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Article

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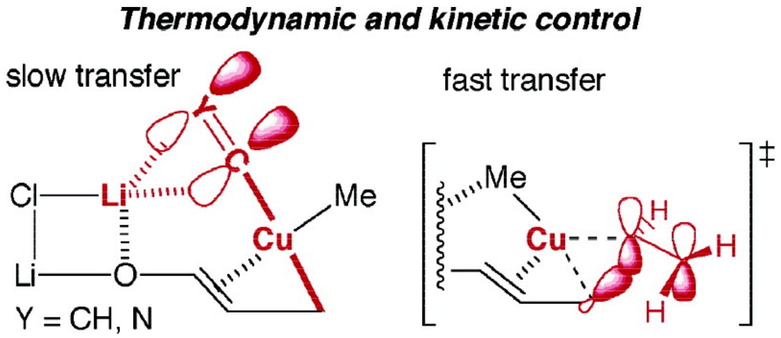

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Thermodynamic and Kinetic Control in Selective Ligand Transfer in Conjugate Addition of Mixed Organocuprate Me(X)CuLi

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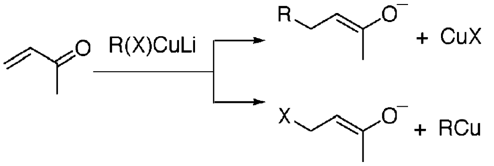
Abstract: Since the proposal of the dummy ligand concept by Corey, it has been widely accepted that the ligand transfer selectivity of a mixed organocuprate (Me(X)CuLi) depends on the Cu−X bond strength. The present B3LYP density functional studies on the $Me_2(X)Cu(III)\cdot OMe_2$, π-allyl Cu(III), and Me(X)-Cu(III)LiCl·LiCl reacting with acrolein showed that the ligand transfer selectivity of the conjugate addition depends on two factors, thermodynamic stability (X = *tert*-butyl, ethynyl, cyano, and thiomethyl groups) and kinetic reactivity ((trimethylsilyl)methyl and vinyl groups) of the Cu(III) intermediate formed by complexation of the cuprate and the α,β-unsaturated carbonyl compound. For the typical dummy ligands (X = alkynyl, cyano, and heteroatom ligands), the trans effect and the strong Li−X affinity are the reasons why these ligands stay on the copper atom. In contrast, for the (trimethylsilyl)methyl and vinyl groups, the selectivity depends on the kinetics of reductive elimination of the Cu(III) intermediate. The (trimethylsilyl)methyl transfer is retarded by repulsive four-electron interaction between the lone pair Cu $3d_{xy}$ orbital and the C−Si σ-orbital.

Organocopper(I) reagents are used extensively in organic synthesis for C−C bond formation.[1] The simplest organocopper intermediate RCu is not reactive enough to be synthetically useful, and a more reactive organocopper reagent of a R_2CuLi stoichiometry (e.g., lithium organocuprate) was introduced to the synthetic community in the 1960s. While such a homocuprate R_2CuLi is a useful reagent for nucleophilic delivery of hard anionic nucleophiles, it can transfer only one of the two R ligands to the target electrophile and the other one is lost as an unreactive RCu species. To solve this problem of reagent economy, the concept of a "dummy ligand" by the use of a mixed organocuprate (e.g., R(X)CuLi[2] bearing an alkynyl X group) was introduced by Corey[2a] in 1972 (eq 1). In the mid 1970s, Whitesides,[2c] House,[2d] and Posner[2e] studied in detail the intramolecular ligand transfer selectivity of the mixed organocuprates bearing sp-, sp^2-, sp^3-carbon, and heteroatom ligands. The relative ease of the transfer lies in the order n-Bu ≈ *sec*-Bu > *t*-Bu ≫ Ph > alkynyl[2c] and vinyl > Me ≫ alkynyl.[2d,e]



(eq. 1)

The Corey hypothesis about the dummy ligand design subsequently generated many ideas on the design of nontransferable dummy ligands. During the past decades, mixed organocuprates bearing alkynyl,[2b,c] cyano,[2f,g] phenylthio,[2h] dialkylamino,[2i] and phosphino[2i] have secured their status in organic synthesis. A relatively new ligand introduced by Bertz[2j] is a silylmethyl group (e.g., X = CH_2SiMe_3). He proposed that the silyl group stabilizes the positive charge on the copper atom through "β-cation stabilization", which stays on copper, and also accelerates the transfer of the other ligand on the copper atom. With all these experiments and hypotheses, however, no systematic mechanistic studies have been carried out to probe the origin of ligand transfer selectivity. We have examined in details this issue for a conjugate addition reaction and report herein the full details of the result.[3]

Chemical Models and Computational Methods. Recent experimental[4] and theoretical studies[5] on the conjugate addition of a lithium cuprate to an α,β-unsaturated carbonyl compound

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(1) (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631. (b) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186−204 (c) Nakamura, E.; Mori, S. *Angew. Chem., Int. Engl.* **2000**, *39*, 3751−3771.

(2) (a) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210−7211. (b) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893−3901. (c) Mandeville, W. H.; Whitesides, G. M. *J. Org. Chem.* **1974**, *39*, 400−405. (d) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460−1469. (e) Posner, G. H.; Whitten, C. E.; Sterling, J. J.; Brunelle, D. J. *Tetrahedron Lett.* **1974**, *30*, 2591−2594. (f) Gorlier, J. P.; Hamon, L.; Levisalles, J.; Wagnon, J. *J. Chem. Soc., Chem. Commun.* **1973**, 88. (g) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron.* **1984**, *40*, 5005−5038. (h) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *Am. Chem. Soc.* **1973**, *95*, 7788−7797. (i) Bertz, S. H.; Dabbagh, G.; Villacorta, G. M. *J. Am. Chem. Soc.* **1982**, *104*, 5824−5826. (j) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, P. S. *J. Am. Chem. Soc.* **1996**, *118*, 10906−10907.

(3) Communication: Nakamura, E.; Yamanaka, M. *J. Am. Chem. Soc.* **1999**, *121*, 8941−8942.

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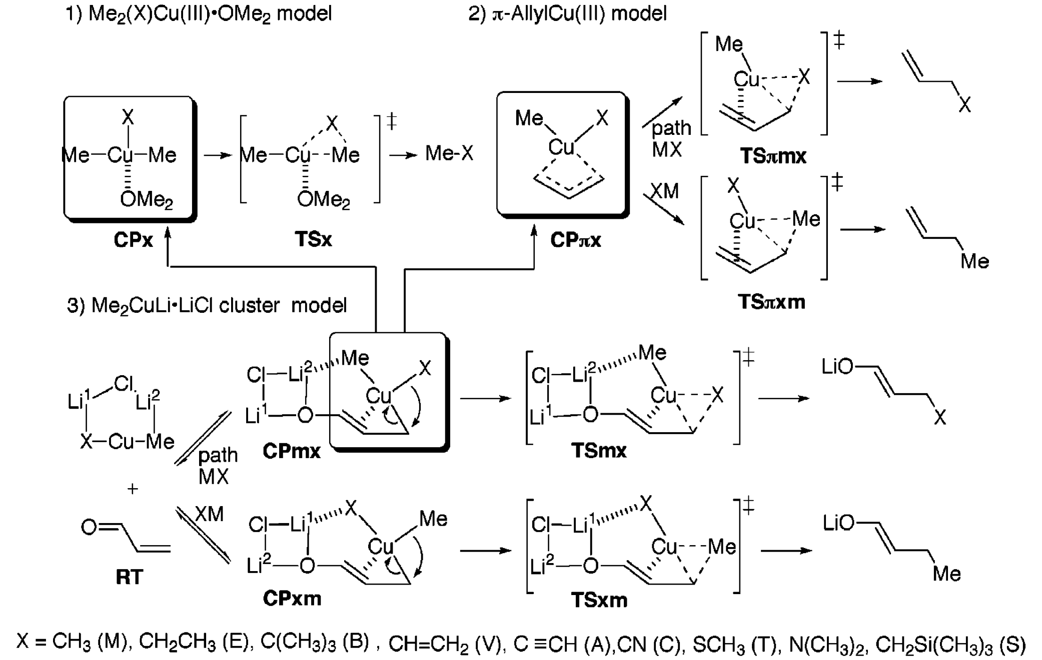
Scheme 1. Three Different Probes (1−3) for the Studies on the Origin of the Ligand Transfer Selectivity



indicated that a tetracoordinated Cu(III) complex is a direct precursor of the product and the rate-determining step is its reductive elimination. Therefore, the selectivity of the ligand transfer from Me(X)CuLi must be determined during the reductive elimination of the Cu(III) complex, which bears four ligands on the Cu(III) atom of formal one negative charge (Me, X, the β-carbon atom of the substrate, and a carbon atom α to the carbonyl group).

