*Award Accounts*
**The Chemical Society of Japan Award for 2002**

# On the Reaction Mechanism of "Higher-Order Cuprate", Alias "Lipshutz Cuprate"

**Eiichi Nakamura* and Naohiko Yoshikai**

Department of Chemistry, The University of Tokyo, Bunkyo-ku, Tokyo 113-0033

Received July 30, 2003; E-mail: nakamura@chem.s.u-tokyo.ac.jp

An organocuprate reagent of the $R_2Cu(CN)Li$ composition introduced by Lipshutz has been frequently used in organic synthesis because its reactivity in some reactions is higher than that of the standard Gilman reagent $R_2CuLi$. The higher reactivity of the Lipshutz cuprate was once ascribed to a dianionic tri-coordinated copper(I) ("higher-order") structure, but numerous structural studies over the last ten years have shown that the Lipshutz cuprate exists as a "cyano-Gilman" ($R_2CuLi\cdot LiCN$) cuprate. This conclusion notwithstanding, our recent theoretical study indicated that a minor and undetectable species such as $R(CN)CuLi\cdot LiR$ may play some roles in the substitution and the addition reactions of the Lipshutz cuprate. The high reactivity of the minor species originates from the anisotropic and multi-coordination capability of the cyanide ligand to metals. Our result accounts for the higher or anomalous reactivity of the Lipsthuz cuprate in some reactions, and further demonstrates the importance of computational study on poly-metallic reaction pathways, where experimental mechanistic information may be difficult to obtain.

The art of chemistry resides in the fact that a chemist can "program" his/her own idea into a molecule, which then may function exactly according to the implemented program. One good example of such programming is catalysis. In any high performance catalysis, a metal catalyst interacts with the substrates, exchanges electrons, and effects bond reorganization as programmed by the chemist. Selection of the catalytic metal atom is the key of the whole programming, but presently the success depends more or less on luck. "Why do you use copper for one reaction and palladium for another?" This is a tough question to answer in the class. Elucidation of the secret of elements is not only the first step in "molecular programming", but also represents the ultimate goal of chemical research.

In the beginning of the 1980s, one of us (EN) discovered the rate-accelerating effect of $Me_3SiCl$ in organocopper chemistry (Scheme 1a),[1] wondered on the mechanism of copper catalysis, and simultaneously learned that quantum mechanical calculations would eventually solve such a problem. Our recent finding that an organocopper reagent quantitatively adds five times to [60]fullerene further fueled our interest in the organocopper reaction mechanisms (Scheme 1b).[2] Organocopper(I) reagents are always molecular aggregates composed of multiple metals and ligands, into which chemists have implemented a variety of effective programs without knowing or likely very often with incorrect ideas on what they are implementing.

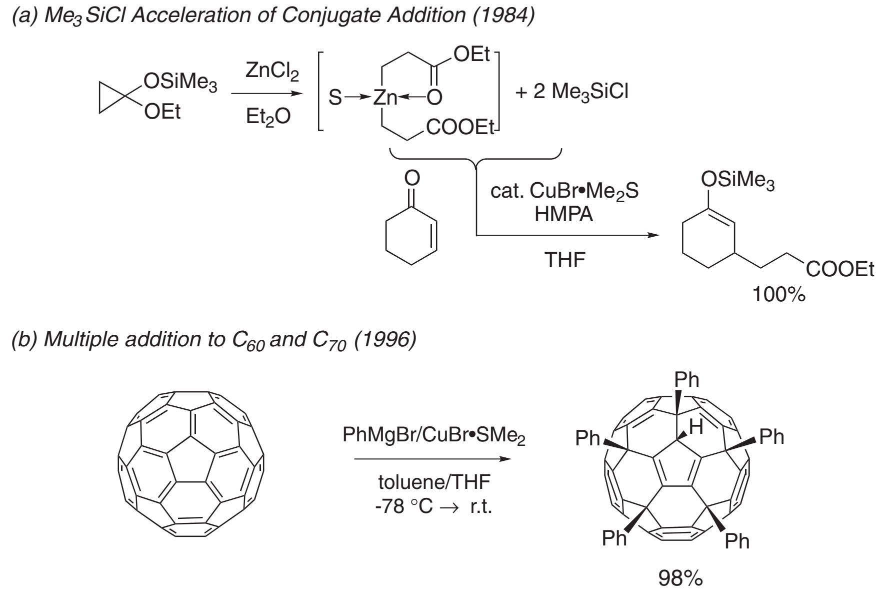
In 1985, EN learned that quantum mechanical calculations might become useful for the studies of catalysis, when Prof. Eiji Osawa of Hokkaido University kindly sent him the MM2 and MNDO programs. Upon starting collaboration with Prof. Keiji Morokuma at the Institute for Molecular Science in 1989, it was felt that quantum mechanical calculations on the complex reaction pathways of organocopper reagents would become feasible within several years. Our first roadmap included studies on a simplified organocopper reagent MeCu on one side,[3] and on a simple aggregate, MeLi dimer on the other.[4] In 1997, we reported the first comprehensive studies on the reaction pathways of $Me_2CuLi\cdot LiCl$ and $[Me_2CuLi]_2$.[5] The transition state of the addition of $[Me_2CuLi]_2$ to acetylene (Fig. 1) was obtained first in 1995[5a] and followed by the determination of the reaction pathway of the conjugate addition to acrolein.[5b]

Further improvement of computational facility and methodology allowed us to study even larger systems after 1998. The mechanistic principles that lie behind the success of standard methodologies such as "dummy ligand" (i.e., ligand transfer selectivity engineered for effective use of organic ligand on copper atom),[6] "Yamamoto's $RCu\cdot BF_3$" (Lewis-acid acceleration),[7] asymmetric conjugate addition,[7] and "higher-order cuprate"[8,9] have been revealed. In all of these studies, we found that the "design" by experimentalists is often based on a misconception, and elucidated what the actual "programs" in the molecule are.[10]

## "Higher-Order Cyanocuprate", Alias "Lipshutz Cuprate"

Among numerous unresolved issues in the structures and the reaction mechanisms of organocopper(I) chemistry,[10,11] there was a problem of "higher-order cyanocuprate".[12,13] This is a copper(I) reagent prepared by addition of two equivalents of

Published on the web January 13, 2004; DOI 10.1246/bcsj.77.1



Scheme 1.

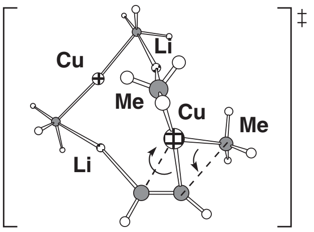
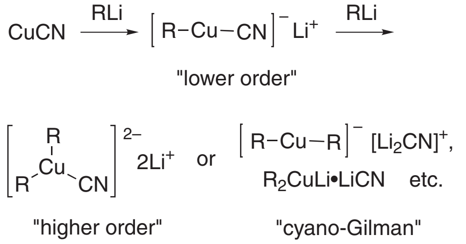


Fig. 1.

an alkyllithium reagent to one equivalent of CuCN, which was introduced by Lipshutz in 1981 (Eq. 1; it will be called “Lipshutz reagent” hereafter).[14] The Lipshutz reagent ($R_2Cu(CN)Li_2$) attracted much attention because its reactivity was sometimes higher than that of a standard Gilman reagent ($R_2CuLi$).[12]



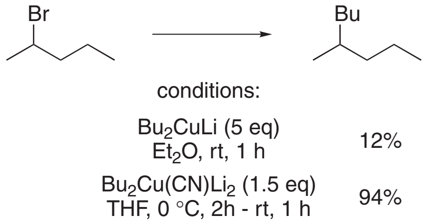
$$\mathrm{CuCN} \xrightarrow{\mathrm{RLi}} \left[\mathrm{R{-}Cu{-}CN}\right]^{-}\mathrm{Li}^{+} \xrightarrow{\mathrm{RLi}}$$

"lower order"

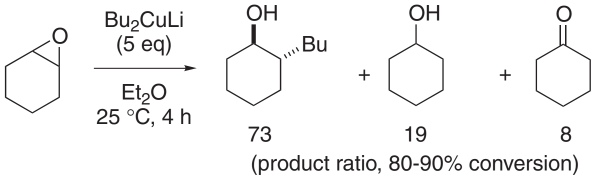
$$\left[\mathrm{R_2Cu(CN)}\right]^{2-}\ 2\mathrm{Li}^{+} \quad \text{or} \quad \left[\mathrm{R{-}Cu{-}R}\right]^{-}[\mathrm{Li_2CN}]^{+},\ \mathrm{R_2CuLi{\bullet}LiCN}\ \text{etc.} \qquad (1)$$

