Communication

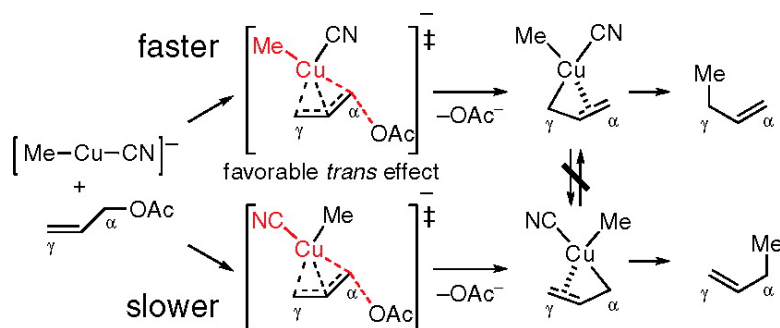# Origin of the Regio- and Stereoselectivity of Allylic Substitution of Organocopper Reagents

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Origin of the Regio- and Stereoselectivity of Allylic Substitution of Organocopper Reagents

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Since the initial report in 1969,[1a] the allylic substitution of organocopper reagents has been among the most important methods for regio- and stereoselective C–C bond formation.[1–3] However, the reactivity profile is more complex and less clearly defined than other organocopper reactions.[4,5] For instance, the *anti*-stereoselective and γ-regioselective reaction of a monoalkyl heterocuprate MeCu(CN)Li with cyclohexenyl acetate[1d] makes a sharp contrast with the reaction of a dialkyl cuprate Me$_2$CuLi, which is also *anti*-selective yet entirely nonregioselective (eq 1).[1b,c,6] Although an allylcopper(III) species is an accepted intermediate in both reactions, the origin of the regiochemical dichotomy has been unclear.[1b–d,7–9] On the basis of a theoretical analysis, we propose that the γ-selectivity is the direct consequence of the asymmetric structure of MeCuCN$^-$ in the oxidative addition step. Thus, MeCu(CN)Li dictates the leaving acetate group to be *trans* to the Me group in the transition state (**TS$_{MC}$'** and **TS$_{MC}$** in Scheme 2), thereby selectively generating a γ-σ-enylcopper(III) intermediate **PD$_{MC}$** that can only give the γ-product. For Me$_2$CuLi, the intermediate **PD** is symmetrical and the reaction is nonregioselective (Scheme 1). The mechanism discussed below may have relevance to the reactions of catalytic copper reagents as well as other transition metal catalysts with allyl electrophiles.

(1)

MeCu(CN)Li	4	96
Me$_2$CuLi	50	50
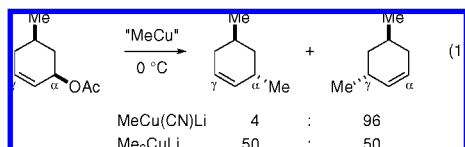
We carried out the theoretical study in two stages for both the homocuprate and the heterocuprate reactions. Thus, we used lithium-free models (e.g., Me$_2$Cu$^-$) to probe the intrinsic reactivity and selectivity, and then cluster models (e.g., [Me$_2$CuLi]$_2$) to examine the effect of Li cations.[10,11] We first describe the reaction of a homocuprate [Me$_2$CuLi]$_2$ with allyl acetate shown in Scheme 1 (see Supporting Information for the lithium-free model). The homocuprate reversibly forms a square-planar olefin π-complex (**CP**, $\Delta E = 5.7$ kcal/mol), which then irreversibly releases an acetate anion in an anti fashion (**TS**, $\Delta E^{\ddagger} = 4.8$ kcal/mol; see also Figure 1a), leading to a symmetrical π-allylcopper(III) complex (**PD**, Figure 1d).[12] During this oxidative addition process, one Li cation (Li^2) assists the C–OAc bond cleavage while the other (Li^1) serves as a bridge between the Me$_2$Cu$^-$ moieties.[4,5] The anti selectivity is the result of the Cu 3d and the C=C π*/C–O σ* orbital interaction as discussed earlier by Corey.[13] The allylcopper(III) intermediate **PD** reductively eliminates either at the α or the γ carbon atom ($\Delta E^{\ddagger} = 14.9$ kcal/mol). If this π-complex is substituted on either the α- or the γ-terminus, the α/γ-regioselectivity depends on the electronic effects of the substituents.[8]
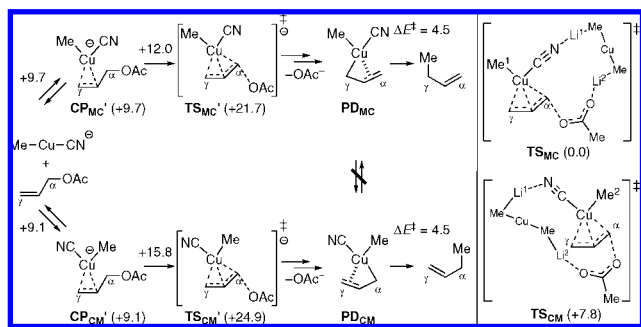
We next discuss the reactions of heterocuprate models.[14] The model reaction between MeCuCN$^-$ and allyl acetate revealed that