The study was carried out in three stages (Scheme 1). To study the activation energy of the reductive elimination in a simple model Cu(III) complex, $Me_2(X)Cu(III){\cdot}OMe_2$[6] was first examined (Scheme 1(1); **CPx**). Next, we examined a π-allyl Cu(III) model **CPπx** (Scheme 1(2)) which is the minimum model to describe the π-allylic nature of the most realistic model. Then, two isomeric transition states (**TSπxm**, Me transfer; **TSπmx**, X transfer) of the reductive elimination were compared.

Finally, we studied the most realistic chemical model (**CPxm**, **mx**) and the transition structures (**TSxm, mx**) for the two isomeric pathways (Scheme 1(3); XM, X bridges Li^1 and Cu,[7] and Me as nucleophile; MX, vice versa) of the reaction of Me(X)CuLi·LiCl with acrolein to probe the ligand transfer selectivity. Thus, we investigated the transfer selectivity in three stages, (1) $Me_2(X)Cu(III){\cdot}OMe_2$ model, (2) π-allyl Cu(III) model, and (3) Me(X)CuLi·LiCl model. Ethynyl (A), CN (C), vinyl (V), CH_2SiMe_3 (S), ethyl (E), *tert*-butyl (B), NMe_2 (N), and SMe_3 (T) groups were studied as models of the ligand used in experiments and were compared with the reference X = Me (M).

All calculations were performed with GAUSSIAN 94[8] and 98[9] program packages. The density functional theoretical (DFT) method was employed using the B3LYP hybrid functional.[10] All geometries were optimized with the basis sets denoted as B3LYP/631AS and B3LYP/321AS, which consisted of the Ahlrichs all-electron SVP basis sets[11] for Cu and of 6-31G-(d)[12] and 3-21G[12] for the rest, respectively. One imaginary frequency for all transition structures and none for stable structures were confirmed by normal coordinate analysis.

Solvent effects were studied about the effect of the bulk polarity (a continuum model), and the effect of explicit solvent molecules (i.e., Me_2O) coordinated to the lithium atoms (a descrete particle model) in the Me(X)Cu(III)LiCl·LiCl model so that all metal atoms become coordinatively saturated in the reaction course. In the continuum model, the single-point energy calculations with the self-consistent reaction field (SCRF) method based on the polarizable conductor calculation model (CPCM,[13] $\epsilon = 4.335$ for Et_2O) were carried out at the B3LYP/

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(4) Frantz, D. E. Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383−3384.

(5) (a) Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4900−4910. (b) Mori, S.; Nakamura, E. *Chem. Eur. J.* **1999**, *5*, 1534−1543. (c) Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2001**, *26*, 5675−5681.

(6) (a) Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11025−11026. (b) Dorigo, A. E.; Wanner, J.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 476−478.

(7) The bridging moiety consists of the X−Cu (Me−Cu) covalent bond and the X−Li (Me−Li) electrostatic interaction. Solvent coordination on Li atoms much weakens the X−Li (Me−Li) interaction.

(8) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision E.2; Gaussian, Inc., Pittsburgh, PA, 1995.

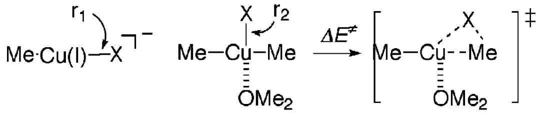
(9) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.6; Gaussian Inc.: Pittsburgh, PA, 1998.

(10) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Solid State* **1988**, *37*, 785−789.

(11) Schäfer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, 97, 2571−2577.

(12) Hehre, W. J.; Radom, L.; von Ragué Schleyer, P.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley: New York, 1986. References cited therein.

Table 1. Cu−X Bond Lengths for Cu(I) and Cu(III) Species and the Activation Energies of the Reductive Elimination of $Me_2(X)Cu(III){\cdot}OMe_2$ at the B3LYP/631AS Level



CPx **TSx**

X	r_1 (Å)	r_2 (Å)	$\Delta E^{\neq}$ (kcal/mol)
Me	1.97	1.94	8.2
C≡CH	1.90	1.83	2.9
C≡N	1.91	1.83	4.0
$CH{=}CH_2$	1.95	1.89	2.5
CH_2SiMe_3	1.99	1.95	7.7
SMe	2.25	2.18	11.5
NMe_2	1.92	1.93	10.3

631AS-optimized geometries. As will be discussed for Figures 8 and 9, the polarity effect was small enough not to affect the nature of our discussion about the "dummy ligand effect". For two cases, X = CN and vinyl, we performed the CPCM calculations under full geometry optimization. As shown in the Supporting Information, the optimized geometry of **CPxm**,**mx** and **TSxm**,**mx** changed from the gas-phase geometry only to the extent of a 0.12 Å difference as to the bond lengths (i.e., 5.5%). In addition, the energetics was found to be essentially the same. Hence we concluded that the effect of the bulk polarity is not the major factor in the dummy ligand problem.

The effect of explicit Me_2O molecules coordinated on the lithium atoms shows a more significant impact on the structures, as one would expect on the basis of the contact-ion-pair nature of the $Me(X)Cu(III)LiCl{\cdot}LiCl$.[14] Thus, when two molecules of Me_2O were allowed to coordinate on each Li atom, the basic solvent molecules cause rupture of the Li-Me or Li-X coordination (to be discussed later).[5c] Such a large geometrical effect however did not change the energetics responsible for the dummy ligand problem.

$Me_2(X)Cu(III){\bullet}OMe_2$ Model Study. We first studied reductive elimination of the Cu(III) intermediates of the simplest model intermediate,[6] $Me_2(X)Cu(III){\cdot}OMe_2$ (**CPx**) for X = Me (denoted as m), ethynyl (a), CN (c), vinyl (v), CH_2SiMe_3 (s), NMe_2 (n), and SMe (t) groups (Table 1). If the ligand transfer selectivity depends only on the nature of the Cu−X bond, this simple model will reproduce the experimental selectivity of the ligand transfer. In agreement with the original concept of the ligand design,[2a] both the Cu(I)−X and the Cu(III)−X bond lengths (r_1 and r_2) in **CPx** are shorter (and expected to be stronger) for X = ethynyl, cyano, and vinyl than for X = Me (Table 1). However, the activation energies of reductive elimination ($\Delta E^{\ddagger}$) for X = ethynyl (+2.9 kcal/mol), CN (+4.0 kcal/mol), and vinyl (+2.5 kcal/mol) are equally much lower than that for X = Me (+8.2 kcal/mol), while those for X = SMe (+11.5 kcal/mol) and NMe_2 (+10.3 kcal/mol) are higher. The activation energy for X = CH_2SiMe_3 (+7.7 kcal/mol) is comparable to that for X = Me. These results disagree entirely with the fact that the vinyl group is predominantly transferred in cuprate conjugate addition but the ethynyl, CN, CH_2SiMe_3, SMe, and NMe_2 groups are not transferred at all.

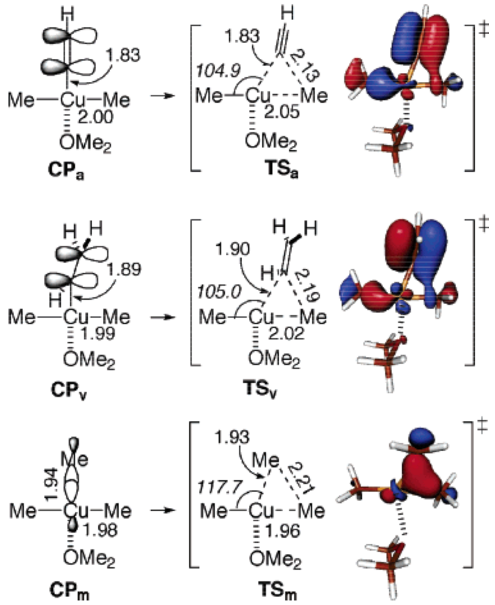


Figure 1. Geometry of **CPx** and **TSx** and Kohn−Sham orbitals of **TSx** at the B3LYP/631AS level (X = ethynyl, vinyl, and Me) in the box. Bond lengths are in Å and angles (in italic) are in degree.

