localized molecular orbitals between $Me_2CuLi \cdot LiCl$ and acetylene in complex CP.

found in the conjugate addition to enals and enones.[16] Since the C–Cu^{III} bond is very unstable, the activation energy for the C–C bond formation via TScc becomes small (< 20 kcal mol^{-1}). In solution, the reaction may directly go to INT1 or related species through an open cluster, as depicted in Scheme 5.

Note that drawing the "organic" arrows and indicating the valence of the metal, as in Scheme 10 (and other schemes in the following paragraphs), are necessarily inaccurate from a purely inorganic or theoretical viewpoint. Nonetheless, we have indicated them to put the theoretical results into the framework of conventional organic chemistry, and to facilitate understanding of the chemistry by organic chemists who are using the reagents in their everyday research life.

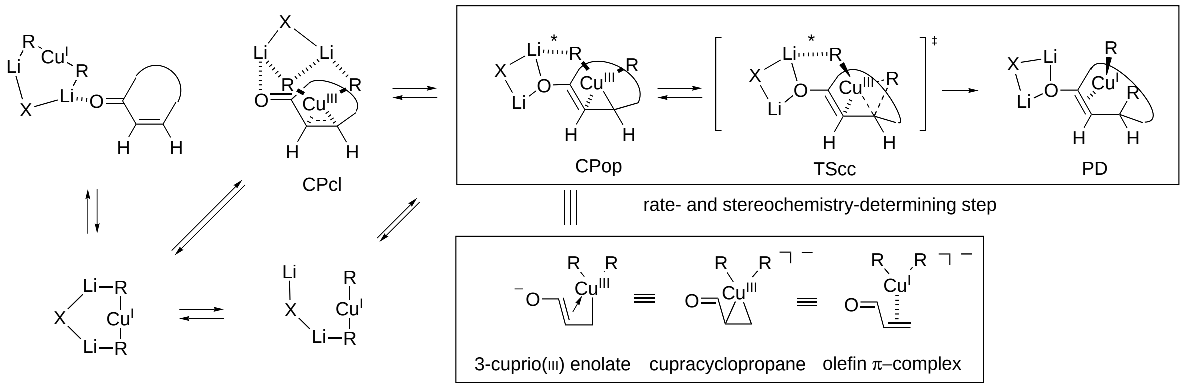
In Figure 2, snapshots of intermediary species on the potential surface of carbocupration are depicted to illustrate the metamorphosis of the reacting complex. The formation of the transient carbolithiated intermediate INT2 is the most striking because recognition of this intermediate provides the key to understanding the kinship of carbocupration, S_N2'-allylation,[15] and conjugate addition.[16]

4.2. The Reaction Pathway of Conjugate Addition

The reaction pathway of the conjugate addition of Me_2CuLi and $Me_2CuLi \cdot LiCl$ has been studied for acrolein[16] and cyclohexenone,[20] and favorably compared for the ^{13}C NMR properties of intermediates, kinetic isotope effects,[207] and the diastereofacial selectivity. The trap-and-bite mechanism also operates in this reaction, as summarized in Scheme 11. As illustrated in Figure 5, the rate-determining step of the reaction (to form TScc) is the C–C bond formation caused by reductive elimination from Cu^{III} to Cu^{I}.

Formation of TScc is also the stage where the enantioface selectivity of the reaction is determined.[20] This statement stands in contrast to the conventional assumption that the face selectivity is achieved in the initial π complexation, which is now shown to represent an equilibrium preceding TScc formation.[208] The calculated activation energy (E_a = 10.6 kcal mol^{-1}), taking into consideration the recently determined solvation of the lithium atoms, shows reasonable agreement with the experimental data (E_a = 17–18 kcal mol^{-1}).[181]

The central feature of the mechanism is the 3-cuprio(III) enolate which is of open dimeric nature. As shown by theory/experiment comparison for ^{13}C NMR spectroscopic results



Scheme 11. Possible pathways for conjugate addition of $(R_2CuLi)_2$ to an enone. Solvent molecules are omitted for clarity. The lithium atoms are fully solvated. The R–Li association is indicated with a starred broken line in CPop and TScc but may be extremely small or nonexistent in solution. X = RCuR, halogen, etc.

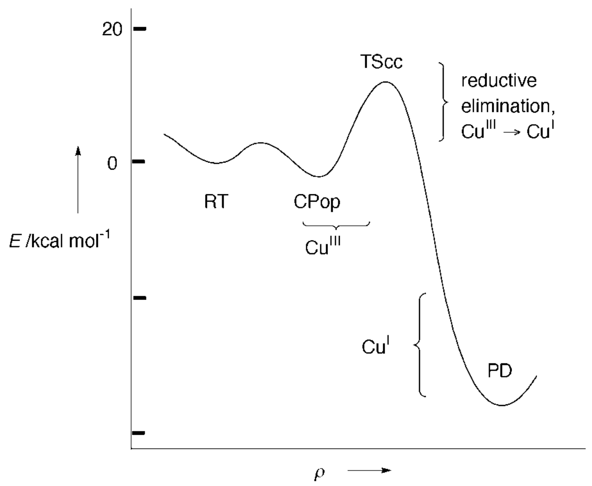


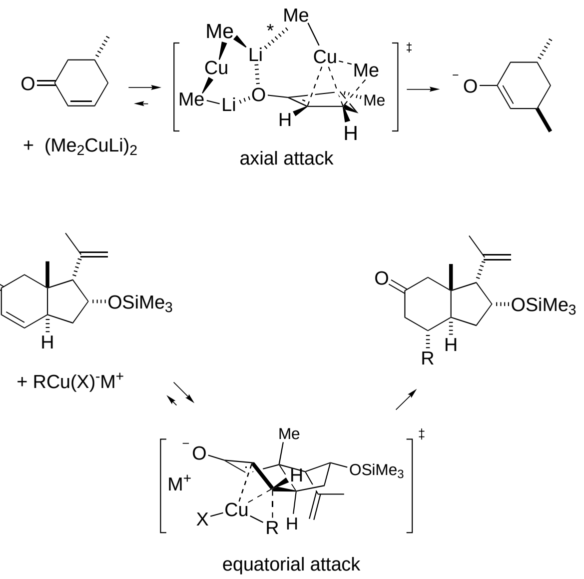
Figure 5. Approximate energy profile of conjugate addition of $(R_2CuLi)_2$ to an enone.

and kinetic isotope effects,[20, 207] this species serves as a direct precursor to the product (PD in Scheme 11, upper box). In this critical complex CPop, there is achieved a copper/olefin (soft/soft) interaction and a lithium/carbonyl (hard/hard) interaction. The open complex may be directly formed through an a open cluster (bottom left of Scheme 11) or by complexation of a closed cluster with the enone (to form Cpcl). Experiments have shown that the enone/lithium complex (top left of Scheme 11) is a dead-end species.[165, 179]

The intermediate CPop is the "β-cuprio ketone" intermediate that has been widely debated in the mechanistic discussions of conjugate addition (compare with Equations (13) and (16)). On the basis of the Nakamura–Morokuma theoretical analysis, one can now consider three limiting structures for CPop that are shown in the lower box in Scheme 11. The reason for the exceptional stability of CPop as a trialkylcopper(III) species can be readily understood with the "3-cuprio(III) enolate" structure where the internal enolate anion acts as a strong stabilizing ligand of the Cu^{III} state.[23]

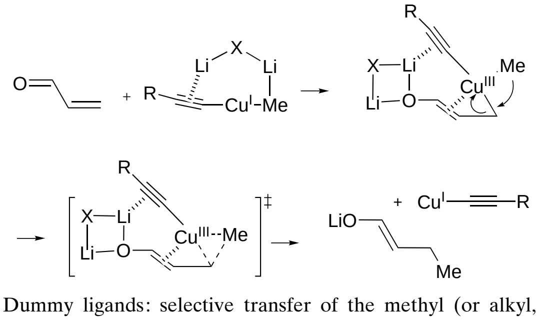
In spite of the apparent difference between conjugate addition and carbocupration reactions (Schemes 8 and 9), the similarity of the key organometallic feature in the two reactions is now evident. In both reactions, inner-sphere electron transfer converts the stable C–Cu^{I} bond to an unstable C–Cu^{III} bond, and the cluster opening generates a nucleophilic tetracoordinated alkyl group. The difference is that the product PD of conjugate addition remains as a lithium enolate complexed with RCu^{I} (Scheme 11), while the initial product of carbocupration (INT2) undergoes further reaction (Li/Cu transmetalation) and generates a new organocuprate compound (Scheme 10). (Note however that this difference could become more subtle since the product of conjugate addition could behave more like an α-cuprio(I) ketone complexed with a lithium cation than a lithium enolate complexed with copper(I)). In both reactions, no evidence of radical intermediates (that is, from SET) was found by theoretical calculations.[15, 16, 20]

Synthetic chemists can now work with three-dimensional pictures of conjugate addition which are available on a web site[*].[20] In the absence of steric hindrance (for example, with 5-methylcyclohexenone), "axial attack" through a half-chair conformation is favored (Scheme 12), while "equatorial attack" through a half-boat conformation is favored under the constraint of bicyclic rings (for example, in the cortisone synthesis in Scheme 3).