"higher order" "cyano-Gilman"

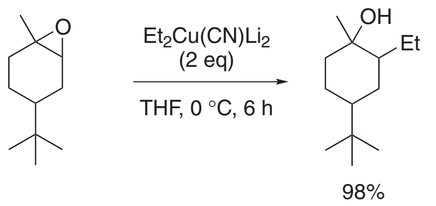
The Lipshutz cuprate is more reactive in the substitution reactions of an alkyl halide (secondary alkyl halide in particular) (Eq. 2)[14–16] and of a highly substituted epoxide (Eqs. 3 and 4).[17,18] Lipshutz considered that the higher reactivity is due to a dianionic cuprate(I) structure $[R_2Cu(CN)]^{2-}\cdot 2Li^+$, where two alkyl and one cyano anions are coordinated to the copper(I) center, and called it “higher-order cuprate”.[19] The Lipshutz cuprate shows reactivities uncommon for the standard Gilman cuprate ($R_2CuLi$), which appeared to support the proposal of the unusual “higher-order” structure. For instance, the Lipshutz cuprate deprotonates terminal alkynes (Eq. 5) rather than undergoing carbocupration,[12,20] and shows a positive Gilman test (Eq. 6, a probe to test the presence of free alkyllithium reagent in the cuprate mixture).[21–23] The Lipshutz cuprate is uniquely effective for biaryl synthesis by oxidative coupling of a diarylcuprate (Eq. 7).[24]



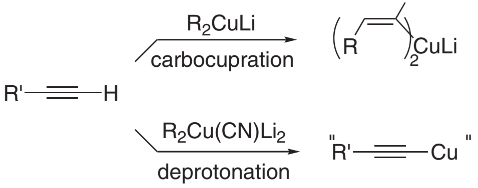
(2)



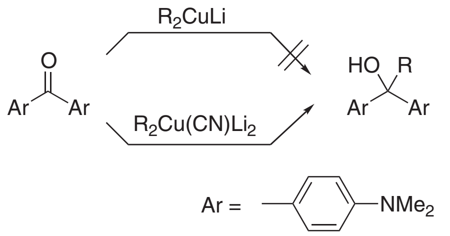
(3)



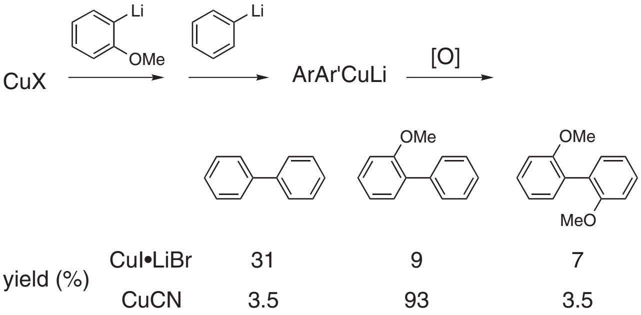
(4)



(5)

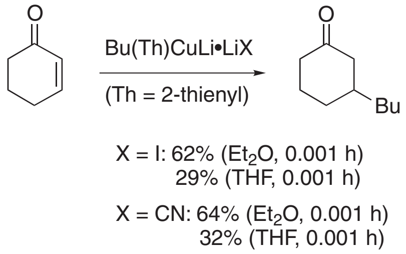


(6)

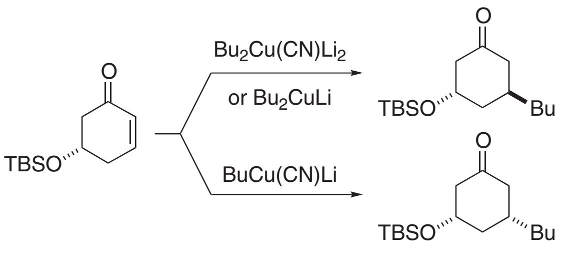


(7)

The Lipshutz cuprate is said to be more reactive toward sterically hindered $\alpha,\beta$-unsaturated ketones,[12] but is no more reactive toward 2-cyclohexenone than the Gilman reagent, as shown by the logarithmic reactivity profile study (Eq. 8).[25] Interestingly, the stereochemistry of the conjugate addition of the Lipshutz cuprate to a 5-siloxycyclohex-2-en-1-one is different from that of the lower-order cyanocuprate (RCu(CN)Li), but is the same as that of the Gilman reagent ($R_2CuLi$) (Eq. 9).[26] This may suggest that the reactive species in conjugate addition of the Lipshutz and the Gilman reagents are the same, while the siloxy oxygen acts as a reagent-directing group in the lower-order cuprate reaction.[27]



(8)



(9)

While the Lipshutz cuprate gained immediate success in the synthetic society,[12] its "higher-order structure" has become the target of controversy since in 1990 the Bertz publication posed a question on its identity.[28] Numerous studies afterward led to a recent conclusion that there is no "higher-order cyanocuprate", that is, the cyanide anion is not bonded to the copper atom.[13,19] Hence, the cuprate in its most stable state must be described as a cyano-Gilman cuprate $R_2CuLi \cdot LiCN$ (Eq. 1 and discussion in the later sections). Cyanide is simply more stable in its lithium complex than being covalently attached to the copper(I) atom to form a "higher-order" structure.[29] Note that here the term "cyano-Gilman" has been used to suggest that a cyano anion is not bound to a copper(I), and does not contain any implication about the exact location of the cyano group.[28]

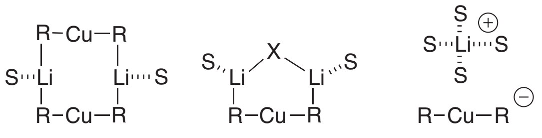
Although the most stable structure of the Lipshutz cuprate is now considered to be the "cyano-Gilman" structure, there still remain the experimental facts that the Lipshutz and the Gilman reagents show different reactivities (vide supra). This suggested to us that some minor unidentified species may be acting as a reactive species. This Account first discusses the structures and the reactivities of the Lipshutz cuprate and then the possibilities of the participation of a minor species in the reactions.

Before discussing the cuprate structures, some general cautions may be given. First, a lithium organocuprate such as $R_2CuLi$ in an ethereal solvent undergoes structural change by cleaving and forming electrostatic bonds around the lithium atom, whereas the coordination environment of the copper atom (covalent) is much more stable. Second, most of the experimental studies on lithium organocuprates discussed below deal with the cuprates by themselves, neither in the presence of a reactant nor during their reactions.[30] As the alkyl anion is consumed by the reaction, the concentration of LiX (X = halide or hetero atoms) increases, and likely changes the structure of the cuprate itself. Therefore the products will become a part of the mobile equilibria, and will inevitably affect the structure and the reactivity of the cuprate.

## Structure of the Lipshutz Cuprate

The structures of the lithium organocuprates in crystals and in solution may be classified into two categories: contact ion pair, such as **1** and **2**, and solvent-separated ion pair, such as **3** (Fig. 2).[31] The contact ion pair may be either a homo-dimer **1** or a hetero-aggregate **2** that contains only one copper atom.[32] In general, the contact ion pair is dominant in weakly solvating solvents such as $Et_2O$ and $Me_2S$, while the solvent-separated ion pair is preferred in solvents with strong coordination ability (THF, crown ether, etc.). Lithium salt has less influence on the ion pair equilibrium than does the solvent.[31b] Although there has been no experimental evidence of the hetero-aggregate **2** for a long time,[33] van Koten recently reported the first crystal structure of this type of complex (Fig. 3).[34]

During the last half of the 1990s, a number of publications against the higher-order structure appeared in print. Penner-Hahn reported that the cyanide anion is not bound to the copper atom either in a $\sigma$- or in a $\pi$-fashion on the basis of careful EXAFS and XANES studies.[35] They also suggested that the



**1** **2** **3**
(X = halogen or CN)

Fig. 2.

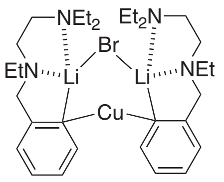
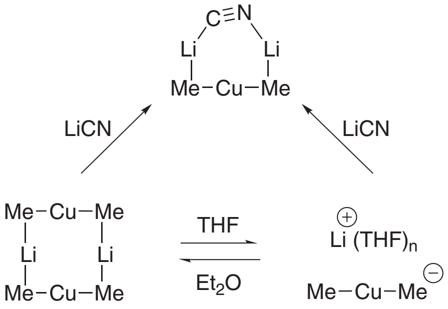


Fig. 3.