To study the origin of the disagreement, the 3D structures and the orbital interactions of **TSm**, **TSv**, and **TSa** were compared. As shown in Figure 1, the C−Cu−X angles of **TSa** (X = ethynyl, 104.9°) and **TSv** (X = vinyl, 105.0°) are smaller than that of **TSm** (X = Me, 117.7°) by ca. 13°. This indicates that the deformation necessary to reach **TSa** and **TSv** is smaller than that to reach **TSm**. As shown in the Kohn−Sham orbitals of these three transition structures, the π-orbital participation was identified in both **TSa** and **TSv** in contrast to the C−Cu σ-orbital observed in **TSm** (Figure 1). The polarizable π-orbitals of ethynyl and vinyl groups can readily interact with the C−Cu σ^*-orbital with only a small geometrical change of the sp or the sp^2 atoms attached to the copper atom. Therefore, we conclude that the smaller activation energies of both **TSa** and **TSv** are due to such π-orbital participation. This π-orbital participation resembles the π-participation in the Wagner−Meerwein rearrangement. The present $Me_2(X)Cu(III){\cdot}OMe_2$ model illustrates that the vinyl group is predominantly transferred due to π-orbital participation but does not account for the very slow transfer of the ethynyl, CN, and CH_2SiMe_3 groups.

π-Allyl Cu(III) Model Study. Since the $Me_2(X)Cu(III){\cdot}OMe_2$ model failed to explain the ligand transfer selectivity observed in the experiments, we improved on the chemical model and employed the π-allyl Cu(III) model **CPπx** (Scheme 1(2)). This model takes into account the π-allyl nature of the β-cuprio(III) intermediates **CPmx** and **CPxm** in the real case but lacks the electron-donating enolate moiety.

The complex **CPπx** can undergo reductive elimination in two ways, via **TSπmx** and **TSπxm** (XM, Me becomes bonded to an allyl end; MX, X bonded to the allyl end) as shown in Scheme 1(2). These model pathways were examined for X = Me (M), ethynyl (A), CN (C), vinyl (V), CH_2SiMe_3 (S), and

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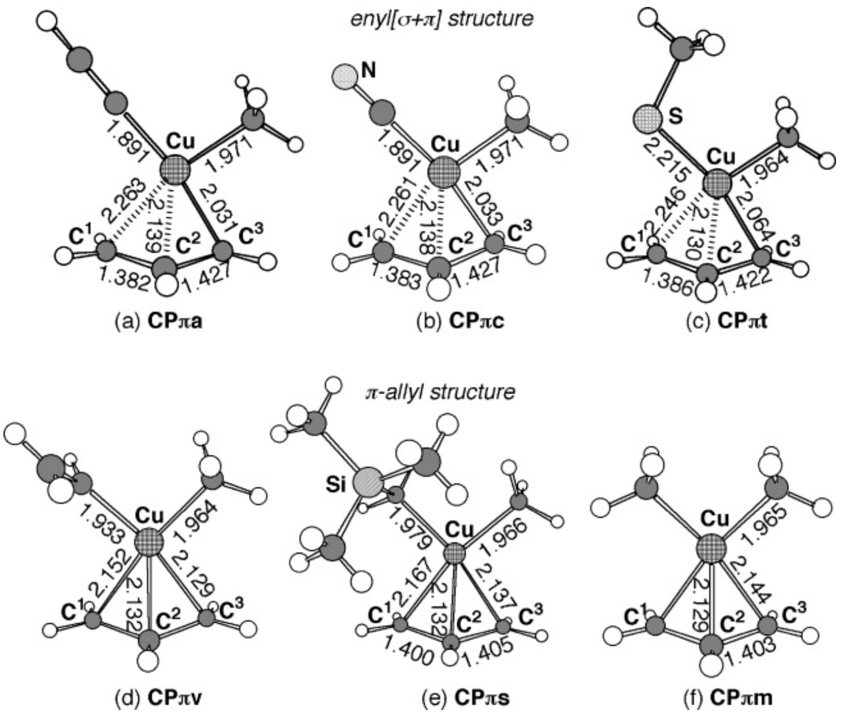
(13) (a) Barone V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995−2001. (b) M Cossi, M.; Rega, N.; Scalmani, G.; Barone. V. *J. Comput. Chem.* **2003**, *24*, 669−681.

(14) (a) John, M.; Auel, C.; Behrens, C.; Marsch, M.; Harms, K.; Bosold, F.; Gschwind, R. M.; Rajamohanan, P. R.; Boche, G. *Chem. Eur. J.* **2000**, *6*, 3060−3068. (b) Gschwind, R. M.; Rajamohanan, P. R.; John, M.; Boche, *Organometallics* **2000**, *19*, 2868−2873. (c) Gschwind, R. M.; Pattuparambil, X. X.; Rajamohanan, P. R.; Auel, C.; Boche, *J. Am. Chem. Soc.* **2001**, *123*, 7299−7304.

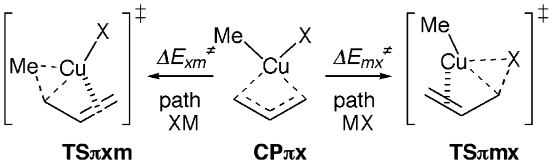


(a) **CPπa** (b) **CPπc** (c) **CPπt**

(d) **CPπv** (e) **CPπs** (f) **CPπm**

Figure 2. 3D structures of (a) **CPπa**, (b) **CPπc**, (c) **CPπt**, (d) **CPπv**, (e) **CPπs**, and (f) **CPπm** at the B3LYP/631AS level.

Table 2. Activation Energies of the Reductive Elimination of the π-allyl Cu(III) Complexes at the B3LYP/631AS Level



X	$\Delta E_{xm}^{\neq}$ (kcal/mol)	$\Delta E_{mx}^{\neq}$ (kcal/mol)
Me	14.3	14.3
C≡CH	6.7	12.0
C≡N	5.4	16.1
CH=CH$_2$	12.7	8.1
CH$_2$SiMe$_3$	13.0	15.9
SMe	8.4	14.6

SMe (T) (Table 2). The relative activation energies reproduce the experimental trend (vinyl > Me ≫ alkynyl, cyano, heteroatom, CH$_2$SiMe$_3$) better than the simpler model. The Me group in **CPπa**, **CPπc**, **CPπt**, and **CPπs** can transfer faster than the ethynyl (+12.0 kcal/mol), CN (16.1 kcal/mol), SMe (14.6 kcal/mol), and CH$_2$SiMe$_3$ (+15.9 kcal/mol) groups. The smaller activation energy for X = vinyl (+8.1 kcal/mol) than that for X = Me (+12.7 kcal/mol) agrees with the experiment.

An interesting new trend was found for the absolute magnitude of the activation barrier. The activation energies of the methyl transfer in the mixed cuprates containing an ethynyl, cyano, and MeS group (via **TSπam**, **TSπcm**, and **TSπtm**; 6.7, 5.4, and 8.4 kcal/mol, respectively) are considerably smaller than and those containing a vinyl and CH$_2$SiMe$_3$ group (via **TSπvm** and **TSπsm**; 12.7 and 13.0 kcal/mol, respectively) are comparable to that in the dimethyl homo cuprate (via **TSπmm**; 14.3 kcal/mol). Such an effect of the X group to accelerate or to decelerate the group transfer of the other group on the cuprate is interesting but has not been reported in the literature.[2c,f] We suspected that the trans effect[15] of the X group is playing a significant role in the mixed cuprate.