Scheme 12. Transition states for diastereoselective conjugate additions. In solution, the lithium and metal (M) cations are fully solvated with solvent molecules. The Me–Li association (*) may be extremely weak or nonexistent in solution. X = RCuR, halogen, etc.

Recognition of the importance of cluster structure led to a new understanding of the role of a dummy ligand (Y) in the chemistry of mixed cuprates MeCu(Y)Li.[22] As shown in Scheme 13 for the case of Y = alkynyl, the transfer of the



Scheme 13. Dummy ligands: selective transfer of the methyl (or alkyl, alkenyl, aryl) group in preference to transfer of the alkynyl group. X = RCuR, halogen, etc.

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[*] http://www.chem.s.u-tokyo.ac.jp/~common/HTML/3D.structure.html for retrieval of the theoretical 3D pictures and coordinates

methyl group is overwhelmingly favored over the transfer of the alkynyl group. This is because the alkynyl group acts as a tight bridge between Cu^{III} and Li$^+$ (Figure 6). Namely, the alkynyl dummy group simultaneously binds to Cu and Li atoms (that is, there is a strong electrostatic interaction between the Li atom and alkynyl group), and hence stays on the copper atom. By default, the much less effective bridging organic ligand is transferred to the enone substrate. This is different to the conventional hypothesis that the Y group forming a stronger Cu–Y bond acts as a better dummy ligand (because it resists transfer), providing an additional illustration of the critical roles of cluster structures in organocopper chemistry.

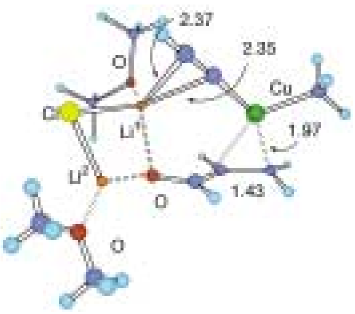
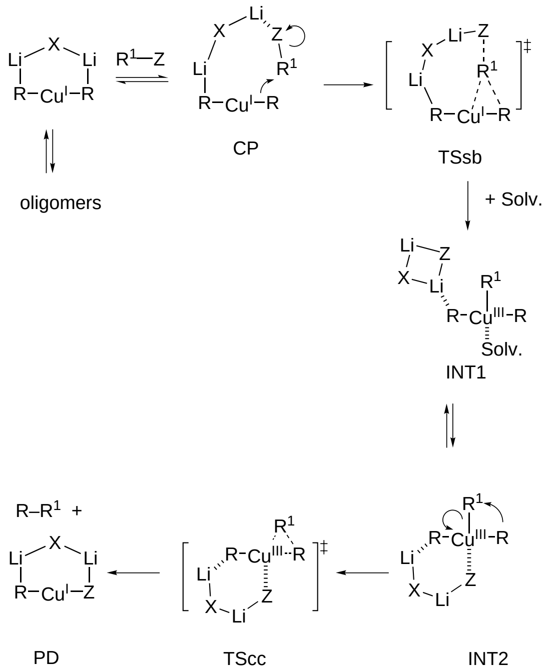


Figure 6. Three dimensional structure of the open complex between acrolein and Me(C$_2$H)CuLi · LiCl, which bears an Me$_2$O group on each lithium atom (B3LYP/631A). Bond lengths are given in angstroms. Color code: Cu = dark green, Li = orange, Cl = light green, O = red, C = dark blue, H = light blue spheres.

4.3. The Reaction Pathway of the S$_N$2 Alkylation Reaction

The alkylation reaction revealed a different mechanistic aspect of the organocuprate reaction. Theoretical analyses of the reactions of alkyl halides (MeI and MeBr)[17] and epoxides (ethylene oxide and cyclohexene oxide)[18] with lithium organocuprate clusters ((Me$_2$CuLi)$_2$ dimer or Me$_2$CuLi · LiCl, Scheme 14 and Figure 7) resolved the long-standing questions on the mechanism of the alkylation reaction. The density functional calculations showed that the rate-determining step of the alkylation reaction (through TSsb) is the substitution of the C–Z bond with an incoming R–Cu σ bond. The linear 3d$_{z^2}$ orbital of copper acts here as the nucleophile, as shown by the LMO illustrated in Figure 8. The computed and the experimental kinetic isotope effects for the reaction of methyl iodide showed good agreement with each other, supporting this conclusion.[209]



Scheme 14. Reaction of R$_2$CuLi · LiX with R^{1}Z. The solvent molecules coordinated to the lithium atoms are omitted for clarity. Z = halogen; X = RCuR, halogen, etc.

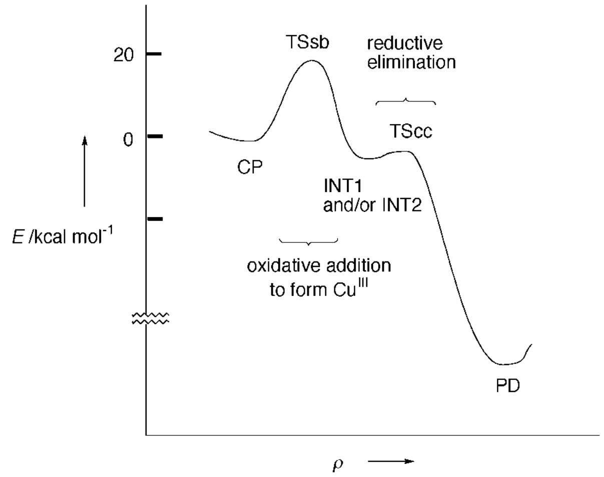


Figure 7. Approximate energy profile of the S$_N$2-substitution reaction between R$_2$CuLi · LiX and R^{1}Z.

Note that one can identify again an open-cluster structure in TSsb where the lithium atom electrophilically activates the leaving group. A trialkylcopper(III) intermediate may form after the rate-determining, halide-displacement step but only as an unstable transient species INT1 or INT2 (Scheme 14). These are trialkylcopper(III) complexes of T-shape geometry with the fourth ligand (solvent or halide) making a square planar structure.[23] The *trans* relationship for the two alkyl groups R is secured by the linear geometry of the organocuprate moiety in the transition state TSsb, which warrants cross-coupling between R and R^1 in TScc. Interestingly, this mechanism is a hybrid of the two previous proposals (shown in Figure 8).

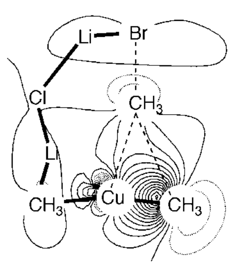
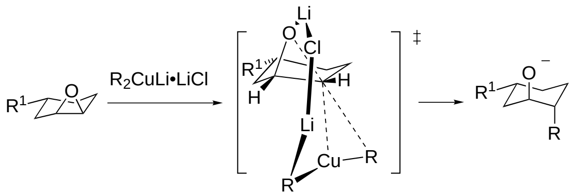


Figure 8. Localized molecular orbitals in the transition state of the S$_N$2 reaction between Me$_2$Cu-Li · LiCl and MeBr.

A similar reaction pathway was found for the S$_N$2 substitution of an epoxide with a lithium organocuprate cluster.[18] In contrast to the MeBr reaction, the configuration of the electrophilic carbon center is already inverted in the transition state, providing the reasoning for the preferred "*trans* diaxial epoxide opening" that has been widely observed in synthetic studies. The transition state of the S_N2 reaction of cyclohexene oxide is shown in Equation (19).