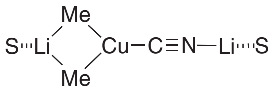
Scheme 2.

Gilman cuprate exists as a homo-dimer in $Et_2O$ and $Me_2S$, and as a solvent-separated ion pair in THF, but that the Lipshutz cuprate always exists as a hetero-aggregate in these solvents (Scheme 2).

This agrees with the cryoscopic study reported by Krause and van Koten, who showed that the Lipshutz cuprate is largely monomeric in THF.[36] They also suggested that "higher-order (or cyano-Gilman)" and "lower-order" cuprates are in equilibrium with each other in solution (Eq. 10).

$$R_2Cu(CN)Li_2 \rightleftharpoons RCu(CN)Li + RLi \qquad (10)$$

In collaboration with experimentalists, Snyder and Frenking performed ab initio calculations on various structural isomers of the $Me_2Cu(CN)Li_2$ stoichiometry and found that the hetero-aggregate **2** is the most stable.[35c,37] The higher-order structure **4** was calculated to be 20–30 kcal/mol higher in energy. Hence they concluded that it was not an important reactive species (Fig. 4).



**4**

Fig. 4.

An NMR study by Bertz indicated that the $^{15}N$ NMR chemical shift values for BuCu(CN)Li and $Bu_2CuLi \cdot LiCN$ are very different from each other.[38] A systematic study by Berger on $Me_2CuLi$, $Me_3CuLi_2$, $Me_2Cu(CN)Li_2$, and MeCu(CN)Li about the $^{13}C$–$^{1}H$ and $^{13}C$–$^{13}C$ scalar coupling and the $^{1}H$–$^{6}Li$, $^{13}C$–$^{6}Li$ dipolar coupling indicated that $Me_2CuLi$, $Me_3CuLi_2$, and $Me_2Cu(CN)Li_2$ share the same $[Me_2Cu]^-$ part structure and that the copper atom in the Lipshutz cuprate $Me_2Cu(CN)Li_2$ does not bear the cyanide anion.[39] This study showed also that the lithium atoms in these cuprates are involved as a part of dynamic equilibria in solution.

While these solution studies were being reported, two crystal structures appeared in print that put an end to the higher-order cuprate controversy. In 1998, van Koten and Boche independently reported the crystal structures of the cuprates of the Lipshutz stoichiometry.[40,41] The van Koten molecule bears an internal amine ligand for a lithium atom, and forms a linear polymeric structure (Fig. 5a). Boche utilized a tridentate ligand pmdeta (*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine) and obtained crystals of a solvent-separated ion pair (Fig. 5b). In both complexes, the cyanide anion is bonded to the lithium atom.

The reaction of two equivalents of $(Me_3Si)CH_2Li$ and one equivalent of CuCN in weakly solvating $Et_2O$ gave the crystals of $[\{[(Me_3Si)CH_2]_2CuLi\}_2] \cdot 3Et_2O$, in which the molecules exist as a homodimeric contact ion pair.[31b] The position of $CN^-$ could not be located, which may suggest the weak interaction between $CN^-$ and the dimeric cuprate or the formation of oligomeric LiCN. The Lipshutz cuprate of the hetero-aggregate structure **2** have not yet been isolated in spite of the effort by van Koten, who applied the same strategy as the one used for

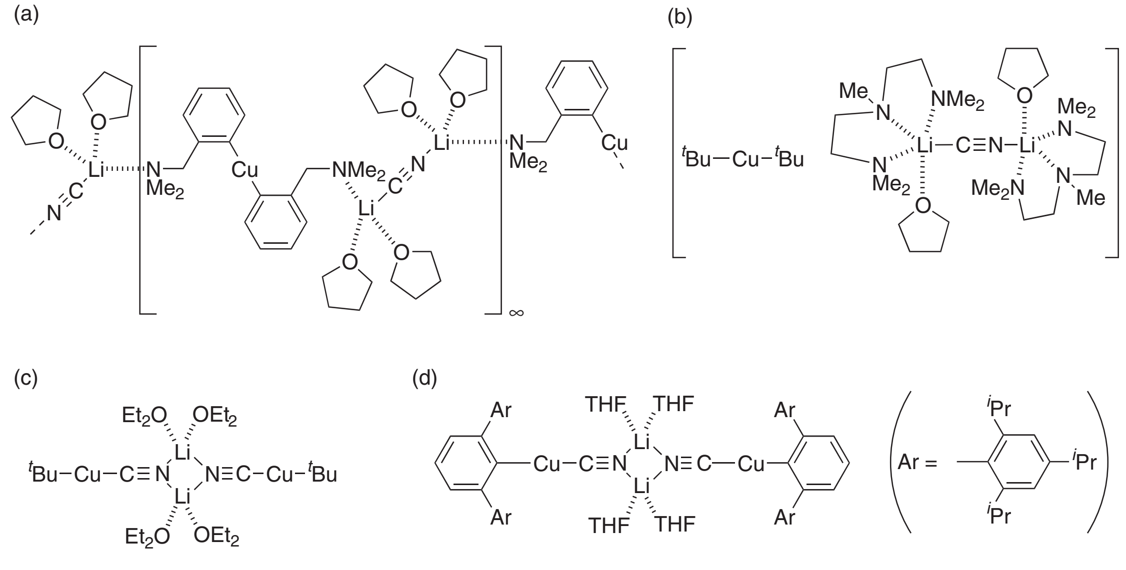


Fig. 5.

the synthesis of the bromocuprate (Fig. 3).[34]

Boche and Power also determined the crystal structures of "lower-order" cyanocuprate (Eq. 1), where the cyanide anion is bonded to one copper and two lithium atoms as shown in Figs. 5c and d, respectively.[41,42] The structure illustrates the fact that the cyanide anion is a potent ligand that can bind simultaneously to copper and to lithium atoms. No such poly-bridging structures have been found previously in the cuprates that contain halide anion(s). This observation provides experimental support to our mechanistic suggestions mentioned below.

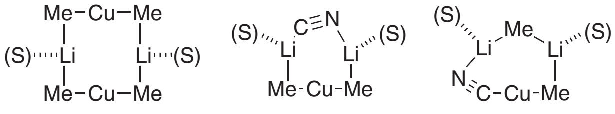
The above experimental and computational data conclusively demonstrated that the Lipshutz cuprate is not a "higher-order" cuprate in its most stable form in solution and in solid-state, but did not yet answer the question, "What is the Lipshutz cuprate?" For instance, how are the $[Me_2Cu]^-$ and the $[Li_2CN]^+$ fragments positioned with each other in solution?

On the basis of extensive $^1H$–$^6Li$ HOE, and $^1H$–$^1H$ NOE analyses, Gschwind and co-workers recently revealed intriguing new data on this issue.[43] They have shown that $Me_2CuLi$ and $Me_2CuLi \cdot LiCN$ exist as a contact ion pair **1** in $Et_2O$ which is weakly basic, while in more strongly coordinating THF, there is a mobile equilibrium between the ion-pair **1** and the solvent-separated ion pair **3**, where the latter is favored. Thus, the Lipshutz cuprate exists in $Et_2O$ as the standard Gilman dimer **1** rather than as the hetero-aggregate **2**. This stands in contrast to the previous suggestion by Penner-Hahn[35] and the assumption used for theoretical studies[35c,37] that the Lipshutz cuprate takes the hetero-aggregate structure **2**. However, one cannot exclude the existence of **2** because of the limitations of the NMR technique for detecting minor structures. For instance, energy difference of less than 3 kcal/mol makes a major/minor isomeric ratio of $10^3$, in which case the minor isomer would be undetectable in experimental structural studies.