To determine the factors that affect the transfer selectivity, both the properties of the π-complex and those of the transition states of reduction elimination were examined carefully. First, the structures of the π-allyl Cu(III) complexes were studied in detail (Figure 2). For X = ethynyl (Figure 2a), CN (b), and SMe (c), the structure is no more C_s symmetric as in **CPπm** (f) and it is now an enyl[$\sigma + \pi$] structure (**CPπa**: Cu−C^1 = 2.263 Å, Cu−C^3 = 2.031 Å. **CPπc**: Cu−C^1 = 2.261 Å, Cu−C^3 = 2.033 Å. **CPπt**: Cu−C^1 = 2.246 Å, Cu−C^3 = 2.064 Å). On the other hand, it is still nearly C_s symmetric for X = vinyl (Figure 2d) and CH$_2$SiMe$_3$ (e) (**CPπv**: Cu−C^1 = 2.152 Å, Cu−C^3 = 2.129 Å, **CPπs**: Cu−C^1 = 2.167 Å, Cu−C^3 = 2.137 Å). It is clear that a strong σ-donor group such as ethynyl, CN, and SMe exerts a trans effect in the reductive elimination reaction.

The Boys localized orbitals (LOs) shown in Figure 3a−d provide a theoretical basis of the enyl[$\sigma + \pi$] and π-allyl structures dichotomy. The enyl[$\sigma + \pi$] nature of **CPπc** and **CPπt** is clearly identifiable in Figure 3a and b, respectively. In the top pictures of parts a and b, a π-orbital in the allyl moiety on the left-hand side is seen (donation from the allyl moiety), and in the bottom row, a σ-orbital composed of the copper 3d$_{xz}$ orbital and the 2p orbital of the right-hand carbon atom is seen (back-donation from the metal atom). It is clear that the π-allyl symmetry is broken by the strongly σ-donative “dummy ligand” on the copper atom (the σ-donor is the sp-carbon for ethynyl and cyano and the 3s,3p orbital for SMe). In contrast, the LOs of the vinyl and CH$_2$SiMe$_3$ π-allyl complexes (**CPπv** and **CPπs**) shown in the top and the bottom of Figure 3c and d are symmetrical with each other (i.e., little perturbed by the substituents).

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(15) (a) Appleton, T. G.; Clark, H. C.; Manzer, L. E. *Coord. Chem. Rev.* **1973**, *10*, 335−422. (b) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 2nd ed.; Wiley and Sons: New York, 1994.

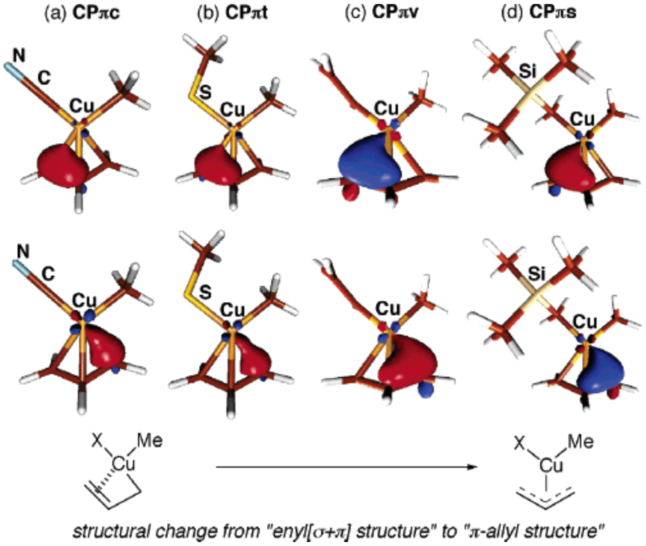

Figure 3. Two localized Kohn−Sham orbitals correspondig to donative (top) and back-donative interactions (bottom) for (a) **CPπc**, (b) **CPπt**, (c) **CPπv**, and (d) **CPπs**.

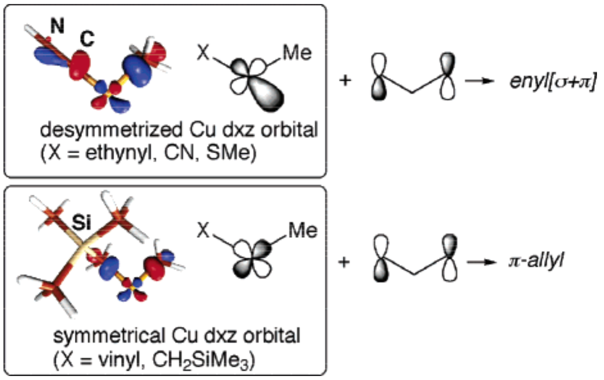

Figure 4. Out-of-phase mixing of the 3d_{xz} orbital of Me(X)Cu(III) and the X and the Me fragments [X = CN (a) and CH$_2$SiMe$_3$ (b)], which will interact with the antisymmetric π-allyl orbital to form an enyl[$\sigma + \pi$] complex for X = CN and a π-allyl complex for X = CH$_2$SiMe$_3$.

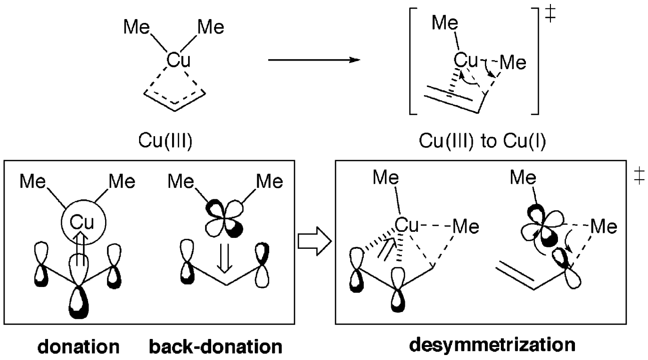

Figure 5. Desymmetrization of donative and back-donative interactions during reductive elimination

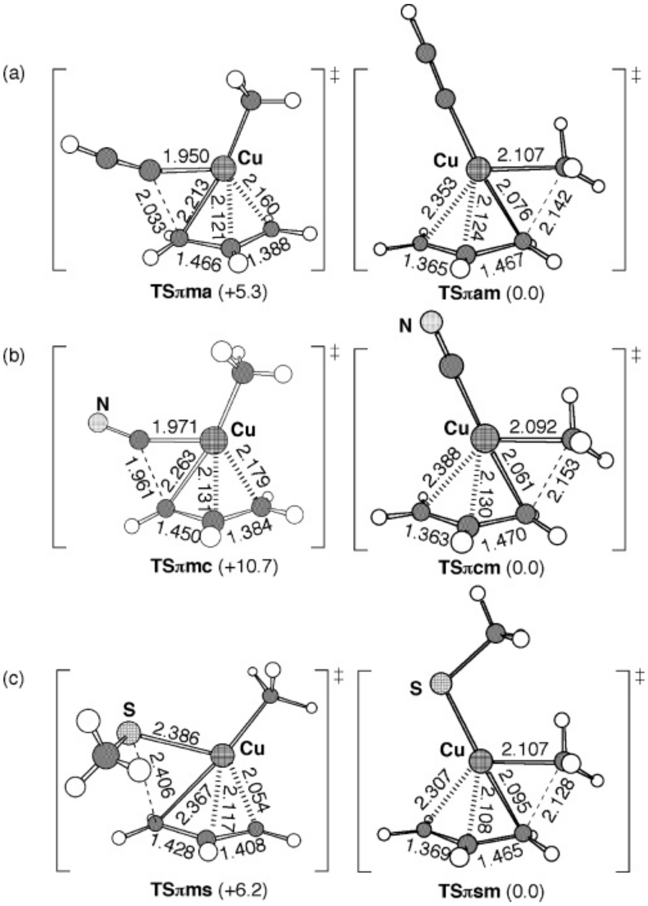

Figure 6. 3D structures of the Cu(III) complexes and the TSs for (a) X = ethynyl, (b) CN, and (c) SMe at the B3LYP/631AS level. The relative energies (kcal/mol) are in parentheses.

Orbital analysis of the MeCuX fragment obtained by dissection of the π-allyl complexes **CPπx** also supports the argument of the trans influence. As shown in Figure 4a, the 3d_{xz} orbital in the MeCu(CN) fragment extends toward the direction opposite to the CN group and will interact with the antisymmetric π-allyl orbital in a nonsymmetric way to form the enyl[$\sigma + \pi$] complex **CPπc**. In contrast, the 3d_{xz} orbital of the MeCu(CH$_2$SiMe$_3$) fragment shown in Figure 4b is symmetrical.