(19)

4.4. Orbital Interactions in Organocuprate Reactions

The Nakamura – Morokuma theoretical analysis revealed an intriguing difference between the addition reactions and the S_N2 alkylation reaction for the geometry of the nucleophilic C–Cu–C moiety. As summarized in Section 2, the C–Cu–C fragment in dicoordinated organocuprate(I) anions found in stable structures is always linear. As the highest occupied molecular orbital (HOMO) of a linear $[R_2Cu]^-$ molecule is largely the $3d_{z^2}$ copper orbital,[19, 21] the linear C–Cu–C group is suitable for interaction with the σ* orbital of MeBr, as illustrated in Figure 9 a.[21]

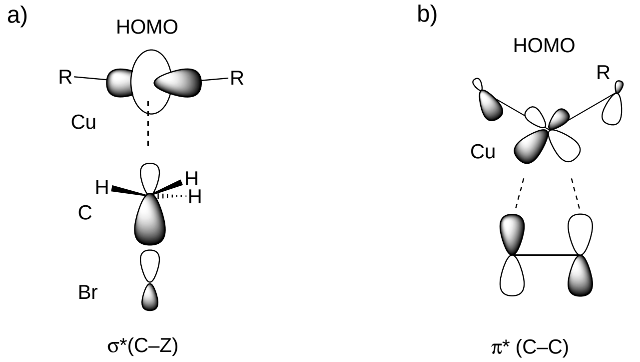


Figure 9. Orbital interactions between $[R_2Cu]^-$ and substrates in: a) an early stage of the reaction with methyl bromide, and b) π-complexation to an acetylene or olefin.

Bending the C–Cu–C moiety to less than 150° causes mixing of the $3d_{xz}$ copper orbital with the 2p methyl orbital to make it the HOMO of the organocuprate (Figure 9 b), which is now suitable for interaction with the π* orbitals of enones and acetylenes. Energy gain through back-donation largely compensates the energy loss associated with the bending (approximately 20 $kcal\,mol^{-1}$ to achieve a 120° angle).

The above analysis for copper also applies to the same class of compounds for gold, which, however, forms much more stable $C-Au^I$ bonds[156] and hence is unreactive. On the other hand, the d orbitals of zinc(II), a main group neighbor, are too low lying to make organozinc compounds as nucleophilic as organocopper compounds.[19]

4.5. The Roles of Cluster Structure in Organocuprate Reactions

The previous experimental and theoretical data point out several important characteristics of organocuprate structures and their reaction mechanisms.

1) The C–Cu–C angle in a covalently bonded $[R_2Cu]^-$ fragment in stationary states is always nearly 180°.[21] In ethereal solution, R_2CuLi exists as higher aggregates, whose Li–R bonds are fractional.[127, 136] One can invariably identify a neutral fragment, R–Cu–R–Li, in crystals of cyclic oligomers and higher polymers (see Scheme 4). Depending on the nature of the reacting electrophiles (σ* or π*), either a linear or a bent conformation of the C–Cu–C moiety becomes important for nucleophilic reactions (Figure 9).[21]
2) Due to the fractional R–Li bonds,[140] clusters and polymers can reversibly form open clusters, which trap the unsaturated substrate through multiple-point binding (see Schemes 10 and 11). Lithium cations assist electron flow from the organocuprate to the electrophile, and to achieve such cooperative action, a cluster of appropriate size may be necessary. Lewis acidic metals other than lithium (for example, Zn^{II}) will also play similar roles. One may appreciate the elegance in the molecular arrangement in the reactions of Me_2CuLi clusters, as illustrated in Figure 10.

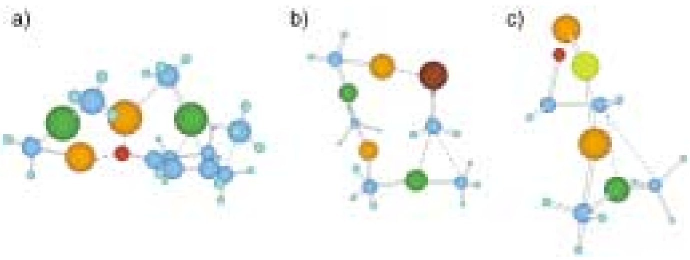


Figure 10. Three-dimensional views of the transition state (B3LYP) of: a) $(Me_2CuLi)_2$ with cyclohexenone, b) $(Me_2CuLi)_2$ with methyl bromide, and c) $Me_2CuLi \cdot LiCl$ with ethylene oxide. Color code: Cu = dark green, Li = orange, Cl = light green, O = red, Br = red with black stripes, C = large blue, H = small blue spheres.

3) A $C-Cu^I$ bond is a stable covalent bond, and is difficult to cleave by itself.[213] After charge transfer from organocuprate(I) to substrate, however, the cleavage of the resulting $R-Cu^{III}$ bond becomes an easy task. The reductive elimination reaction regenerates RCu^I, which may take part in further catalytic cycles. Thus, in copper-catalyzed reactions, excess R^- anion will react with RCu to regenerate the necessary organocuprate species.
4) Although acetylene carbocupration and conjugate addition have previously been considered to be two separate reactions, they have been shown to share essentially the same reaction mechanism. The kinship among carbocupration, conjugate addition, S_N2' allylation,[15] and S_N2 alkylation has now been established, through the Nakamura – Morokuma theoretical studies.

5) Demonstration of the critical role of the open conformation of the polymetallic clusters highlights the theoretical analysis of the organocuprate chemistry. Polymetallic clusters in various synthetic reactions are currently attracting the attention of synthetic and mechanistic chemists alike.[210–216]

5. Summary and Outlook

Wherefore art thou copper? The uniqueness of the organocopper chemistry stems primarily from the fact that copper lies on the border line between main group and transition metal elements. Comparison may be made for the neighboring elements, Ni^0, Cu^I, Ag^I, Au^I, and Zn^{II}, all of which are in the d^{10} configuration. The energy levels of the 3d orbitals in copper(I) compounds are much higher than in zinc(II), and become even higher upon mixing with the 2p orbital of the alkyl ligand through $[R_2Cu]^-$ formation.[15, 21] A redox system such as the Cu^I/Cu^{III} system is unavailable for zinc(II). Organonickel and organosilver species are not as stable and are hence much less synthetically viable than organocopper(I) reagents. Organogold(I) species are too stable to be synthetically useful. The C–Cu–C angle is intimately connected to the reactivities of the diorganocuprate(I), and the Lewis acid (often Li$^+$) in organocuprate clusters provides a push–pull electronic assistance for charge transfer from Cu^I to the electrophile. The diversity of the coordination structures revealed by calculations indicates that organocopper chemistry represents an ultimate "supramolecular chemistry" that chemists have exploited for a long time without knowing it. Numerous other aspects of organocopper chemistry await further mechanistic studies. The importance of R_3Cu^{III} species is now fully recognized,[23] and needs more careful attention in the future studies of mechanistic and synthetic organocopper chemistry.

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[1] a) J. G. Bednorz, K. A. Müller, *Z. Phys. B* **1986**, *64*, 189–193; b) L. Gao, Y. Y. Xue, F. Chen, Q. Xiong, R. L. Meng, D. Ramirez, C. W. Chu, J. H. Eggert, H. K. Mao, *Phys. Rev. B* **1994**, *50*, 4260.

[2] a) S. J. Lippard, *Science* **1995**, *268*, 996–997; b) N. Kitajima, Y. Morooka, *Chem. Rev.* **1994**, *94*, 737–757; c) M. J. Henson, P. Mukherjee, D. E. Root, T. D. P. Stack, E. I. Solomon, *J. Am. Chem. Soc.* **1999**, *121*, 10332–10345, and references therein.

[3] J. F. Normant, *Synthesis* **1972**, 63–80; G. H. Posner, *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, New York, **1980**; Y. Yamamoto, *Angew. Chem.* **1986**, *98*, 945–957; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 947–959.

[4] E. Nakamura, *Synlett* **1991**, 539–547.

[5] B. H. Lipshutz, S. Sengupta, *Org. React.* **1992**, *41*, 135–631.

[6] a) *Organocopper Reagents* (Ed.: R. J. K. Taylor), Oxford University Press, Oxford, **1994**; b) B. H. Lipshutz in *Comprehensive Organometallic Chemistry II, Vol. 12* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, pp. 59–130; c) N. Krause, A. Gerold, *Angew. Chem.* **1997**, *109*, 194–213; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186–204; d) Y. Ibuka, Y. Yamamoto, *Synlett* **1992**, 769–777.

[7] a) G. H. Posner, *Org. React.* **1972**, *19*, 1–113; b) J. A. Kozlowski in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 169–198; c) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**.

[8] J. F. Normant, A. Alexakis, *Synthesis* **1981**, 841–870.

[9] a) G. H. Posner, *Org. React.* **1975**, *22*, 253–400; b) J. M. Klunder, G. H. Posner in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 207–239.

[10] J. A. Marshall, *Chem. Rev.* **1989**, *89*, 1503–1511.

[11] M. S. Kharasch, P. O. Tawney, *J. Am. Chem. Soc.* **1941**, *63*, 2308–2315.