## Reactivity of the Lipshutz Cuprate

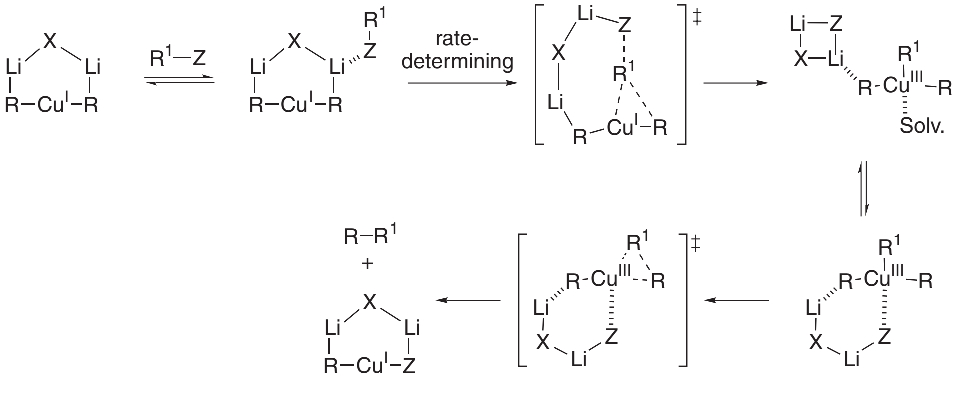
Our previous studies indicated that the contact ion pairs **1** and **2** possess essentially the same reactivity profile (though their rates may differ from each other by one order of magnitude) while **3** is far less reactive.[5] This is in agreement with the fact that the conjugate addition of $Me_2CuLi$ is significantly retarded in the presence of [12]crown-4.[44] Similarly, the conjugate addition of both the Gilman and the Lipshutz cuprates is faster in $Et_2O$ than in THF (Eq. 8).[25] All these data indicate that the Lewis acidity of lithium atoms is critical for the reactivity of an organocuprate.

The foregoing results indicated that the Lipshutz cuprate (in its most stable form) is no more than a variant of the Gilman cuprate such as **5a** and **5b** in Fig. 6, and strongly suggest that the substitution and the conjugate addition reactions of these cuprates would involve similar reactive intermediates (Schemes 3 and 4).[5,45,46] This might then lead to the second conclusion that the higher reactivity of the Lipshutz reagent in substitution reactions and their anomalous reactivities

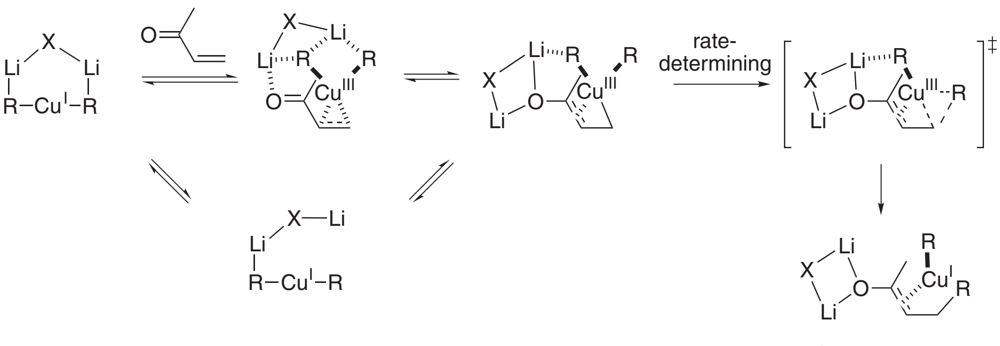


**5a** **5b** **5c**

Fig. 6.



Scheme 3. Reaction pathway of the substitution of an alkyl halide with a lithium organocuprate cluster.

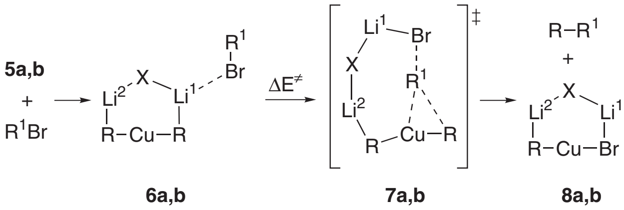


Scheme 4. Reaction pathway of the conjugate addition of a lithium organocuprate cluster to an $\alpha,\beta$-unsaturated carbonyl compound.

(Eqs. 2–7) would reflect only the perturbation effects of the cyanide anion on the lithium atom. However, this conclusion seems rather unlikely. In the following sections, we will suggest that the chemistry of the Lipshutz cuprate forces one to consider the participation of minor structural isomers such as **5c** in the reactions (Fig. 6).

The known anomaly of the Lipshutz reagent such as positive Gilman test (Eq. 6) becomes very reasonable if we accept that the reagent generates free alkyllithium species in equilibrium with the major Gilman-type complex. Previous calculations indicated indeed that the MeLi-outside complex (MeCu(CN)-Li•MeLi, **5c**) is only several kcal/mol less stable than the LiCN-outside complex **5b**;[35c] that is, the cyanide anion that has high affinity to copper(I) can drive out MeLi from the Gilman structure ($[Me_2Cu]^-$). We therefore compared the reactivities of the major and the minor structural isomers of the Lipshutz reagent in the substitution reaction and in the addition reaction to acetylene.[8,9,47]

We first describe the comparison between the Gilman reagent **5a** and the CN-bridged hetero-aggregate **5b** in substitution of methyl bromide (Scheme 5). The activation energy of the rate-limiting halide-displacement process was found to be much lower (by ca. 4 kcal/mol) for **5b** (21.3 kcal/mol) than for **5a** (25.1 kcal/mol) (Fig. 7). The chloro-bridged analog of **5b** has essentially the same activation energy (24.9 kcal/mol).[45]



Scheme 5. Substitution reaction between $R_2CuLi \cdot LiX$ (R = Me, series **a**: X = RCuR, series **b**: X = CN) and $R^1Br$ ($R^1$ = Me).

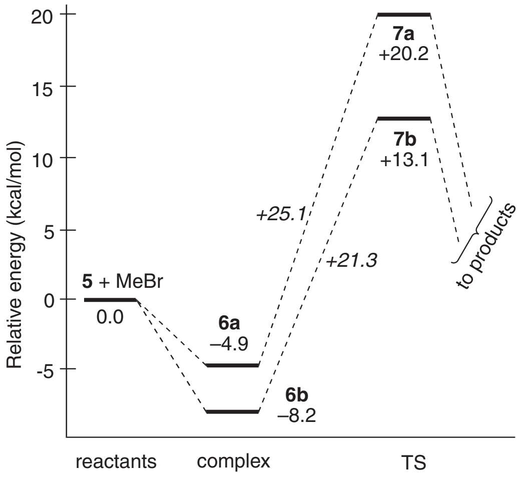


Fig. 7. Energetics of the $S_N2$ reaction of $[Me_2CuLi]_2$ (series **a**) and $Me_2CuLi \cdot LiCN$ (series **b**) with MeBr (B3LYP/631A). The potential energies of **5** + MeBr in series **a** and **b** are set to be equal to zero.

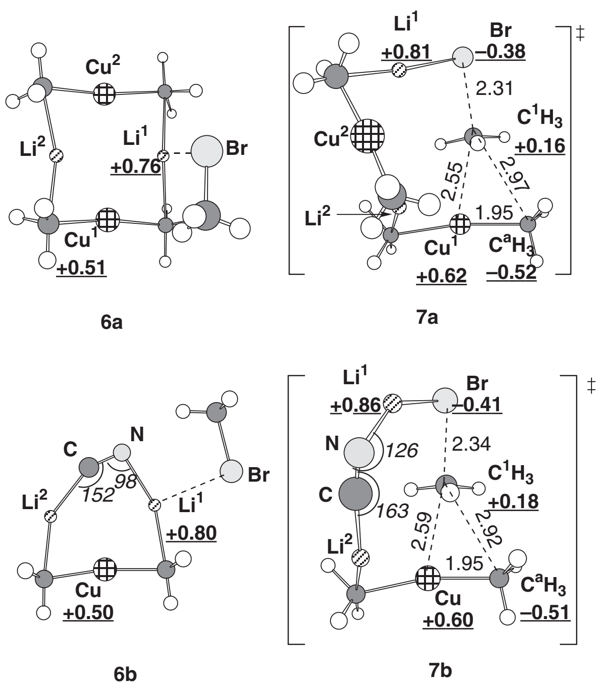


Fig. 8. 3-D structures of the complex and the TS in series **a** and **b** (B3LYP/631A). Numbers refer to bond lengths in Å, bond angles (italic) in degrees, and natural charges (underlined and bold).