Finishing with the analysis of the π-complexes, we next discuss the transition states of the reductive elimination process (Figures 5 and 6). We start with the orbital interactions for X = ethynyl, CN, and SMe. As described in the preceding article,[16] the symmetrical complex **CPπm** undergoes desymmetrization of the donative and back-donative interactions upon going to the TS of the reductive elimination (e.g., **TSπmm**). Figure 5 shows schematically this process, where the Cu(III) center becomes reduced by recovering two electrons from the allylic moiety through back-donative interaction in **TSπmm**.[16] Since the π-allyl Cu(III) complexes for X = ethynyl, CN, and SMe are unsymmetrical in such a way that the resulting enyl[$\sigma + \pi$]-like structures are similar to the TS of the methyl group transfer (**TSπam**, **TSπcm**, and **TSπsm**, Figure 6), the methyl transfer is hence preferred but not the alternative path (**TSπma**, **TSπmc**, or **TSπms**).

The characters of the TSs for X = vinyl and the CH$_2$SiMe$_3$ are entirely different. The trans effect of these groups is small, and the activation energies of the Me transfer (**TSπvm**, +12.7 kcal/mol; **TSπsm**, +13.0 kcal/mol) remain similar to that of **TSπmm** (+14.3 kcal/mol). The vinyl transfer via **TSπmv** is preferred because of the π-orbital participation already discussed in Figure 1. On the other hand, the CH$_2$SiMe$_3$ transfer is retarded relative to the methyl transfer. It is because of destabilization of the four-electron interaction[17] between the occupied Cu 3d_{xy}

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(16) Yamanaka, M.; Kato, S.; Nakamura E. *J. Am. Chem. Soc.* **2004**, *126*, 6287−6293.

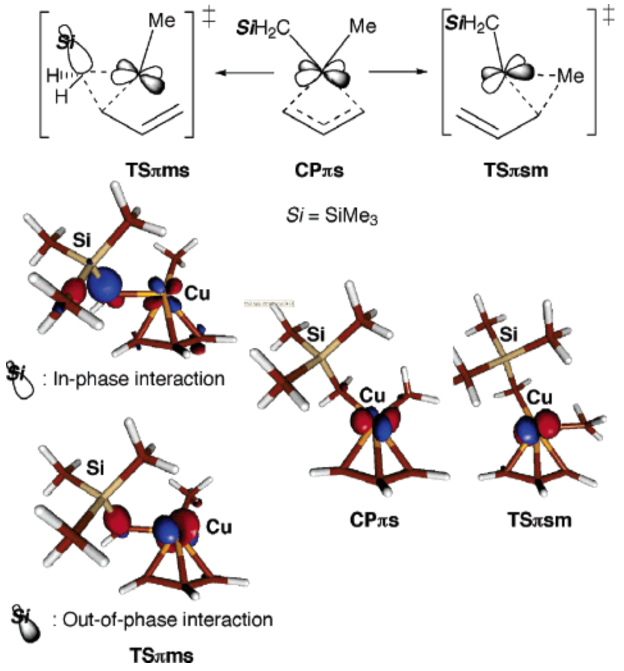
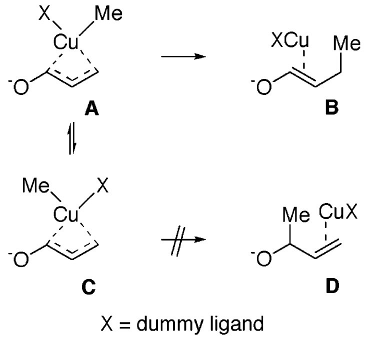


Figure 7. Kohn−Sham orbital description of the four-electron interaction between the Cu 3d$_{xy}$ orbital and C−Si σ-orbital in **TSπms**. Note that the 3d$_{xy}$, which is a lone pair in **CPπs**, mixes with the 3d$_{xz}$ in **TSπms** and, hence, raises the energy.

Scheme 2



orbital and C−Si σ-orbital in **TSπms** (Figure 7). The Kohn−Sham orbitals of the π-complex and the TS for X = CH_2SiMe_3 illustrate that this unfavorable interaction occurs only in the **TSπms** (CH_2SiMe_3 transfer) but neither in **CPπs** nor in **TSπsm** (Me transfer), where the Cu 3d$_{xy}$ orbital remains as a lone pair orbital. In summary, the selective Me transfer for X = ethynyl, CN, and SMe is due to the σ-donation effect (trans effect) of the X group, the vinyl transfer due to π-participation in the TS, and the slow transfer of the CH_2SiMe_3 group due to unfavorable C−Si/3d$_{xy}$ four-electron interaction.

Me(X)Cu(III)LiCl·LiCl Model Study. The π-allyl Cu(III) model indicated that a σ-donative X group directs the delivery of the Me group to the allylic carbon trans to the X group. Straightforward application of this argument predicts that the Cu(III) intermediate **A** in Scheme 2 should give the 1,4-adduct **B**, while the isomer **C** should produce the 1,2-adduct **D**. Obviously, this cannot be true. One must not forget that the electron-donating effect of the oxygen anion on the allylic moiety in **A** and **C** is so powerful that the **C**-to-**D** path is prohibited.[16] The effects of the X group and the oxygen anion are mismatched in **C**. Thus, the isomer **C** will dissociatively isomerize to **A**, which then will give **B**. Are there any other factors involved in the transfer selectivity? We next studied more realistic models Me(X)CuLi·LiCl.

In the Me(X)Cu(III)LiCl·LiCl model, we can address the issue of the electrostatic interaction between the X group and Li atoms in the Li−Cu cluster structure. Two isomeric pathways (path MX, XM) of the Li−Cu cluster model in Scheme 1c were studied for X = ethynyl (A), CN (C), SMe (T), Et (E), *t*-Bu (B), CH_2SiMe_3 (S), and vinyl (V). We compared the relative energies of the Cu(III) complexes (**CPxm,mx**) and the transition states (**TSxm,mx**) to the reactants for the isomeric pathways of XM and MX (Figure 8) and thus can classify the transfer selectivity into two categories; thermodynamic or kinetic control. In most of the cases, the selectivity of the ligand transfer primarily depends on the thermodynamic stability of a Cu(III) complex over the other (Figure 8b−g).[18] For instance, **CPxm** bearing the X ligand bridging Li and Cu is overwhelmingly more stable than **CPmx** (13.1−22.4 kcal/mol) for X = ethynyl, CN, and SMe. Therefore, the relatively small difference of the activation energies of the reductive elimination step (+0.7−3.3 kcal/mol) does not affect at all the ligand transfer selectivity (Figure 8b−e). Solvent coordination (two molecules of Me_2O on each of the two Li atoms, Figure 8c vs d) does not change the overwhelming thermodynamic preference of the selective Me transfer in the reaction of Me(CN)Cu(III)LiCl·LiCl. The structure of the solvated molecules will be discussed later about Figure 11. Similarly, the *t*-Bu transfer is preferred over the Me transfer, although the *t*-Bu transfer is kinetically (sterically) more difficult (+13.5 kcal/mol) than the Me transfer (+8.6 kcal/mol) (Figure 8g). The methyl and ethyl groups are very similar to each other, and therefore the Et transfer is comparable to the Me transfer (Figure 8f).

Unlike the above cases, the ligand transfer selectivity in the cases of X = CH_2SiMe_3 and vinyl is determined by the kinetic reactivity of the Cu(III) complex. The reductive elimination of the Me group is more facile (+9.5 kcal/mol) than that of the CH_2SiMe_3 group (+11.2 kcal/mol) (Figure 8h). More careful studies are necessary for X = vinyl, where the energies of the two isomeric **TSxm** and **TSmx** are very close to each other (Figure 8i; **TSmv**, −4.1 kca/mol; **TSvm**, −5.8 kcal/mol). When two molecules of Me_2O were allowed to coordinate to each Li atom, the transition state of the vinyl transfer **TSmv•S** became 1.8 kcal/mol more stable than that of the Me transfer **TSvm•S** (Figure 8j). Though probably by chance, this reproduces very well the experimental selectivity (vinyl transfer favored over methyl transfer by 29:1, namely 1.6 kcal/mol at −20 °C). The structures of the solvated molecules will be discussed later (Figure 15).