[12] J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, **1987**, Chap. 14.

[13] a) A. E. Jukes, *Adv. Organomet. Chem.* **1974**, *12*, 215–322; G. van Koten, J. G. Noltes in *Comprehensive Organometallic Chemistry*, *Vol. 2* (Eds.: G. Wilkinson, F. G. A. Stone), Pergamon, Oxford, **1982**, pp. 709–763; b) G. van Koten, S. L. James, J. T. B. H. Jastrzebski in *Comprehensive Organometallic Chemistry II*, *Vol. 3* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, pp. 57–133; c) P. P. Power, *Prog. Inorg. Chem.* **1991**, *39*, 75–11.

[14] R. A. J. Smith, A. S. Vellekoop in *Advances in Detailed Reaction Mechanisms*, *Vol. 3* (Ed.: J. M. Coxon), JAI, Greenville, CT, **1994**, pp. 79–130.

[15] E. Nakamura, S. Mori, M. Nakamura, K. Morokuma, *J. Am. Chem. Soc.* **1997**, *119*, 4887–4899.

[16] E. Nakamura, S. Mori, K. Morokuma, *J. Am. Chem. Soc.* **1997**, *119*, 4900–4910.

[17] E. Nakamura, S. Mori, K. Morokuma, *J. Am. Chem. Soc.* **1998**, *120*, 8273–8274.

[18] S. Mori, E. Nakamura, K. Morokuma, *J. Am. Chem. Soc.* **2000**, *122*, 7294–7307.

[19] S. Mori, E. Nakamura, *J. Mol. Struct. (Theochem)* **1999**, *461–462*, 167–175.

[20] S. Mori, E. Nakamura, *Chem. Eur. J.* **1999**, *5*, 1534–1543.

[21] S. Mori, E. Nakamura, *Tetrahedron Lett.* **1999**, *40*, 5319–5322; S. Mori, A. Hirai, M. Nakamura, E. Nakamura, *Tetrahedron* **2000**, *56*, 2805–2807.

[22] E. Nakamura, M. Yamanaka, *J. Am. Chem. Soc.* **1999**, *121*, 8941–8942.

[23] E. Nakamura, M. Yamanaka, S. Mori, *J. Am. Chem. Soc.* **2000**, *122*, 1826–1827.

[24] J. Munch-Petersen, *J. Org. Chem.* **1957**, *22*, 170–176.

[25] H. Gilman, R. G. Jones, L. A. Woods, *J. Org. Chem.* **1952**, *17*, 1630–1634.

[26] G. Costa, A. Camus, L. Gatti, N. Marsich, *J. Organomet. Chem.* **1966**, *5*, 568–572.

[27] H. O. House, W. L. Respess, G. M. Whitesides, *J. Org. Chem.* **1966**, *31*, 3128–3141.

[28] E. J. Corey, G. H. Posner, *J. Am. Chem. Soc.* **1967**, *89*, 3911–3912; E. J. Corey, G. H. Posner, *J. Am. Chem. Soc.* **1968**, *90*, 5615–5616.

[29] G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, H. O. House, *J. Am. Chem. Soc.* **1969**, 91, 4871–4882.

[30] R. Anderson, C. A. Henrick, J. B. J. Siddall, *J. Am. Chem. Soc.* **1970**, *92*, 735–737; R. J. Anderson, *J. Am. Chem. Soc.* **1970**, *92*, 4978–4980; R. W. Herr, C. R. Johnson, *J. Am. Chem. Soc.* **1970**, *92*, 4980–4981; J. Staroscik, B. Rickborn, *J. Am. Chem. Soc.* **1971**, *93*, 3046–3047; D. M. Wieland, C. R. Johnson, *J. Am. Chem. Soc.* **1971**, *93*, 3047–3049.

[31] Compare with: H. L. Goering, S. Kantner, *J. Org. Chem.* **1981**, *46*, 2144–2148.

[32] A. Alexakis, J. Normant, J. Villiéras, *Tetrahedron Lett.* **1976**, 3461–3462.

[33] B. H. Lipshutz, J. A. Kozlowski, C. M. Breneman, *J. Am. Chem. Soc.* **1985**, *107*, 3197–3204.

[34] a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, 1011–1014; b) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.

[35] a) K. Maruyama, Y. Yamamoto, *J. Am. Chem. Soc.* **1977**, *99*, 8068–8070; b) Y. Yamamoto, K. Maruyama, *J. Am. Chem. Soc.* **1978**, *100*, 3240–3241.

[36] A. B. Smith III, P. J. Jerris, *J. Am. Chem. Soc.* **1981**, *103*, 194–195.

[37] B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock, *J. Am. Chem. Soc.* **1990**, *112*, 5869–5871.

[38] Y. Horiguchi, E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1989**, *111*, 6257–6265.

[39] E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1984**, *106*, 3368–337.

[40] J. Enda, I. Kuwajima, *J. Am. Chem. Soc.* **1985**, *107*, 5495–550.

[41] E. Nakamura, S. Matsuzawa, Y. Horiguchi, I. Kuwajima, *Tetrahedron Lett.* **1986**, *27*, 4029–4032.

[42] E. J. Corey, N. W. Boaz, *Tetrahedron Lett.*, **1985**, *26*, 6015–6018; E. J. Corey, N. W. Boaz, *Tetrahedron Lett.*, **1985**, *26*, 6019–6022.

[43] A. Alexakis, J. Berlan, Y. Besace, *Tetrahedron Lett.* **1986**, *27*, 1047–1050.

[44] Y. Horiguchi, S. Matsuzawa, E. Nakamura, I. Kuwajima, *Tetrahedron Lett.* **1986**, *27*, 4025–4028; S. Matsuzawa, Y. Horiguchi, E. Nakamura, I. Kuwajima, *Tetrahedron* **1989**, *45*, 349–362.

[45] R. J. Linderman, A. Godfrey, *Tetrahedron Lett.* **1986**, *27*, 4553.

[46] E. Nakamura in *Organocopper Reagents* (Ed.: R. J. K. Taylor), Oxford University Press, Oxford, **1994**, Chap. 6, pp. 129–142.

[47] E. Nakamura, S. Aoki, H. Oshino, I. Kuwajima, *J. Am. Chem. Soc.* **1985**, *109*, 8056–8066.

[48] Reviews: a) E. Nakamura, *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 931–938; b) "Metal Homoenolates": I. Kuwajima, E. Nakamura in *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, Chap. 1.14; c) M. Nakamura, E. Nakamura, *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 632–644.

[49] E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1977**, *99*, 7360–7361; E. Nakamura, H. Oshino, I. Kuwajima, *J. Am. Chem. Soc.* **1986**, *108*, 3745–3755.

[50] a) Y. Tamaru, H. Ochiai, T. Nakamura, Z. Yoshida, *Angew. Chem.* **1987**, *99*, 1193–1195; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1157–1159; b) Y. Tamaru, H. Ochiai, F. Sanda, Z.-i. Yoshida, *Tetrahedron Lett.* **1985**, *26*, 5529–5532; c) Y. Tamaru, H. Ochiai, T. Nakamura, K. Tsubaki, Z. Yoshida, *Tetrahedron Lett.* **1985**, *26*, 5559–5562.

[51] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; b) P. Knochel, *Synlett* **1995**, 393–403.

[52] P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117–2188.

[53] E. Nakamura in *Organometallic Chemistry, A Manual*, 2nd ed. (Ed.: M. Schlosser), Wiley, New York, in preparation.

[54] M. Arai, E. Nakamura, B. H. Lipshutz, *J. Org. Chem.* **1991**, *56*, 5489–5491.

[55] B. H. Lipshutz, E. L. Ellsworth, *J. Am. Chem. Soc.* **1990**, *112*, 7440–7441.

[56] B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock, *J. Am. Chem. Soc.* **1990**, *112*, 5869–5871.

[57] T. Ibuka, H. Minakata, *Synth. Commun.* **1980**, *10*, 119–125.

[58] M. Arai, B. H. Lipshutz, E. Nakamura, *Tetrahedron* **1992**, *48*, 5709–5718.

[59] A. Alexakis, J. F. Normant, *Isr. J. Chem.* **1984**, *24*, 113–117.

[60] A. T. Stoll, E.-i. Negishi, *Tetrahedron Lett.* **1985**, *26*, 5671–5674.

[61] J. Berlan, J. Besace, E. Stephan, P. Cresson, *Tetrahedron Lett.* **1985**, *26*, 5765–5768.

[62] E. Nakamura, M. Isaka, S. Matsuzawa, *J. Am. Chem. Soc.* **1988**, *110*, 1297–1298.