The higher reactivity of the cyanocuprate **5b** derives from both the structural and the electrostatic effects of the $[Li^2–CN–Li^1]^+$ moiety. Thus, the structural change of the $[Li^2–CN–Li^1]^+$ moiety from **6b** to **7b** is energetically favorable because the $[Li^2–CN–Li^1]^+$ moiety prefers the linear geometry to the bent one (Fig. 8). Electronically speaking, the lithium atom $Li^1$ in the $[Li^2–CN–Li^1]^+$ fragment is more Lewis acidic than that in the $[Li^2–Me–Cu–Me–Li^1]^+$ fragment; hence it more efficiently activates methyl bromide. This is evident from the fact that the $Li^1$–Br bond in **7b** ($Li^1$: +0.86, Br: −0.41) is more polarized than that in **7a** ($Li^1$: +0.81, Br: −0.38) (Fig. 8).

Is the Lipshutz cuprate, then, only a minor variant for the Gilman reagent? This idea was found to be incorrect when we examined the $S_N2$ reaction of minor isomer **5c** (Fig. 9). If we take a look at the bromide displacement TSs, the energy difference of the TSs **7b** and **7c** is extremely small (0.5 kcal/mol). Since the Curtin–Hammett conditions is satisfied by the fast equilibrium between **5b** and **5c**, the latter must also take part in the alkylation reaction (Fig. 9).

The anisotropy of the metal/cyanide coordination also accounts for the stability of **7c** (and the instability of **6c**, see Fig. 9b). In the TS **7c**, both the copper and the lithium ($Li^2$) metals are coordinated to the cyanide anion in the favorable $\sigma$-fashion, whereas in **5c** and **6c** the lithium atom ($Li^2$) is $\pi$-coordinated to the cyanide anion. Another favorable factor may be the perfect T-shaped coordination geometry of the copper atom in **7c**, which goes directly to the T-shaped copper(III) intermediate with minimum motion (see Scheme 3). In this TS, the $3d_{z^2}$ orbital can interact very effectively with the C–Br $\sigma^*$ orbital (Fig. 10).[48]

It is known experimentally that the Lipshutz cuprate is par-

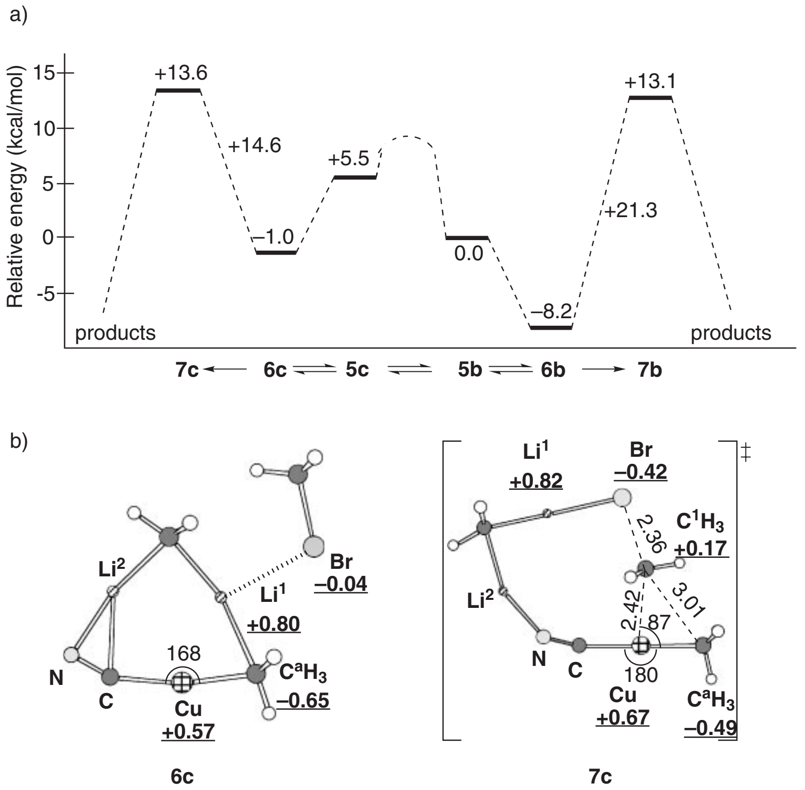


Fig. 9. Energetics of the $S_N2$ reaction of $Me_2CuLi \cdot LiCN$ (**5b**) and $Me(CN)CuLi \cdot LiMe$ (**5c**) with MeBr (a) and the 3-D structures of **6c** and **7c** (b).

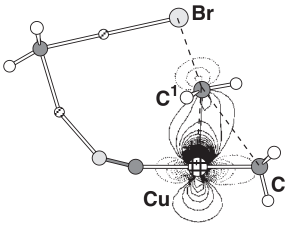


Fig. 10. Localized Kohn–Sham orbital of the bromide displacement TS **7c** in the Cu–$C^a$–$C^1$ plane. The contour intervals are 0.025 $e \cdot au^{-3}$.

ticularly useful for the substitution reaction with secondary alkyl halides or highly substituted epoxides.[14,17] In fact, the difference between the reactivity of **5c** and that of **5b** becomes even more pronounced in the reaction with isopropyl bromide (Fig. 11).

How about the addition reactions? Experiments showed little difference of the reactivity in the conjugate addition (Eq. 8),[25] which however does not necessarily indicate that the reactive species in the two reagents are the same. We studied the addition of **5b** or **5c** to acetylene as a model reaction (Scheme 6). As seen in the energy diagram in Fig. 12, the solvated cyanocopper complex **5c·S** becomes significantly stabilized upon complex-

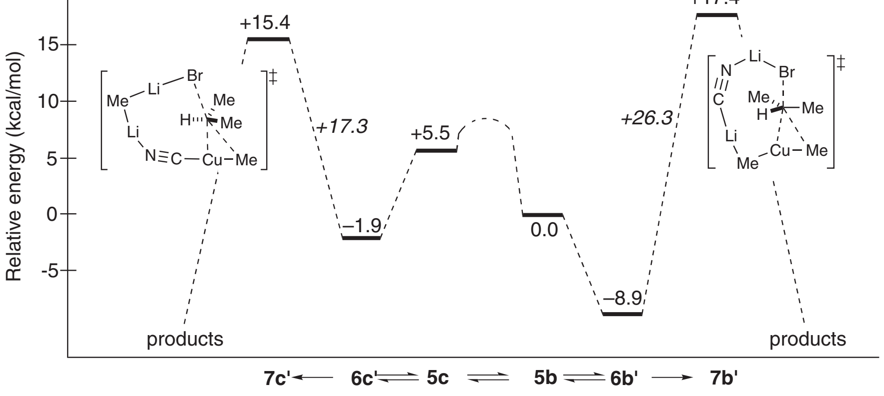
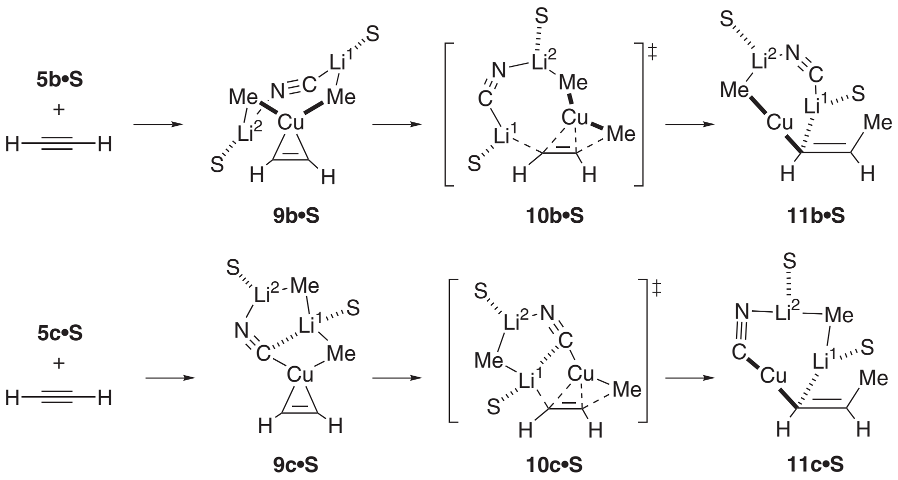


Fig. 11. Energetics of the $S_N2$ reaction of $Me_2CuLi \cdot LiCN$ (**5b**) and $MeCu(CN)Li \cdot LiMe$ (**5c**) with isopropyl bromide (B3LYP/631A).



(S = $Me_2O$, where S is included: Solvated intermediates are indicated as **9b•S.**)

Scheme 6. Reaction pathways of the addition of $Me_2CuLi{\cdot}LiCN$ (**5b**) or $Me(CN)CuLi{\cdot}LiMe$ (**5c**) to an acetylene.