The energetics of the dummy ligand problem obtained under the above gas-phase conditions remains unchanged even when solvent polarity is considered. As is clear from comparison of the gas-phase data in Figure 8 and the data obtained by SCRF

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(17) Example for controlling of stereochemistry by destabilizing four-electron interaction; (a) Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471−477. (b) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989−7991.

(18) The energy comparison is made here for **CPxm** and **CPmx**, which are in mobile equilibrium with each other. Therefore Curtin−Hammet boundary conditions are satisfied (see ref 5b), and one needs to consider only the energies of the **TS**s for the analysis of ligand transfer selectivity. The energy of the reactants serves only as a reference zero point.

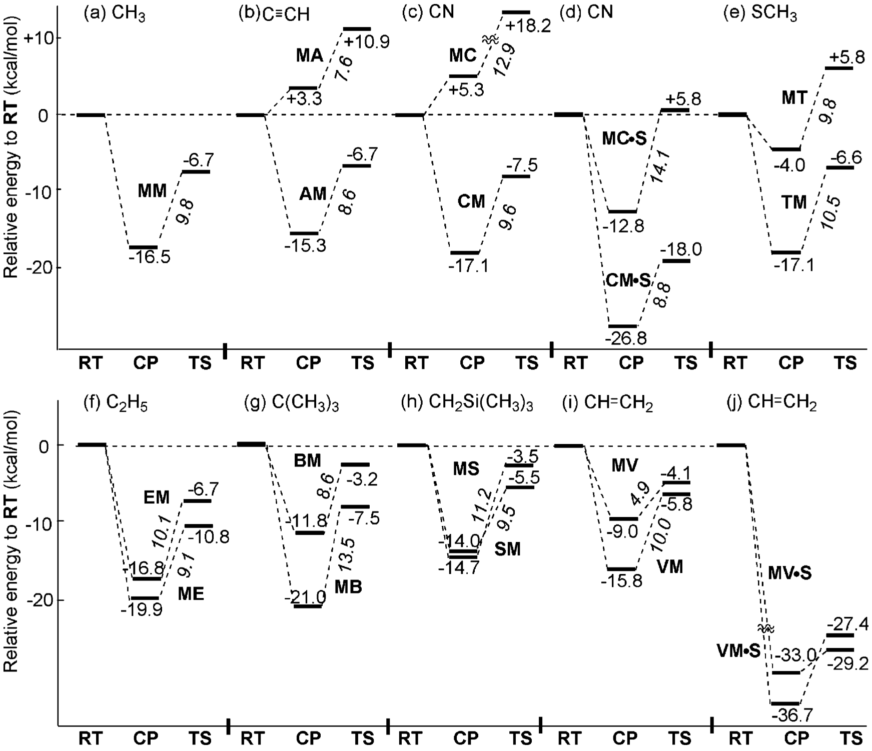

Figure 8. Energetics for two isomeric pathways controlled by (b−g) thermodynamic stability and (h−j) kinetic reactivity in the conjugate addition of Me(X)Cu(III)Li•LiCl at the B3LYP/631AS level and (a) energetics of the conjugate addition of Me_2CuLi•LiCl. Solvent coordination models in (d) X = CN and in (j) X = vinyl are at the B3LYP/321AS level. The activation energies are shown in italics.

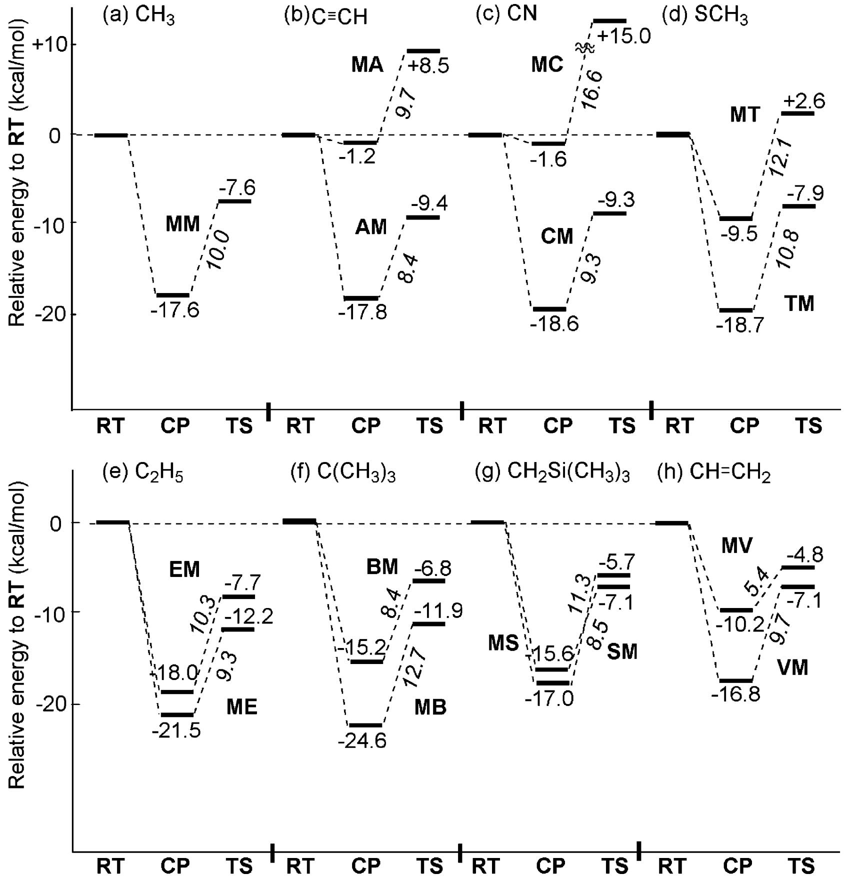

Figure 9. Single-point energy calculations with the self-consistent reaction field (SCRF) method based on the polarizable conductor calculation model (CPCM, $\epsilon = 4.335$ for Et_2O) at the B3LYP/631AS-optimized geometries. The activation energies are shown in italics.

single-point energy calculations in Figure 9, the solvent polarity does not affect the ligand transfer selectivity much, especially for the dummy ligand reactions (Figure 9a−d) where the gas-phase thermodynamic preference is overwhelming.

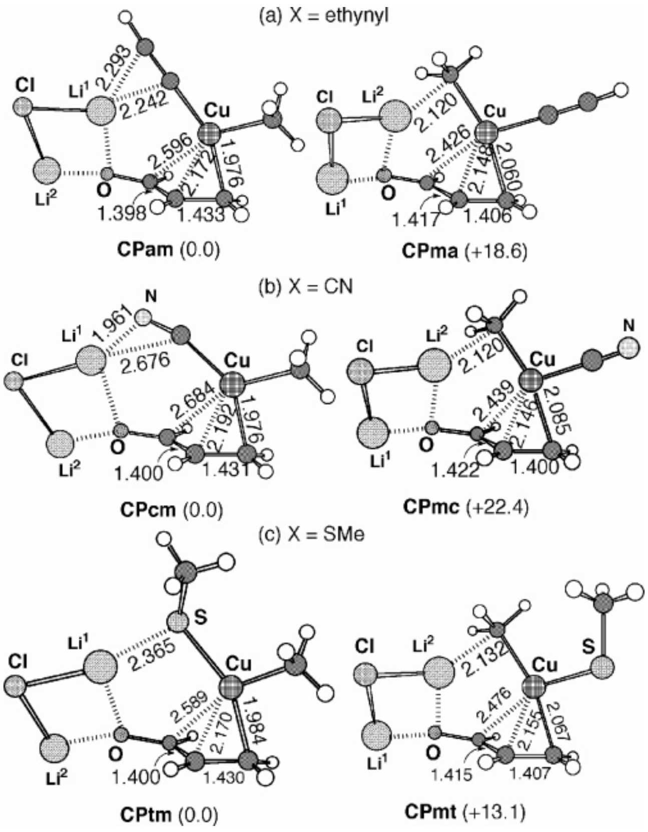

Figure 10. 3D structures of the Cu(III) complexes in path XM and MX for (a) X = ethynyl, (b) CN, and (c) SMe. Bond lengths are in Å, and the relative energies (kcal/mol) are in parentheses at the B3LYP/631AS level.