[63] a) B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771–806; b) T. Kanai, Y. Nakagawa, K. Tomioka, *J. Syn. Org. Chem. Jpn.* **1996**, *35*, 474–480; c) G. van Koten, *Pure Appl. Chem.* **1994**, *66*, 1455–1462; d) A. Alexakis, J. C. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* **1993**, *4*, 2427–2430; e) A. Alexakis in *Transition Metal Catalysed Reactions* (Eds.: S.-I. Murahashi, S. G. Davies), Blackwell Science, Oxford, UK, **1999**, pp. 303.

[64] a) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem.* **1997**, *109*, 2733–2736; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620–2623; b) A. K. H. Knöbel, I. H. Escher, A. Pfaltz, *Synlett* **1997**, 1429–1431; c) R. Naasz, L. A. Arnold, M. Pineschi, E. Keller, B. L. Feringa, *J. Am. Chem. Soc.* **1999**, *121*, 1104–1105.

[65] M. Sawamura, H. Iikura, E. Nakamura, *J. Am. Chem. Soc.* **1996**, *118*, 12850–12851.

[66] M. Sawamura, H. Iikura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **1998**, *120*, 8285–8286.

[67] H. Iikura, S. Mori, M. Sawamura, E. Nakamura, *J. Org. Chem.* **1997**, *62*, 7912–7913.

[68] H. O. House, *Acc. Chem. Res.* **1976**, *9*, 59–67.

[69] J. Berlan, J.-P. Battioni, K. Koosha, *Tetrahedron Lett.* **1976**, 3351–3354; K. Koosha, J. Berlan, M.-L. Capmau, W. Chodkiewicz, *Bull. Chim. Soc. Fr. II* **1975**, 1284–1291; K. Koosha, J. Berlan, M.-L. Capmau, W. Chodkiewicz, *Bull. Chim. Soc. Fr.* **1975**, 1291–1294; J. Berlan, J.-P. Battioni, K. Koosha, *Bull. Chim. Soc. Fr.* **1978**, II 183–190; J. Berlan, J.-P. Battioni, K. Koosha, *J. Organomet. Chem.* **1978**, *152*, 359–365; J. Berlan, K. Koosha, *J. Organomet. Chem.* **1978**, *153*, 99–106; J. Berlan, K. Koosha, *J. Organomet. Chem.* **1978**, *153*, 107–113.

[70] E. J. Corey, D. J. Beames, *J. Am. Chem. Soc.* **1972**, *94*, 7210–7211.

[71] a) E. J. Corey, D. M. Floyd, B. H. Lipshutz, *J. Org. Chem.* **1978**, *43*, 3418–3420; b) H. O. House, M. J. Umen, *J. Org. Chem.* **1973**, *38*, 3893–3901; c) W. H. Mandeville, G. M. Whitesides, *J. Org. Chem.* **1974**, *39*, 400–405.

[72] a) J. P. Gorlier, L. Hamon, J. Levisalles, J. Wagnon, *J. Chem. Soc. Chem. Commun.* **1973**, 88; b) B. H. Lipshutz, R. S. Wilhelm, J. A. Kozlowski, *Tetrahedron* **1984**, *40*, 5005–5038.

[73] S. H. Bertz, G. Dabbagh, G. M. Villacorta, *J. Am. Chem. Soc.* **1982**, *104*, 5824–5826; compare with: G. H. Posner, C. E. Whiten, *Tetrahedron Lett.* **1973**, 1815–1818; G. H. Posner, C. E. Whiten, J. J. Sterling, *J. Am. Chem. Soc.* **1973**, *95*, 7788–7800.

[74] Magnesium mixed organocuprates: J. Drouin, F. Leyendecker, J.-M. Conia, *New. J. Chem.* **1978**, *2*, 267–270; F. Leyendecker, J. Drouin, J.-M. Conia, *New. J. Chem.* **1978**, *2*, 271–274.

[75] C. Ouannes, G. Dressaire, Y. Langlois, *Tetrahedron Lett.* **1977**, 815–818.

[76] S. H. Bertz, C. P. Gibson, G. Dabbagh, *Organometallics* **1988**, *7*, 227–232.

[77] A. Alexakis, D. Jachiet, J. F. Normant, *Tetrahedron* **1986**, *42*, 5607–5619; A. Ghribi, A. Alexakis, J. F. Normant, *Tetrahedron Lett.* **1984**, *25*, 3075–3078; A. Ghribi, A. Alexakis, J. F. Normant, *Tetrahedron Lett.* **1984**, *25*, 3079–3082.

[78] S. Flemming, J. Kabbara, K. Nickisch, J. Westermann, J. Mohr, *Synlett* **1995**, 183–185.

[79] S. Matsuzawa, M. Isaka, E. Nakamura, I. Kuwajima, *Tetrahedron Lett.* **1989**, *30*, 1975–1978; M. Arai, T. Nemoto, Y. Ohashi, E. Nakamura, *Synlett* **1992**, 309–310.

[80] For some mechanistic proposals, see: a) B. H. Lipshutz, S. H. Dimock, B. James, *J. Am. Chem. Soc.* **1993**, *115*, 9283–9284; b) S. H. Bertz, G. Miao, B. E. Rossiter, J. P. Snyder, *J. Am. Chem. Soc.* **1995**, *117*, 11023–11024; c) S. H. Bertz, A. Chopra, M. Eriksson, C. A. Ogle, P. Seagle, *Chem. Eur. J.* **1999**, *5*, 2680–2691.

[81] Y. Horiguchi, M. Komatsu, I. Kuwajima, *Tetrahedron Lett.* **1989**, *30*, 7087–7090.

[82] B. H. Lipshutz, D. H. Aue, B. James, *Tetrahedron Lett.* **1996**, *37*, 8471–8474.

[83] M. Eriksson, A. Johansson, M. Nilsson, T. Olsson, *J. Am. Chem. Soc.* **1996**, *118*, 10904–10905.

[84] M. Bergdahl, E.-L. Lindstedt, M. Nilsson, T. Olsson, *Tetrahedron* **1988**, *44*, 2055–2062.

[85] a) E. C. Ashby, J. Lin, J. J. J. Watkins, *J. Org. Chem.* **1977**, *42*, 1099–1102; b) E. C. Ashby, J. J. Lin, *J. Org. Chem.* **1977**, *42*, 2805–2808.

[86] a) H. Westmijze, H. Kleijn, J. Meijer, P. Vermeer, *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 98–102; b) D. L. J. Clive, V. Farina, P. L. Beaulieu, *J. Org. Chem.* **1982**, *47*, 2572–2582.

[87] T. L. Macdonald, W. C. Still, *J. Am. Chem. Soc.* **1975**, *97*, 5280–5281; W. C. Still, T. L. Macdonald, *Tetrahedron Lett.* **1976**, *31*, 2659–2662.

[88] E. C. Ashby, J. J. Watkins, *J. Am. Chem. Soc.* **1977**, *99*, 5312–5317.

[89] S. H. Bertz, G. Dabbagh, *J. Am. Chem. Soc.* **1988**, *110*, 3668–3670.

[90] M. M. Olmstead, P. P. Power, *J. Am. Chem. Soc.* **1989**, *111*, 4135–4136.

[91] F. Olbrich, J. Kopf, E. Weiss, *Angew. Chem.* **1993**, *105*, 1136; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1077–1079.

[92] B. H. Lipshutz, R. S. Wilhelm, J. A. Kozlowski, *Synthesis* **1987**, 325–341; B. H. Lipshutz, R. S. Wilhelm, D. M. Floyd, *J. Am. Chem. Soc.* **1981**, *103*, 7672–7674; B. H. Lipshutz, J. Kozlowski, R. S. Wilhelm, *J. Am. Chem. Soc.* **1982**, *104*, 2305–2307; B. H. Lipshutz, *Tetrahedron Lett.* **1983**, *24*, 127–130; B. H. Lipshutz, K. Siegmann, E. Garcia, F. Kayser, *J. Am. Chem. Soc.* **1993**, *115*, 9276–9282.

[93] S. H. Bertz, *J. Am. Chem. Soc.* **1990**, *112*, 4031–4032; S. H. Bertz, *J. Am. Chem. Soc.* **1991**, *113*, 5470–5471; S. H. Bertz, *Chem. Eng. News* **1997**, *75*(15), 4.

[94] S. H. Bertz, K. Nilsson, Ô. Davidson, J. P. Snyder, *Angew. Chem.* **1998**, *110*, 327–331; *Angew. Chem. Int. Ed.* **1998**, *37*, 314–317.