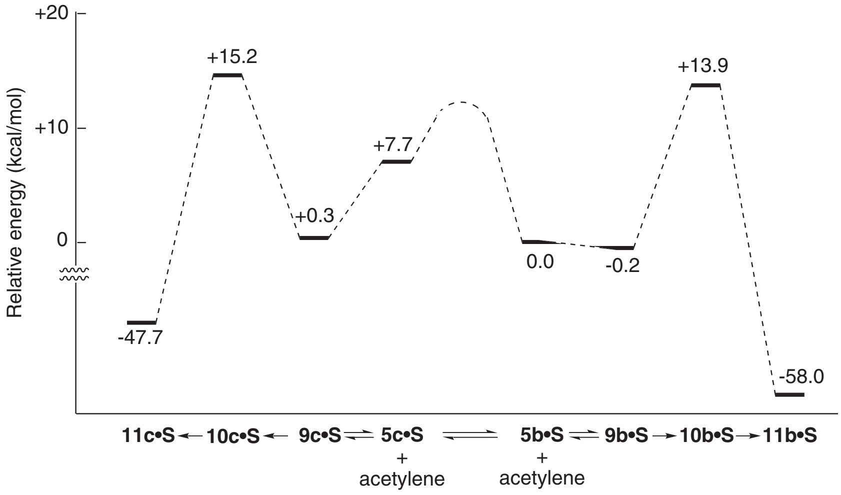


Fig. 12. Energetics of the addition of $Me_2CuLi{\cdot}LiCN$ (**5b**) and $Me(CN)Cu{\cdot}LiMe$ (**5c**) to acetylene coordinated with two molecules of $Me_2O$ on lithium atoms (B3LYP/631AS).

ation with acetylene, whereas the cyano-Gilman complex **5b·S** does not. As the result, the energies of the two TSs **10b·S** and **10c·S** become very close to each other. Assuming again the Curtin–Hammett conditions, **5c·S** should be as reactive as **5b·S**.

The geometrical flexibility of the cyanide coordination to metal atoms also accounts for the large stabilization of the mixed cuprate **5c·S** upon the acetylene complexation. The $\pi$-complexation of the Gilman-type cuprate **5b·S** with acetylene is not an energetically favorable process, because two factors compete with each other: $\pi$-Complexation of a cuprate deforms the linear C–Cu–C structure into a bent form (so that the $3d_{xz}$ orbital can mix with the filled orbital of the alkyl ligands), and the energy loss by this deformation nearly cancels the energy gain due to the metal/acetylene orbital interactions.[5a,48] Upon formation of the complex **9c·S** and the TS **10c·S** from **5c·S**, on the other hand, bending of the C–Cu–C moiety causes significant structural reorganization. Here the cyanide group becomes coordinated not only to the Cu and $Li^2$ atoms but also to the $Li^1$ atom to provide extra stabilization (Fig. 13).

This unique coordination ability characteristic of the cyano group is seen also in the chemistry of the "lower-order" cyanocuprate MeCu(CN)Li (Fig. 14).[6,49] Thus, being coordinated both to the copper(III) and to the lithium atoms, the cyano group remains on the copper atom ("dummy ligand") leaving the methyl group to be transferred preferentially to acrolein in the reductive elimination process.

Taking some pre-equilibria into account, we suggest that the addition reaction of the Lipshutz reagent can take place through either of the two pathways shown in Scheme 7 (note that deprotonation is faster than the carbocupration in the actual reaction (Eq. 5)).[12] The cuprate bending being an essential character of any $\pi$-complex formation in cuprate chemistry,[10] we consider that the above discussion holds also for the conjugate addition. The relative importance of the two reactive species would depend on the substrate and the reaction conditions.

If one accepts the suggestion that the minor species **5c** plays a role in the major pathway, it becomes trivial to understand the

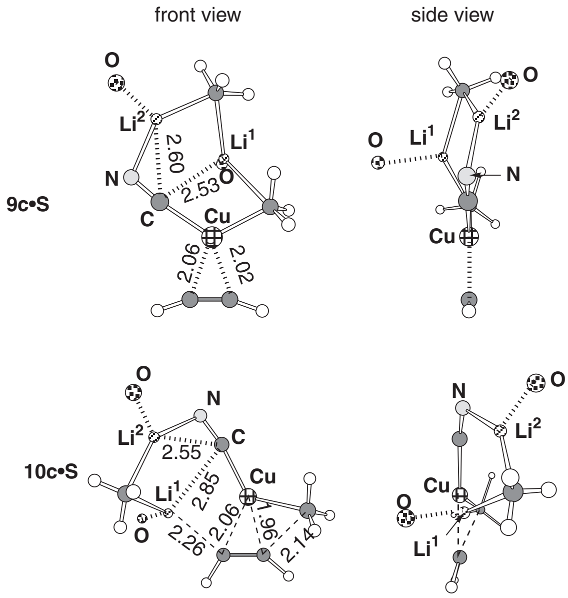


Fig. 13. 3-D structures of the $\pi$-complex **9c·S** and the carbocupration TS **10c·S**. Methyl groups of $Me_2O$ molecules are omitted for clarity.

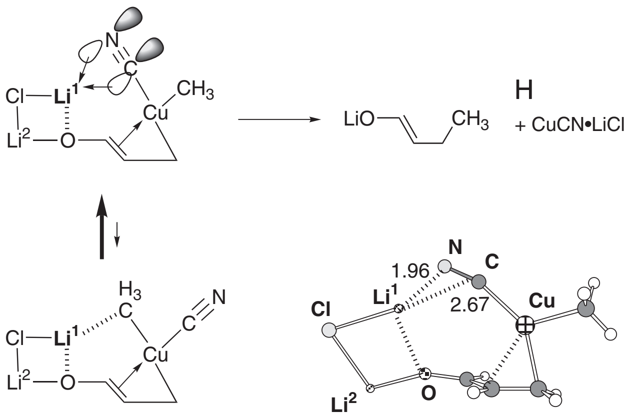
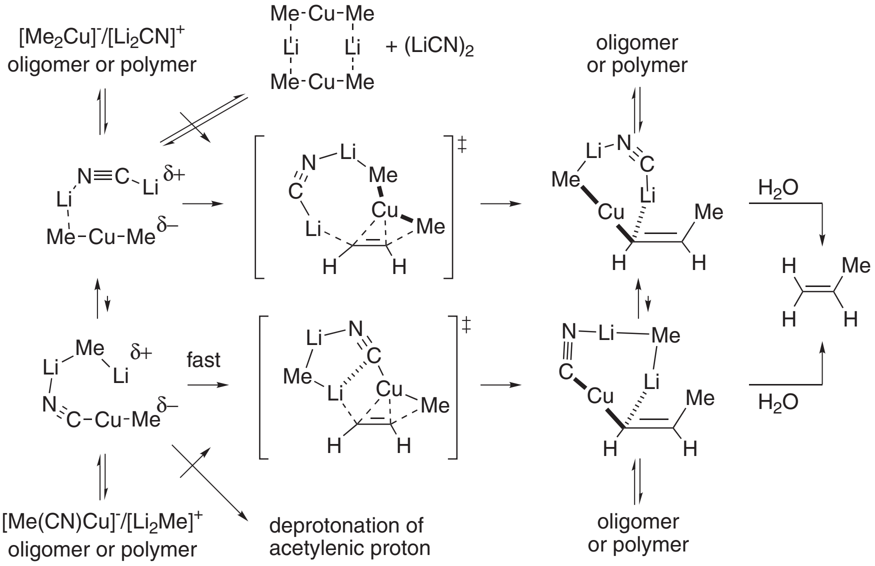
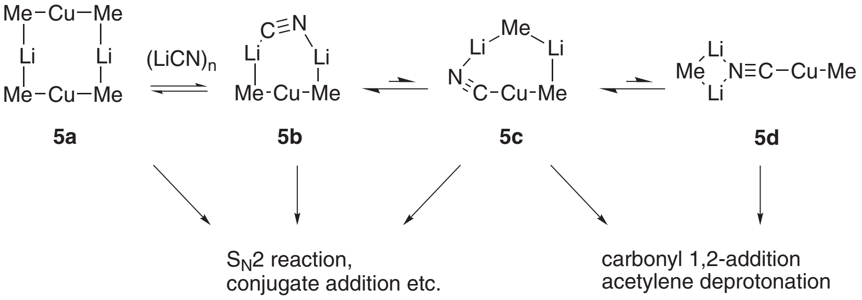


Fig. 14.

experimental facts that suggest the presence of an alkyllithium in the Lipshutz cuprate (e.g., positive Gilman test).[22] A series of equilibria that lead to the side reactions are illustrated in Scheme 8. Since the carbonyl addition of an alkyllithium may take place via a cluster species, the species responsible for the Gilman test may be either **5c** or **5d** (cf. Figs. 5c and d). The complex **5d** is similar to a methyllithium dimer that rap-



Scheme 7. Reaction pathways of the addition of the Lipshutz cuprate to acetylene.