(1) Thermodynamic Stability Control of the Ligand Transfer Selectivity. For the typical dummy ligand (X = ethynyl, CN, and SMe), the large energy difference between two isomeric Cu(III) complexes persists in the TS. One can readily identify the tight π-coordination between the electron-rich ethynyl and CN groups and the Li^1 atom in **CPam** and **CPcm** (Figure 10a and b). Note that the π-coordinated metal/alkynyl structure seen here is ubiquitous in crystals.[19] In these complexes, the Me group becomes tetracoordinated and ready for the reductive elimination via a pentacoordinated TS (cf. **TSxm** in Scheme 1).[20] In the alternative paths (e.g., **CPma** and **CPmc**) the Me group weakly coordinates to the Li^2 atom, and therefore the complexes are not stable at all. The structural feature around the Cu(III) center is also affected by the X group (Figure 10). The structures around the Cu(III) center in **CPam** and **CPcm** are more enyl[$\sigma + \pi$]-like, while those in **CPma** and **CPmc** are more π-allyl-like, which agrees with the π-allyl Cu(III) model study. In conclusion, the overwhelming stabilization of **CPam** and **CPcm** by the strong attractive interaction between Li^1 and the alkynyl ligand as well as the trans effect and the donating effect of the X group prevents the transfer of the X group.

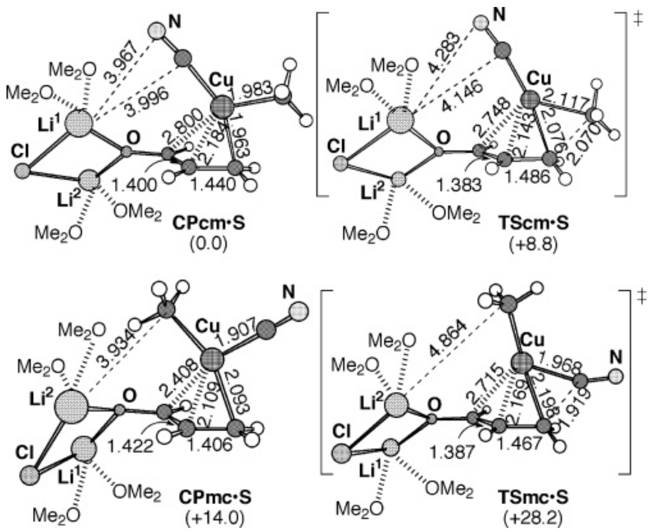

Figure 11. 3D structures of the Cu(III) complexes and the TSs bearing two Me_2O on each Li atom for X = CN (**CPmc•S** and **CPcm•S**) at the B3LYP/321AS level. Bond lengths are in Å, and the relative energies (kcal/mol) are in parentheses.

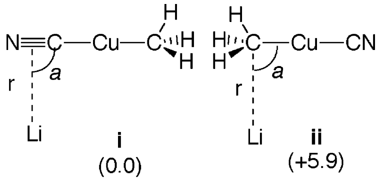

Figure 12. A model system to probe the electrostatic interaction between cyanide and a distant lithium cation. Relative energies in kcal/mol are in parentheses. Li cation is fixed just below the center between C and N in **i** and just below Me in **ii**. Angle *a* is frozen at *a* = 90°, and the distance *r* is at *r* = 4.0 Å.

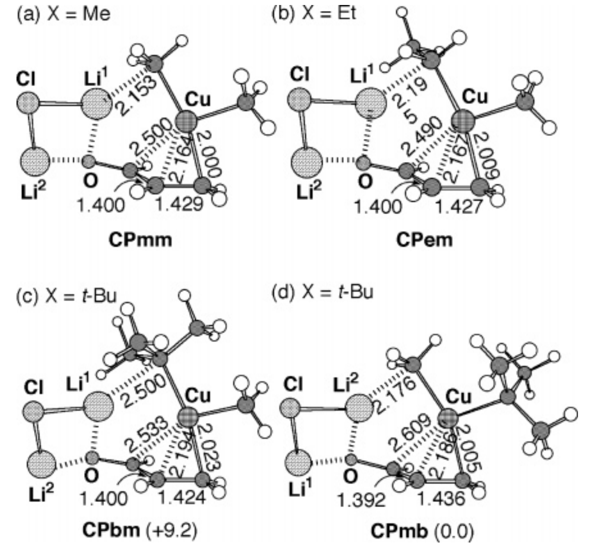

Figure 13. 3D structures of the Cu(III) complexes in XM pathways for (a) X = Me, (b) Et, and (c) *t*-Bu and (d) in the MX pathway for X = *t*-Bu. Bond lengths are in Å, and the relative energies (kcal/mol) are in parentheses.

The structures of the fully solvated **CPmc•S** and **CPcm•S** bearing two molecules of Me_2O coordinating on each Li atom are compared. The solvent coordination on the Li atoms elongates the Li^1−X or the Li^2−Me distance and slightly enhances the enyl[$\sigma + \pi$] character in **CPcm•S** and the π-allyl character in **CPmc•S** (Figure 11). The transition structures around the Cu(III) center in **TScm•S** and **TSmc•S** are similar to those of **TSπcm** and **TSπmc**, respectively. Despite the very long Li−X distances, solvent coordination does not much affect

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(19) (a) Goldfuss, B.; Schleyer, P. v. R.; Hampel, F. *J. Am. Chem. Soc.* **1997**, *119*, 1072. (b) Varga, V.; Mach, K.; Thewalt, H. U. *J. Organomet. Chem.* **1996**, *506*, 109. (c) Edwards, A. J.; Fallaize, A.; Raithby, P. R.; Rennie, M. A. A.; Steiner, A.; Verhorevoot, K. L.; Wright, D. S. *J. Chem. Soc., Dalton Trans.* **1996**, 133−137.

(20) Such consideration also accounts for the low reactivities of bis(alkynyl) homocuprates in terms of the thermodynamic problem in dissociation of the Li−X bond in the starting cuprate cluster.

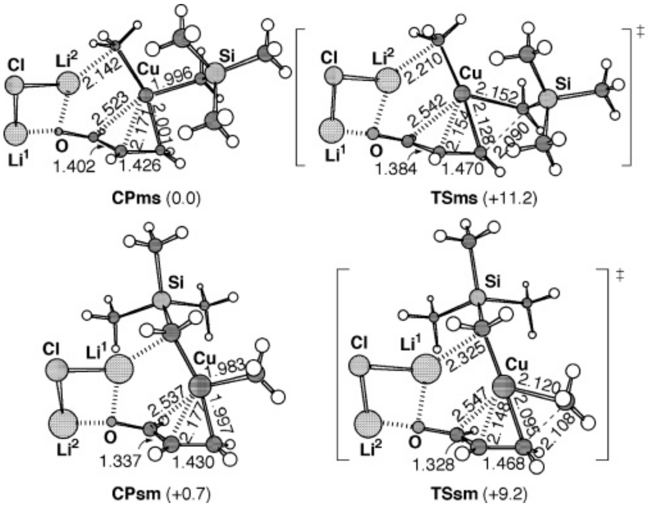

Figure 14. 3D structures of the Cu(III) complexes and the TSs for X = CH_2SiMe_3 at the B3LYP/631AS level. Bond lengths are in Å, and the relative energies (kcal/mol) are in parentheses.

the relative stability between two isomeric complexes **CPmc•S** and **CPcm•S**. The latter remains to be more stable than the former by 14.0 kcal/mol, suggesting the electrostatic effect persists despite the long Li−X distances.

To study the long-range effect of the electrostatic effect, two simple models MeCu(CN)Li (**i**) and LiMeCuCN (**ii**) were examined at the B3LYP/631AS level with a frozen angle of Cu−X−Li = 90° and length of X−Li = 4.0 Å (Figure 12). The species **i** wherein Li and CN are put closer together is 5.9 kcal/mol more stable than **ii** wherein Li and Me are put closer together. The 5.9 kcal/mol energy difference is significant enough to affect the stability of the isomeric complexes.

The case of X = SMe exactly follows those of X = ethynyl and CN. The SMe group simultaneously coordinates to the Cu(III) and the Li^1 atom in **CPtm**, and the π-allyl Cu(III) structure resembles those for X = ethynyl and CN (Figure 10c): the enyl[σ+π]-like structure around the Cu(III) center is found in **CPtm** similar to **CPam** and **CPcm**, while π-allyl-like structure in **CPmt**. Other hetero dummy ligands should behave exactly in the same manner.