[95] B. H. Lipshutz, S. Sharma, E. L. Ellsworth, *J. Am. Chem. Soc.* **1990**, *112*, 4032–4034; B. H. Lipshutz, B. James, *J. Org. Chem.* **1994**, *59*, 7585–7587.

[96] a) T. Stemmler, J. E. Penner-Hahn, P. Knochel, *J. Am. Chem. Soc.* **1993**, *115*, 348–350; b) T. M. Barnhart, H. Huang, J. E. Penner-Hahn, *J. Org. Chem.* **1995**, *60*, 4310–4311.

[97] T. L. Stemmler, T. M. Barnhart, J. E. Penner-Hahn, C. E. Tucker, P. Knochel, M. Böhme, G. Frenking, *J. Am. Chem. Soc.* **1995**, *117*, 12 489–12 497.

[98] B. H. Lipshutz, K. L. Stevens, B. James, J. G. Pavlovich, J. P. Snyder, *J. Am. Chem. Soc.* **1996**, *118*, 6796–6797; B. H. Lipshutz, J. Keith, D. J. Buzard, *Organometallics* **1999**, *18*, 1571–1574.

[99] a) J. P. Snyder, D. P. Spangler, J. R. Behling, B. E. Rossiter, *J. Org. Chem.* **1994**, *59*, 2665–2667; b) J. P. Snyder, S. H. Bertz, *J. Org. Chem.* **1995**, *60*, 4312–4313; c) H. Huang, K. Alvarez, Q. Cui, T. M. Barnhart, J. P. Snyder, J. E. Penner-Hahn, *J. Am. Chem. Soc.* **1996**, *118*, 8808–8816; erratum: H. Huang, K. Alvarez, Q. Cui, T. M. Barnhart, J. P. Snyder, J. E. Penner-Hahn, *J. Am. Chem. Soc.* **1996**, *118*, 12 252.

[100] G. Boche, F. Bosold, M. Marsch, K. Harms, *Angew. Chem.* **1998**, *110*, 1779–1781; *Angew. Chem. Int. Ed.* **1998**, *37*, 1684–1686.

[101] C. M. P. Kronenburg, J. T. B. H. Jastrzebski, A. L. Spek, G. van Koten, *J. Am. Chem. Soc.* **1998**, *120*, 9688–9689.

[102] S. H. Bertz, G. Dabbagh, *J. Chem. Soc. Chem. Commun.* **1982**, 1030–1032.

[103] S. H. Bertz, G. Miao, M. Eriksson, *Chem. Commun.* **1996**, 815–816.

[104] T. A. Mobley, F. Müller, S. Berger, *J. Am. Chem. Soc.* **1998**, *120*, 1333–1334.

[105] N. Krause, *Angew. Chem.* **1999**, *111*, 83–85; *Angew. Chem. Int. Ed.* **1999**, *38*, 79–81.

[106] J. A. Cabezas, A. C. Oehlschlager, *J. Am. Chem. Soc.* **1997**, *119*, 3878–3886.

[107] W. C. Still, J. A. Schneider, *Tetrahedron Lett.* **1980**, *21*, 1035–1038.

[108] G. M. Whitesides, J. SanFilippo, Jr., C. P. Casey, E. J. Panek, *J. Am. Chem. Soc.* **1967**, *89*, 5302–5303.

[109] G. H. Posner, J.-S. Ting, C. M. Lentz, *Tetrahedron* **1976**, *32*, 2281–2287.

[110] P. Kocienski, S. Wadman, K. Cooper, *J. Am. Chem. Soc.* **1989**, *111*, 2363–2365.

[111] G. V. Buxton, J. C. Green, *J. Chem. Soc. Faraday Trans.* **1978**, *74*, 697–714.

[112] J. K. Kochi, *Acc. Chem. Res.* **1974**, *7*, 351–360; compare with: I. Ryu, M. Ando, A. Ogawa, S. Murai, N. Sonoda, *J. Am. Chem. Soc.* **1983**, *105*, 7192–7194.

[113] Metastable dimethylgold(II) clusters were recently trapped. See: D. Zhu, S. V. Lindeman, J. K. Kochi, *Organometallics* **1999**, *18*, 2241–2248.

[114] P. S. Coan, K. Folting, J. C. Huffman, G. Caulton, *Organometallics* **1989**, *8*, 2724–2728; R. Lingnau, J. Strähle, *Angew. Chem.* **1988**, *100*, 409; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 436.

[115] S. Sakaki, Y. Musashi, *Inorg. Chem.* **1995**, *34*, 1914–1923.

[116] M. D. Janssen, M. A. Corsten, A. L. Spek, D. M. Grove, G. van Koten, *Organometallics* **1996**, *15*, 2810–2820.

[117] M. F. Lappert, R. Pearce, *J. Chem. Soc. Chem. Commun.* **1973**, 24–25; J. A. J. Jarvis, R. Pearce, M. F. Lappert, *J. Chem. Soc. Dalton Trans.* **1977**, 999–1003.

[118] M. M. Olmstead, P. P. Power, *J. Am. Chem. Soc.* **1990**, *112*, 8008–8014.

[119] C.-S. Hwang, P. P. Power, *Organometallics* **1999**, *18*, 697–700.

[120] H. Hope, M. M. Olmstead, P. P. Power, J. Sandell, X. Xu, *J. Am. Chem. Soc.* **1985**, *107*, 4337–4338.

[121] a) J. P. Snyder, G. E. Tipsword, D. J. Spangler, *J. Am. Chem. Soc.* **1992**, *114*, 1507–1510; b) See also Ref. [99a].

[122] S. F. Martin, J. R. Fishpaugh, J. M. Power, D. M. Giolando, R. A. Jones, C. M. Nunn, A. H. Cowley, *J. Am. Chem. Soc.* **1988**, *110*, 7226–7228.

[123] C.-S. Hwang, P. P. Power, *J. Am. Chem. Soc.* **1998**, *120*, 6409–6410.

[124] G. van Koten, J. G. Noltes, *J. Chem. Soc. Chem. Commun.* **1972**, 940–941.

[125] R. G. Pearson, C. D. Gregory, *J. Am. Chem. Soc.* **1976**, *98*, 4098–4104.

[126] G. van Koten, J. T. B. H. Jastrzebski, F. Muller, C. H. Stam, *J. Am. Chem. Soc.* **1985**, *107*, 697–698.

[127] N. P. Lorenzen, E. Weiss, *Angew. Chem.* **1990**, *102*, 322–324; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 300–302.

[128] M. M. Olmstead, P. P. Power, *Organometallics* **1990**, *9*, 1720–1722.

[129] 3D structures searched by Cambridge Structural Database System in April, 1999.

[130] H. Huang, C. H. Liang, J. E. Penner-Hahn, *Angew. Chem.* **1998**, *110*, 1628–1630; *Angew. Chem. Int. Ed.* **1998**, *37*, 1564–1566.

[131] S. I. Khan, P. G. Edwards, H. S. H. Yuan, R. Bau, *J. Am. Chem. Soc.* **1985**, *107*, 1682–1684.

[132] E. Nakamura, *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 985–994.

[133] B. H. Lipshutz, J. Keith, D. J. Buzard, *Organometallics* **1999**, *18*, 1571–1574.

[134] T. M. Barnhart, H. Huang, J. E. Penner-Hahn, *J. Org. Chem.* **1995**, *60*, 4310–4311.

[135] A. Gerold, J. T. B. H. Jastrzebski, C. M. P. Kronenburg, N. Krause, G. van Koten, *Angew. Chem.* **1997**, *109*, 778–780; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 755–757.

[136] T. Stemmler, J. E. Penner-Hahn, P. Knochel, *J. Am. Chem. Soc.* **1993**, *115*, 348–350.

[137] S. H. Bertz, A. S. Vellekoop, R. A. J. Smith, J. P. Snyder, *Organometallics* **1995**, *14*, 1213–1220.

[138] M. Böhme, G. Frenking, M. T. Reetz, *Organometallics* **1994**, *13*, 4237–4245.

[139] G. Fraenkel, M. Henrichs, J. M. Hewitt, B. M. Su, M. J. Geckele, *J. Am. Chem. Soc.* **1980**, *102*, 3345–3350.

[140] J. Heinzer, J. F. M. Oth, D. Seebach, *Helv. Chim. Acta* **1985**, *68*, 1848–1862.

[141] G. Hallnemo, C. Ullenius, *Tetrahedron* **1983**, *39*, 1621–1625.

[142] C. L. Kingsbury, R. A. J. Smith, *J. Org. Chem.* **1997**, *62*, 4629–4634; C. L. Kingsbury, R. A. J. Smith, *J. Org. Chem.* **1997**, *62*, 7637–7643.