Scheme 8. Alkylcuprate(I)-like and alkyllithium-like reaction pathways of the Lipshutz reagent (solvent molecules on the lithium atoms are omitted).

idly undergoes addition to a carbonyl compound through a six-centered mechanism.[4] It may be necessary to comment in this context that the current level of theoretical calculations does not permit comprehensive comparison of all reactive intermediates (**5a**, **b**, **c**, etc.) for every reaction, and hence that there still remains a plenty of space for speculations.

Even with all the analyses of the structures and the nucleophilic reactivities of the Lipshutz cuprate, we have no clue yet to understand the special reactivity of the Lipshutz cuprate in the oxidative coupling reaction (Eq. 7). Apparently, there are still many problems to be examined in the Lipshutz chemistry or in the chemistry of copper itself.

In summary, the nucleophilic chemistry of the Lipshutz and the Gilman cuprates share the same essentials of the mechanisms in that the reaction involves a two-electron nucleophilic attack of the copper atom to an electrophilic substrate activated by one or more Lewis acidic lithium metal(s).[10] The complexity of the Lipshutz cuprate, however, stems from the fact that the cyanide anion may sometimes be coordinated to copper. The "higher-order cuprate" controversy resulted from the two factors involved in the system: The Lipshutz mixture contains one equivalent more of an anion than what the copper(I) can hold, and the cyanide anion possesses much wider possibility of metal coordination than an alkyl or a halide anion. The latter makes the minor intermediates in solution more reactive than the major one. The analysis described above provides an interesting study of a case in which thermodynamically unstable compound (and hence undetectable by experiments) acts as a kinetically active species. This is the case where experimental studies fail to give reasonable answers, and need support from the theoretical and computational studies.

## Epilogue

Implementing any program into a metal catalyst so that it acts exactly as a chemist hopes for is a difficult task. Here one finds a number of issues to be examined: (1) flexibility of metal/ligand coordination, (2) complex potential surface of the reaction of metal-containing aggregates, (3) fluxional behavior of solvent, and (4) d-orbitals that contribute to the high polarizability of the catalyst/substrate complex. Even with so much knowledge on organometallic chemistry, it is difficult for bench chemists to control these multi-dimensional problems in catalysis only by design. Theory and computations are useful to analyze these issues but not (yet) sufficient to design the whole catalytic system. Theory and computations however suggest a number of possibilities that are not available by experiments. Bench chemists with intuition and creativity cultivated through theoretical analysis can therefore enjoy their work more than those who only do experiments.[50]

The present research was supported by a Grant-in-Aid for Scientific Research (Specially Promoted Research) and The 21st Century COE Programs in Fundamental Chemistry. Generous allotment of computational time from Research Center for Computational Science, Okazaki National Institutes and Intelligent Modeling Laboratory, The University of Tokyo, is gratefully acknowledged. N. Y. thanks JSPS for a predoctoral fellowship.

## References

1 E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, **106**, 3368 (1984); E. Nakamura, *Synlett*, **1991**, 539; E. Nakamura, "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press (1994), Chapter 6.

2 M. Sawamura, H. Iikura, and E. Nakamura, *J. Am. Chem. Soc.*, **118**, 12850 (1996); E. Nakamura and M. Sawamura, *Pure Appl. Chem.*, **73**, 355 (2001); E. Nakamura, *Pure Appl. Chem.*, **75**, 427 (2003); M. Sawamura, N. Nagahama, M. Toganoh, U. E. Hackler, H. Isobe, E. Nakamura, S.-Q. Zhou, and B. Chu, *Chem. Lett.*, **2000**, 1098; S. Zhou, C. Burger, B. Chu, M. Sawamura, N. Nagahama, M. Toganoh, U. E. Hackler, H. Isobe, and E. Nakamura, *Science*, **291**, 1944 (2001); M. Sawamura, K. Kawai, Y. Matsuo, K. Kanie, T. Kato, and E. Nakamura, *Nature*, **419**, 702 (2002).

3 E. Nakamura, Y. Miyachi, N. Koga, and K. Morokuma, *J. Am. Chem. Soc.*, **114**, 6686 (1992); E. Nakamura, M. Nakamura, Y. Miyachi, N. Koga, and K. Morokuma, *J. Am. Chem. Soc.*, **115**, 99 (1993).

4 M. Nakamura, E. Nakamura, N. Koga, and K. Morokuma, *J. Am. Chem. Soc.*, **115**, 11016 (1993); M. Nakamura, E. Nakamura, N. Koga, and K. Morokuma, *J. Chem. Soc., Faraday Trans.*, **29**, 1789 (1994).

5 a) E. Nakamura, S. Mori, M. Nakamura, and K. Morokuma, *J. Am. Chem. Soc.*, **119**, 4887 (1997). b) E. Nakamura, S. Mori, and K. Morokuma, *J. Am. Chem. Soc.*, **119**, 4900 (1997).

6 E. Nakamura and M. Yamanaka, *J. Am. Chem. Soc.*, **121**, 8941 (1999).

7 E. Nakamura, M. Yamanaka, and S. Mori, *J. Am. Chem. Soc.*, **122**, 1826 (2000).

8 E. Nakamura, M. Yamanaka, N. Yoshikai, and S. Mori, *Angew. Chem., Int. Ed.*, **40**, 1935 (2001).

9 M. Yamanaka, S. Mori, and E. Nakamura, *Bull. Chem. Soc. Jpn.*, **75**, 1815 (2002).

10 E. Nakamura and S. Mori, *Angew. Chem., Int. Ed.*, **39**, 3750 (2000).

11 "Modern Organocopper Chemistry," ed by N. Krause, Wiley-VCH, Weinheim (2002); B. H. Lipshutz and S. Sengupta, *Org. React.*, **41**, 135 (1992); S. Woodward, *Chem. Soc. Rev.*, **29**, 393 (2000).

12 B. H. Lipshutz, R. S. Wilhelm, and J. A. Kozlowski, *Tetrahedron*, **49**, 3943 (1984); B. H. Lipshutz, *Synthesis*, **1987**, 325; B. H. Lipshutz, *Synlett*, **1990**, 119; B. H. Lipshutz, "Organometallics in Synthesis," 2nd edition, ed by M. Schlosser, Wiley, Chichester (2002), pp. 665–815.

13 N. Krause, *Angew. Chem., Int. Ed.*, **38**, 79 (1999).

14 B. H. Lipshutz, R. S. Wilhelm, and D. M. Floyd, *J. Am. Chem. Soc.*, **103**, 7672 (1981).

15 G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Am. Chem. Soc.*, **91**, 4871 (1969).

16 Radical mechanism has been considered to be plausible for the reaction of secondary alkyl iodide: B. H. Lipshutz and R. S. Wilhelm, *J. Am. Chem. Soc.*, **104**, 4696 (1982); B. H. Lipshutz, R. S. Wilhelm, J. A. Kozlowski, and D. Parker, *J. Org. Chem.*, **49**, 3928 (1984); S. H. Bertz, G. Dabbagh, and A. M. Mujsce, *J. Am. Chem. Soc.*, **113**, 631 (1991).

17 B. H. Lipshutz, J. Kozlowski, and R. S. Wilhelm, *J. Am. Chem. Soc.*, **104**, 2305 (1982).

18 R. W. Herr, D. M. Wieland, and C. R. Johnson, *J. Am. Chem. Soc.*, **110**, 366 (1988).

19 For a discrete higher order cuprate $Ph_3CuLi_2$, see: S. H.

Bertz and G. Dabbagh, *J. Am. Chem. Soc.*, **110**, 366 (1988); M. M. Olmstead and P. P. Power, *J. Am. Chem. Soc.*, **111**, 4135 (1989).

20 Only a silyl Lipshutz cuprate undergoes addition to terminal alkynes: I. Fleming and F. Roessler, *J. Chem. Soc., Chem. Commun.*, **1980**, 276.