It looks curious that transfer of the sterically demanding *t*-Bu transfer is preferred to the Me transfer (Figure 8g). For both cases of X = Et and *t*-Bu groups, the stability of the complexes, **CPxm** and **CPmx**, determines the transfer selectivity. In these cases, the trans effect of the X group is very small and the π-allyl Cu(III) structure are similar to that of **CPmm** (X = Me). The thermodynamic stability of the Cu(III) complex depends solely on the Li^1−X electrostatic interaction. Note that the Li^1−X length becomes long (Me < Et < *t*-Bu, Figure 13a, b, and c), as the X group becomes larger. The energy between **CPbm** and **CPmb** (9.2 kcal/mol) diminishes as it goes to the TS (4.3 kcal/mol), which is likely due to the steric hindrance of the *t*-Bu group. The selectivity of the ligand transfer in these cases is also controlled by the thermodynamic stability of the Cu(III) complex.

(2) Kinetic Reactivity Control of the Ligand Transfer Selectivity. An intriguing feature of the energetics for X = CH_2SiMe_3 is that the thermodynamic preference in the complex is reversed in the TS. As a result, the CH_2SiMe_3 transfer is less kinetically favored than the Me transfer by 2.0 kcal/mol, which agrees with the experimental results. As shown in Figure 14, **CPms** and **CPsm** are similar to each other in structure and in energy: the trans effect of the CH_2SiMe_3 group must be quite small.

On the basis of this and the foregoing analysis for the simple π-allyl model, we conclude that the slower CH_2SiMe_3 transfer is due to the repulsive four-electron interaction[17] between the occupied Cu $3d_{xy}$ orbital and the C−Si σ-orbital. In our advanced models, we could not find evidence in support of the Bertz/Snyder hypothesis[2j] of "β-cation stabilization effect" of the silyl group on the positively charged copper center.

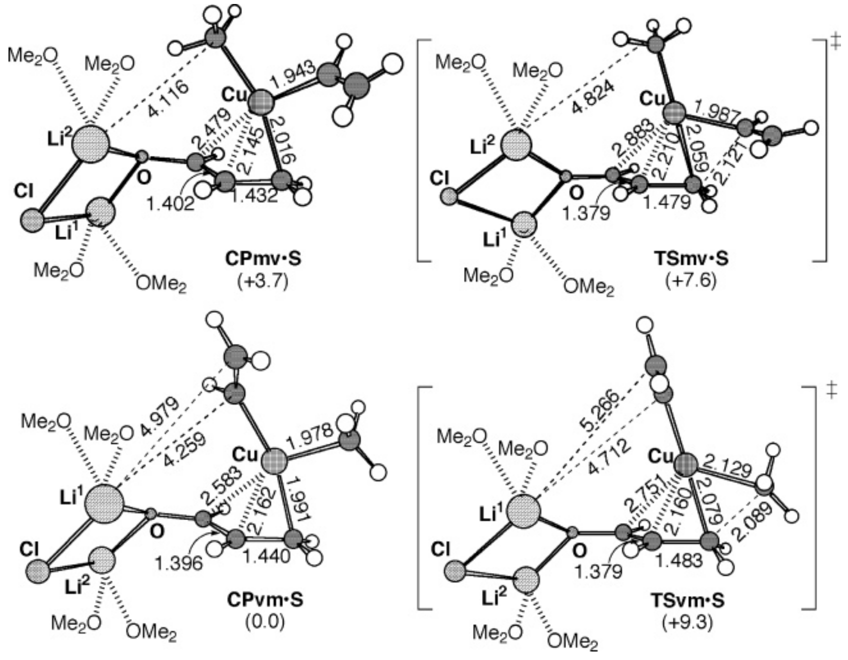

Figure 15. 3D structures of the solvated Cu(III) complexes and the TSs for X = vinyl are at the B3LYP/321AS level. Bond lengths are in Å, and the relative energies (kcal/mol) are in parentheses.

When X = vinyl, Me_2O coordination to the lithium atom changed the transfer selectivity favoring the vinyl transfer (as in the experiments). The solvent coordination (Figure 15) causes a structural change similar to the case of X = CN (i.e., attenuation of the Lewis acidity of Li^2 in Figure 11).

Conclusion

We have discussed the geometry, energetics, and orbital interactions of the ligand transfer selectivity in the conjugate addition of mixed organocuprates by the use of three chemical models; $Me_2(X)Cu(III)\cdot OMe_2$, π-allyl Cu(III), and Me(X)-Cu(III)LiCl·LiCl models. We have discerned four independent factors that underlie the selectivity problem: (1) the trans effect of the X group (σ-donation), (2) electrostatic or covalent interaction between X and the lithium cation, (3) π-participation for X = vinyl, and (4) C−Si interaction with the copper $3d_{xy}$ lone pair in the TS of reductive elimination for X = CH_2SiMe_3.

Cooperation of these factors leads to the following two classifications of the transfer selectivity: (1) thermodynamic stability control and (2) kinetic reactivity control (Figure 16). In the first category, the ligand transfer selectivity is controlled by the thermodynamic stability of the isomeric Cu(III) complex (X = Et, *t*-Bu, ethynyl, CN, and SMe). The selectivity depends mainly on an electronic factor. For typical dummy ligands (e.g., X = ethynyl, CN, and SMe), the strong Li−X affinity and the trans effect of the X group stabilize **CPxm** and let the X group stay on copper. The Et and *t*-Bu groups are transferred preferentially, since they have less affinity to the lithium cation and hence can be easily removed from the copper/lithium coordination sphere.

In the second category, the ligand transfer selectivity depends on the kinetics of the reductive elimination of the Cu(III) complex (X = CH_2SiMe_3 and vinyl) depending on the intrinsic transfer ability of the X group. The CH_2SiMe_3 transfer is retarded by the disfavored four-electron interaction between the occupied Cu $3d_{xy}$ orbital and C−Si σ-orbital. The vinyl transfer is preferred because of the π-orbital participation in the reductive elimination.

The present study has shown that the problem of the reactivities of mixed lithium organocuprates includes a number of fundamental issues of transition metal chemistry and arises from the fact that the metal complex involves multiple metal atoms and organic groups of diverse characters. We suggest that the intricate cooperative effects of transition metals and Lewis acidic metals in such heterometallic clusters are silently playing important roles in various catalytic and synthetic reactions:[21] studies on these effects will continue to receive the interest of chemists in the coming decades.

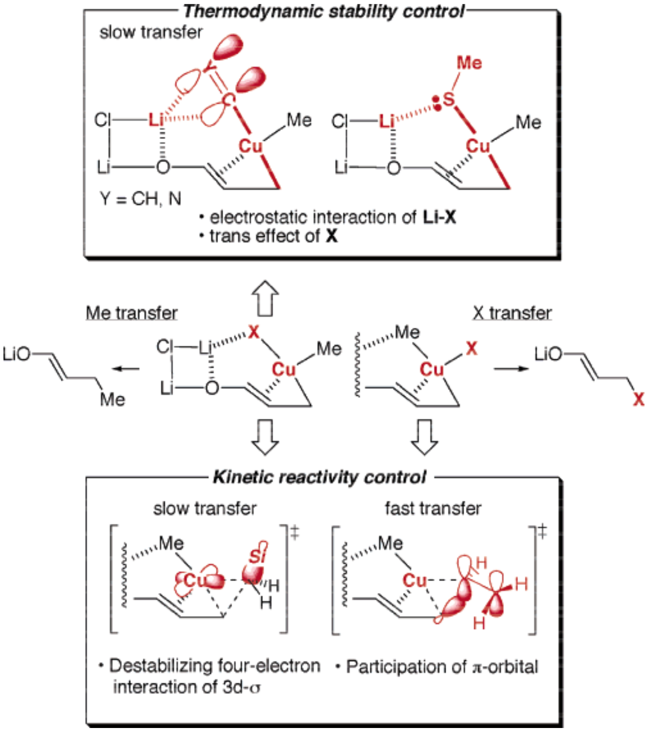

Figure 16. Two categories of the ligand transfer selectivity in the conjugate addition reaction of the mixed organocuprates

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Supporting Information Available: Cartesian coordinates of the representative stationary points (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc*. **2004**, *126*, 12264−12265.