[143] C. L. Kingsbury, K. S. Sharp, R. A. J. Smith, *Tetrahedron* **1999**, *55*, 14 693–14 700.

[144] C. Kappenstein, R. P. Hugel, *Inorg. Chem.* **1978**, *17*, 1945–1949; P. Chaudhuri, K. Oder, K. Wieghardt, J. Weiss, J. Reedijk, V. Hinrichs, J. Wood, A. Ozarowski, H. Stratemaier, D. Reinen, *Inorg. Chem.* **1986**, *25*, 2951–2958; J. Cernak, J. Chomic, C. Kappenstein, M. Dunaj-Jurco, *Z. Kristallogr.* **1994**, *209*, 43.

[145] a) M. A. Willert-Porada, D. J. Burton, N. C. Baenziger, *J. Chem. Soc. Chem. Commun.* **1989**, 1633–1634; b) D. Naumann, T. Roy, K.-F. Tebbe, W. Crump, *Angew. Chem.* **1993**, *105*, 1555–1556; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1482–1483; c) R. Eujen, B. Hoge, D. J. Brauer, *J. Organomet. Chem.* **1996**, *519*, 7–20.

[146] a) A. E. Dorigo, J. Wanner, P. von R. Schleyer, *Angew. Chem.* **1995**, *107*, 492–494; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 476–478; b) J. P. Snyder, *J. Am. Chem. Soc.* **1995**, *117*, 11 025–11 026.

[147] J. P. Snyder, *Angew. Chem.* **1995**, *107*, 112–113; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 80–81.

[148] M. Kaupp, H. G. von Schnering, *Angew. Chem.* **1995**, *107*, 1076; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 986.

[149] J. P. Snyder, *Angew. Chem.* **1995**, *107*, 1076–1077; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 986–987; compare with: J. K. Bera, A. G. Samuelson, J. Chandrasekhar, *Organometallics* **1998**, *17*, 4136–4145.

[150] R. A. Poirier, G. A. Ozin, D. F. Mcintosh, G. Csizmadia, R. Daudel, *Chem. Phys. Lett.* **1983**, *191*, 221–229.

[151] T. Ziegler, V. Tschinke, A. Becke, *J. Am. Chem. Soc.* **1987**, *109*, 1351–1358.

[152] A. E. Dorigo, K. Morokuma, *J. Am. Chem. Soc.* **1989**, *111*, 4635–4643; A. E. Dorigo, K. Morokuma, *J. Am. Chem. Soc.* **1989**, *111*, 6524–6536.

[153] E. Nakamura, Y. Miyachi, N. Koga, K. Morokuma, *J. Am. Chem. Soc.* **1992**, *114*, 6686–6692; E. Nakamura, M. Nakamura, Y. Miyachi, N. Koga, K. Morokuma, *J. Am. Chem. Soc.* **1993**, *115*, 99–106.

[154] C. W. Bauschlicher, Jr., S. R. Langhoff, H. Partridge, L. A. Barnes, *J. Chem. Phys.* **1989**, *91*, 2399–2411.

[155] I. Antes, G. Frenking, *Organometallics* **1995**, *14*, 4263–4268; compare with: M. Böhme, G. Frenking, *Chem. Phys. Lett.* **1994**, *224*, 195–199.

[156] P. Belanzoni, M. Rosi, A. Sgamellotti, E. J. Baerends, C. Floriani, *Chem. Phys. Lett.* **1996**, *257*, 41–48.

[157] C. Sosa, J. Andzelm, B. C. Elkin, E. Wimmer, K. D. Dobbs, D. A. Dixon, *J. Phys. Chem*. **1992**, *96*, 6630–6636.

[158] M. Böhme, G. Frenking, M. T. Reetz, *Organometallics* **1994**, *13*, 4237–4245.

[159] H. O. House, W. L. Respess, G. M. Whitesides, *J. Org. Chem.* **1966**, *31*, 3128–3141.

[160] K. Yamamoto, H. Ogura, J.-i. Jukuta, H. Inoue, K. Hamada, Y. Sugiyama, S. Yamada, *J. Org. Chem.* **1998**, *63*, 4449–4458.

[161] H. O. House, M. J. Umen, *J. Am. Chem. Soc.* **1972**, *94*, 5495–5497.

[162] J. Munch-Petersen, C. Bretting, P. M. Jørgensen, S. Refu, V. K. Andersen, *Acta Chem. Scand.* **1961**, *15*, 277–292; see also: Y. Yamamoto, J. Yamada, T. Uyehara, *J. Am. Chem. Soc.* **1987**, *109*, 5820–5822.

[163] E. J. Corey, F. J. Hannon, N. W. Boaz, *Tetrahedron* **1989**, *45*, 545–555.

[164] A. S. Vellekoop, R. A. J. Smith, *J. Am. Chem. Soc.* **1994**, *116*, 2902–2913.

[165] S. R. Krauss, S. G. Smith, *J. Am. Chem. Soc.* **1981**, *103*, 141–148.

[166] H. O. House, K. A. J. Snoble, *J. Org. Chem.* **1976**, *41*, 3076–3083.

[167] C. P. Casey, M. C. Cesa, *J. Am. Chem. Soc.* **1979**, *101*, 4236–4244.

[168] S. H. Bertz, G. Dabbagh, J. M. Cook, V. Honkan, *J. Org. Chem.* **1984**, *49*, 1739–1743.

[169] D. J. Hannah, R. A. J. Smith, *Tetrahedron Lett.* **1975**, 187–190; R. A. J. Smith, D. J. Hannah, *Tetrahedron* **1979**, *35*, 1183–1189.

[170] C. P. Casey, R. A. Boggs, *Tetrahedron Lett.* **1971**, *27*, 2455–2458.

[171] G. M. Whitesides, P. E. Kendall, *J. Org. Chem.* **1972**, *37*, 3718–3725; F. Näf, P. Degen, *Helv. Chim. Acta* **1971**, *54*, 1939–1949.

[172] H. Yamataka, N. Fujimura, Y. Kawafuji, T. Hanafusa, *J. Am. Chem. Soc.* **1987**, *109*, 4305–4308.

[173] Y. Chounan, T. Ibuka, Y. Yamamoto, *J. Chem. Soc. Chem. Commun.* **1994**, 2003–2004.

[174] Y. Yamamoto, S. Nishii, T. Ibuka, *J. Am. Chem. Soc.* **1988**, *110*, 617–618.

[175] Y. Chounan, H. Horino, T. Ibuka, Y. Yamamoto, *Bull. Chem. Soc. Jpn.* **1997**, *50*, 1953–1959.

[176] C. T. Wigal, J. R. Grunwell, J. Hershberger, *J. Org. Chem.* **1991**, *56*, 3759–3761; S. J. Anderson, W. T. Hopkins, C. T. Wigal, *J. Org. Chem.* **1992**, *57*, 4304–4305.

[177] J. Berlan, J.-P. Battioni, K. Koosha, *Bull. Chim. Soc. Fr.* **1979**, II 183–190.

[178] G. Hallnemo, T. Olsson, C. Ullenius, *J. Organomet. Chem.* **1984**, *265*, C22–C24; G. Hallnemo, T. Olsson, C. Ullenius, *J. Organomet. Chem.* **1985**, *282*, 133–144; B. Christenson, G. Hallnemo, C. Ullenius, *Chem. Scr.* **1987**, *27*, 511–512; C. Ullenius, B. Christenson, *Pure Appl. Chem.* **1988**, *60*, 57–64.

[179] N. Krause, R. Wagner, A. Gerold, *J. Am. Chem. Soc.* **1994**, *116*, 381–382.

[180] S. Sharma, A. C. Oehlschlager, *Tetrahedron* **1991**, *47*, 1177–1184; S. H. Bertz, R. A. J. Smith, *J. Am. Chem. Soc.* **1989**, *111*, 8276–8277; B.-S. Lou, G. Li, F.-D. Lung, V. J. Hruby, *J. Org. Chem.* **1995**, *60*, 5509–5514.

[181] J. Canisius, A. Gerold, N. Krause, *Angew. Chem.* **1999**, *111*, 1727–1730; *Angew. Chem. Int. Ed.* **1999**, *38*, 1644–1646.

[182] J. Klein, R. Levene, *J. Chem. Soc. Perkin Trans. 2* **1973**, 1971–1979.

[183] N. Krause, *Tetrahedron Lett.* **1989**, *30*, 5219–5222.