21 H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

22 A. Alexakis, unpublished results cited in Ref. 8.

23 B. H. Lipshutz, J. A. Kozlowski, and C. M. Breneman, *J. Am. Chem. Soc.*, **107**, 3197 (1985).

24 B. H. Lipshutz, K. Siegmann, E. Garcia, and F. Kayser, *J. Am. Chem. Soc.*, **115**, 9276 (1993).

25 S. H. Bertz, G. Miao, and M. Eriksson, *Chem. Commun.*, **1996**, 815; S. H. Bertz, M. Eriksson, G. Miao, and J. P. Snyder, *J. Am. Chem. Soc.*, **118**, 10906 (1996); S. H. Bertz, A. Chopra, M. Eriksson, C. A. Ogle, and P. Seagle, *Chem.—Eur. J.*, **5**, 2680 (1999).

26 G. Hareau-Vittini, S. Hikichi, and F. Sato, *Angew. Chem., Int. Ed.*, **37**, 2099 (1998); G. P.-J. Hareau, M. Koiwa, S. Hikichi, and F. Sato, *J. Am. Chem. Soc.*, **121**, 3640 (1999).

27 Note that the authors propose a "higher-order" structure as the intermediate in the Lipshutz cuprate reaction.

28 S. H. Bertz, *J. Am. Chem. Soc.*, **112**, 4031 (1990); B. H. Lipshutz, S. Sharma, and E. L. Ellsworth, *J. Am. Chem. Soc.*, **112**, 4032 (1990); S. H. Bertz, *J. Am. Chem. Soc.*, **113**, 5470 (1991).

29 NMR study of stannylvinyl cyanocuprate ($^2J_{\mathrm{C–CN}}$ coupling) supported the possibility of a higher-order structure, although it is not conclusive: J. A. Cabezas and A. C. Oehlschlager, *J. Am. Chem. Soc.*, **119**, 3878 (1997).

30 $\pi$-Complex between a cuprate and an $\alpha,\beta$-unsaturated carbonyl compound has been studied by several groups. However, most of them focused on the copper/C–C double bond interaction and did not elucidate the aggregation state of the cuprate moiety. For example, see: N. Krause, R. Wagner, and A. Gerold, *J. Am. Chem. Soc.*, **116**, 381 (1994); S. H. Bertz, C. M. Carlin, D. A. Deadwyler, M. D. Murphy, C. A. Ogle, and P. H. Seagle, *J. Am. Chem. Soc.*, **124**, 13650 (2002).

31 a) R. M. Gschwind, P. R. Rajamohanan, M. John, and G. Boche, *Organometallics*, **19**, 2868 (2000). b) M. John, C. Auel, C. Behrens, M. Marsch, K. Harms, F. Bosold, R. M. Gschwind, P. R. Rajamohanan, and G. Boche, *Chem.—Eur. J.*, **6**, 3060 (2000).

32 For a cuprate structure with higher aggregation number, see: X. L. Xie, C. Auel, W. Henze, and R. M. Gschwind, *J. Am. Chem. Soc.*, **125**, 1595 (2003).

33 S. H. Bertz, A. S. Vellekoop, R. A. J. Smith, and J. P. Snyder, *Organometallics*, **14**, 1213 (1995).

34 C. M. P. Kronenburg, J. T. B. H. Jastrzebski, J. Boersma, M. Lutz, A. L. Spek, and G. van Koten, *J. Am. Chem. Soc.*, **124**, 11675 (2002).

35 a) T. Stemmler, J. E. Penner-Hahn, and P. Knochel, *J. Am. Chem. Soc.*, **115**, 348 (1993). b) T. M. Barnhart, H. Huang, and J. E. Penner-Hahn, *J. Org. Chem.*, **60**, 4310 (1995). c) T. L. Stemmler, T. M. Barnhart, J. E. Penner-Hahn, C. E. Tucker, P. Knochel, M. Böhme, and G. Frenking, *J. Am. Chem. Soc.*, **117**, 12489 (1995). d) H. Huang, C. H. Liang, and J. E. Penner-Hahn, *Angew. Chem., Int. Ed.*, **37**, 1564 (1998).

36 A. Gerold, J. T. B. H. Jastrzebski, C. M. P. Kronenburg, N. Krause, and G. van Koten, *Angew. Chem., Int. Ed.*, **36**, 755 (1997).

37 J. P. Snyder, D. P. Spangler, J. R. Behling, and B. E. Rossiter, *J. Org. Chem.*, **59**, 2665 (1994); J. P. Snyder and S. H. Bertz, *J. Org. Chem.*, **60**, 4312 (1995); H. Huang, K. Alvarez, Q. Cui, T. M. Barnhart, J. P. Snyder, and J. E. Penner-Hahn, *J. Am. Chem. Soc.*, **118**, 8808 (1996).

38 S. H. Bertz, K. Nilsson, Ö. Davidsson, and J. P. Snyder, *Angew. Chem., Int. Ed.*, **37**, 314 (1998).

39 T. A. Mobley, F. Müller, and S. Berger, *J. Am. Chem. Soc.*, **120**, 1333 (1998).

40 C. M. P. Kronenburg, J. T. B. H. Jastrzebski, A. L. Spek, and G. van Koten, *J. Am. Chem. Soc.*, **120**, 9688 (1998).

41 G. Boche, F. Bosold, M. Marsch, and K. Harms, *Angew. Chem., Int. Ed.*, **37**, 1684 (1998).

42 C. S. Huang and P. P. Power, *J. Am. Chem. Soc.*, **120**, 6409 (1998).

43 R. M. Gschwind, X. Xie, P. R. Rajamohanan, C. Auel, and G. Boche, *J. Am. Chem. Soc.*, **123**, 7299 (2001).

44 C. Ouannes, G. Dressaire, and Y. Langlois, *Tetrahedron Lett.*, **18**, 815 (1977).

45 a) E. Nakamura, S. Mori, and K. Morokuma, *J. Am. Chem. Soc.*, **120**, 8273 (1998). b) S. Mori, E. Nakamura, and K. Morokuma, *J. Am. Chem. Soc.*, **122**, 7294 (2000).

46 a) S. Mori and E. Nakamura, *Chem.—Eur. J.*, **5**, 1534 (1999). b) M. Yamanaka and E. Nakamura, *Organometallics*, **20**, 5675 (2001).

47 Cuprate structures other than **5a**–**5c** have been also examined to find that it did not change the conclusion presented here. See Refs. 8 and 9 for details.

48 S. Mori and E. Nakamura, *Tetrahedron Lett.*, **40**, 5319 (1999).

49 J. P. Gorlier, L. Hamon, J. Levisalles, and J. Wagnon, *J. Chem. Soc., Chem. Commun.*, **1973**, 88.

50 For computational studies on reaction pathways of organometallic (other than copper) aggregate/cluster, see: A. Hirai, M. Nakamura, and E. Nakamura, *J. Am. Chem. Soc.*, **121**, 8941 (1999); M. Yamanaka and E. Nakamura, *J. Am. Chem. Soc.*, **123**, 1703 (2001); E. Nakamura, N. Yoshikai, and M. Yamanaka, *J. Am. Chem. Soc.*, **124**, 7181 (2002); M. Nakamura, A. Hirai, and E. Nakamura, *J. Am. Chem. Soc.*, **125**, 2341 (2003).

Eiichi Nakamura received degrees in chemistry from Tokyo Institute of Technology (B.S. with Prof. T. Mukaiyama and Ph.D. with Prof. I. Kuwajima). After postdoctoral work with Prof. G. Stork at Columbia University, he came back to his Alma Mater and was promoted to the rank of professor. In 1995, he moved to the University of Tokyo. He also holds a position of Senior Research Fellow at the Japan Society for Promotion of Science (JSPS). He has been honored with The Chemical Society of Japan Award for Young Chemists (1984), The Japan IBM Prize (1993), Elected Fellow of the American Association for the Advancement of Science (1998), The Nagoya Medal of Organic Chemistry (2001), and The Chemical Society of Japan Award (2003). He is currently serving as an Associate Editor of *Organic Letters*. His research field includes synthetic, organometallic, bioorganic, and computational/theoretical chemistry, all of which focus on reactive intermediates.

Naohiko Yoshikai received M.S. degree in chemistry from the University of Tokyo in 2002, and currently pursuing his Ph.D. studies under the guidance of Professor E. Nakamura. He has been a JSPS predoctoral fellow since 2002.