[184] E. J. Corey, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1969**, *91*, 1851–1852; J. B. Siddall, M. Biskup, J. H. Fried, *J. Am. Chem. Soc.* **1969**, *91*, 1852–1854; J. Klein, R. M. Turckel, *J. Am. Chem. Soc.* **1969**, *91*, 6186–6187; J. Klein, N. Aminadav, *J. Chem. Soc. C* **1970**, 1380–1385; Y. Yamamoto, H. Yatagai, K. Maruyama, *J. Org. Chem.* **1979**, *44*, 1744–1746; J. P. Marino, R. J. Linderman, *J. Org. Chem.* **1981**, *46*, 3696–3702; I. Fleming, D. A. Perry, *Tetrahedron* **1981**, *37*, 4027–4034.

[185] K. Nilsson, C. Ullenius, N. Krause, *J. Am. Chem. Soc.* **1996**, *118*, 4194–4195.

[186] K. Nilsson, T. Andersson, C. Ullenius, *J. Organomet. Chem.* **1997**, *546*, 591–595; K. Nilsson, T. Andersson, C. Ullenius, A. Gerold, N. Krause, *Chem. Eur. J.* **1998**, *4*, 2051–2508.

[187] J. Normant, G. Cahiez, J. Villieras, *J. Organomet. Chem.* **1975**, *92*, C28-C30.

[188] Reviews: J. M. Klunder, G. H. Posner in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 207–239.

[189] R. W. Herr, D. M. Wieland, C. R. Johnson, *J. Am. Chem. Soc.* **1970**, *92*, 3813–3814; C. R. Johnson, R. W. Herr, D. M. Wieland, *J. Org. Chem.* **1973**, *38*, 4263–4268; compare with: M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, S. Inoue, *J. Org. Chem.* **1975**, *40*, 2009–2011.

[190] M. J. Eis, B. Ganem, *Tetrahedron Lett.* **1985**, *26*, 1153–1156.

[191] a) C. R. Johnson, G. A. Dutra, *J. Am. Chem. Soc.* **1973**, *95*, 7783–7787; b) B. H. Lipshutz, R. S. Wilhelm, *J. Am. Chem. Soc.* **1982**, *104*, 4696–4698.

[192] C.-y. Guo, M. L. Brownawell, J. San Filippo, Jr, *J. Am. Chem. Soc.* **1985**, *107*, 6028–6030.

[193] S. Komiya, T. A. Albright, R. Hoffmann, J. K. Kochi, *J. Am. Chem. Soc.* **1976**, *98*, 7255–7265.

[194] S. Komiya, T. A. Albright, R. Hoffmann, J. K. Kochi, *J. Am. Chem. Soc.* **1976**, *98*, 8440–8447.

[195] A. Tamaki, J. K. Kochi, *J. Organomet. Chem.* **1973**, *51*, C39–C42.

[196] J. Stein, J. P. Fackler, Jr., C. Paparizos, H.-W. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 2192–2198.

[197] J. P. Collman, *Acc. Chem. Res.* **1968**, *1*, 136–143.

[198] E. C. Ashby, R. N. DePriest, A. Tuncay, S. Srivastava, *Tetrahedron Lett.* **1982**, *23*, 5251–5254.

[199] E. C. Ashby, D. Coleman, *J. Org. Chem.* **1987**, *52*, 4554–4565; S. H. Bertz, G. Dabbagh, A. M. Mujsce, *J. Am. Chem. Soc.* **1991**, *113*, 631–636.

[200] H. L. Goering, C. C. Tseng, *J. Org. Chem.* **1983**, *48*, 3986–3990; H. L. Goering, S. S. Kantner, *J. Org. Chem.* **1984**, *49*, 422–426; H. L. Goering, S. S. Kantner, E. P. Seitz, Jr., *J. Org. Chem.* **1985**, *50*, 5495–5499.

[201] a) M. A. Sevin, W. Chodkiewicz, P. Cadiot, *Tetrahedron Lett.* **1965**, 1953–1959; b) P. Rona, P. Crabbé, *J. Am. Chem. Soc.* **1968**, *90*, 4733–4734; P. Rona, P. Crabbé, *J. Am. Chem. Soc.* **1969**, *91*, 3289–3292; J. L. Luche, E. Barreiro, J. M. Dollat, P. Crabbé, *Tetrahedron Lett.* **1975**, 4615–4618; J.-M. Dollat, J.-L. Luche, P. Crabbé, *J. Chem. Soc. Chem. Commun*. **1977**, 761–762; c) P. Vermeer, J. Meijer, L. Brandsma, *Rec. Trav. Chim. Pays-Bas* **1975**, *94*, 112–114; A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *J. Am. Chem. Soc.* **1990**, *112*, 8042–8047.

[202] C. Gallina, P. G. Ciattini, *J. Am. Chem. Soc.* **1979**, *101*, 1035–1036; H. L. Goering, S. S. Kantner, C. C. Tseng, *J. Org. Chem.* **1983**, *48*, 715–721.

[203] J.-E. Bäckvall, M. Sellén, B. Grant, *J. Am. Chem. Soc.* **1990**, *112*, 6615–6621; E. S. M. Persson, J.-E. Bäckvall, *Acta. Chem. Scand.* **1995**, *49*, 899–906.

[204] E. Nakamura, K. Sekiya, M. Arai, S. Aoki, *J. Am. Chem. Soc.* **1989**, *111*, 3091–3093.

[205] M. Nakamura, E. Nakamura, N. Koga, K. Morokuma, *J. Chem. Soc. Faraday Trans.* **1994**, *90*, 1789–1798; K. Kubota, S. Mori, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **1998**, *120*, 13334–13341.

[206] P. B. Armentrout, R. Georgiadis, *Polyhedron* **1988**, *7*, 1573–1581.

[207] D. E. Frantz, D. A. Singleton, J. P. Snyder, *J. Am. Chem. Soc.* **1997**, *119*, 3383–3384.

[208] B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771–806.

[209] Note that, in contrast to MeI, secondary iodides do not react in an S_N2 manner. See Ref. [18].

[210] M. Nakamura, E. Nakamura, N. Koga, K. Morokuma, *J. Am. Chem. Soc.* **1993**, *115*, 11016–11017.

[211] S. Mori, B.-H. Kim, M. Nakamura, E. Nakamura, *Chem. Lett.* **1997**, 1079–1080.

[212] E. Kaufmann, P. von R. Schleyer, K. N. Houk, Y.-D. Wu, *J. Am. Chem. Soc.* **1985**, *107*, 5560–5562.

[213] M. P. Bernstein, D. B. Collum, *J. Am. Chem. Soc.* **1993**, *115*, 789–790; P. G. Willard, Q.-Y. Liu, *J. Am. Chem. Soc.* **1993**, *115*, 3380–3381; F. E. Romesberg, D. B. Collum, *J. Am. Chem. Soc.* **1995**, *117*, 2166–2178; K. W. Henderson, A. E. Dorigo, Q.-Y. Liu, P. G. Willard, P. von R. Schleyer, P. R. Bernstein, *J. Am. Chem. Soc.* **1996**, *118*, 1339–1347; compare with: E. L. Coitiño, E. Ciuffarin, F. M. Floris, J. Tomasi, *J. Phys. Chem. A* **1998**, *102*, 8369–8376.

[214] M. Schlosser, G. Jan, E. Byrne, J. Sicher, *Helv. Chim. Acta* **1973**, *56*, 1630–1637; M. Schlosser, T. D. An, *Angew. Chem.* **1981**, *93*, 1114; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 1039–1041; M. G. Stanton, C. B. Allen, R. M. Kissling, A. L. Lincoln, M. R. Gagné, *J. Am. Chem. Soc.* **1998**, *120*, 5981–5989; E. K. van den Beuken, B. L. Feringa, *Tetrahedron* **1998**, 12985–13011.

[215] See: H. Suzuki, H. Omori, Y. Moro-oka, *Organometallics* **1988**, *7*, 2579–2581; H. Suzuki, H. Omori, D. H. Lee, Y. Yoshida, M. Fukushima, M. Tanaka, Y. Moro-oka, *Organometallics* **1994**, *13*, 1129–1146; M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290–1310; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236–1256; see also: T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783–4784; I. Ojima, M. Okabe, K. Kato, H. B. Kwon, I. T. Horváth, *J. Am. Chem. Soc.* **1988**, *110*, 150–157; H. Steinhagen, G. Helmchen, *Angew. Chem.* **1996**, *108*, 2489–2492; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2339–2342; S. J. Lippard, *Science* **1995**, *268*, 996–997.

[216] E. Nakamura, A. Hirai, M. Nakamura, *J. Am. Chem. Soc.* **1998**, *120*, 5844–5845; A. Hirai, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **1999**, *121*, 8665– 8666.