Scheme 1. Reaction of [Me$_2$CuLi]$_2$ and Allyl Acetate[a]
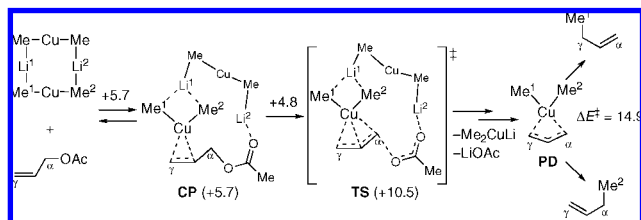
[a] Relative energies and energy changes (ZPE corrected) are shown in kcal/mol.

Scheme 2. Reaction of Cyanocuprate and Allyl Acetate[a]

[a] Relative energies and energy changes (ZPE corrected) are shown in kcal/mol.

the trans effects is the first important reason for the γ-selectivity. We located diastereomeric π-complexes and oxidative addition TSs (**CP$_{MC}$'/TS$_{MC}$'** and **CP$_{CM}$'/TS$_{CM}$'**, Scheme 2) and found that **TS$_{MC}$'** is more stable than **TS$_{CM}$'** by 3.2 kcal/mol. These TSs lead to enyl [$\sigma + \pi$] copper(III) complexes **PD$_{MC}$** and **PD$_{CM}$** (equivalent with each other in the present model, Figure 1e), respectively,[15,16] with retention of the coordination geometry of the Cu atom.

These Cu(III) intermediates can be viewed as a T-shaped Cu(III) species bearing an internal olefin as a two-electron donor. The methyl group and the sp^3 carbon of the allyl group are *cis* to each other, and hence undergo reductive elimination to produce butene with an activation energy as low as 4.5 kcal/mol.[16] Interconversion between **PD$_{MC}$** and **PD$_{CM}$** is unlikely in light of the configurational (i.e., *cis/trans*) stability of a tetracoordinated planar organocopper(III) complex at a synthetically relevant temperature.[17] Therefore, the γ-regioselectivity (eq 1) is the result of the lower energy of **TS$_{MC}$'**.

Molecular orbital analysis of the copper and the allyl acetate fragments in the TS provides a reason why **TS$_{MC}$'** is favored over **TS$_{CM}$'**. The HOMO of the MeCuCN$^-$ fragment (Figure 2a) that is bent as in the TS is mainly composed of an out-of-phase interaction of the Cu 3d$_{xz}$ orbital and the ligand orbitals,[18] where the 3d$_{xz}$ orbital is desymmetrized because of the different σ-donor ability (trans effect) of the Me (stronger) and CN (weaker) ligands.[19] Thus, the
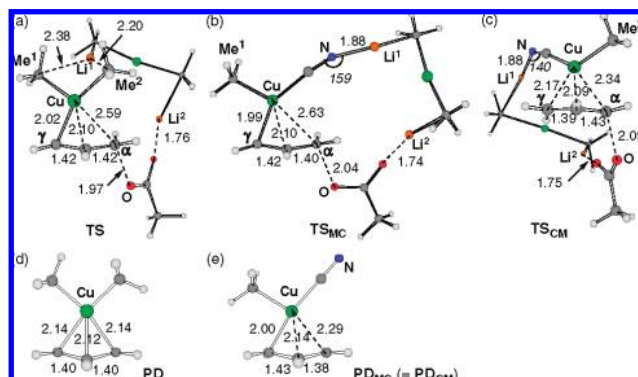
Figure 1. Structures of the transition states and the allylcopper(III) intermediates in the reactions of homo- (Scheme 1) and heterocuprates (Scheme 2). Bond lengths are in Å and bond angles (italic) are in deg.
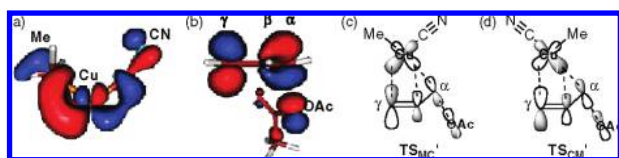

Figure 2. Fragment MO analysis. (a) HOMO (Cu $3d_{xz}$ orbital) of a bent MeCu(CN)$^-$ fragment. (b) LUMO (π^*/σ^* mixed orbital) of allyl acetate with elongated C—O bond (1.9 Å). (c and d) Schematic representations of the HOMO/LUMO interaction in $\mathbf{TS_{MC}}'$ and $\mathbf{TS_{CM}}'$.

Cu d-orbital on the side of the Me group (red) is significantly larger than that on the CN side (blue). The C—OAc bond cleavage results in the mixing of C=C π^* and C—O σ^* orbitals (Figure 2b) and hence the LUMO lobe becomes larger on the γ-carbon atom. As the result, MeCuCN$^-$ enjoys a better HOMO/LUMO overlap with allyl acetate in $\mathbf{TS_{MC}}'$ than in $\mathbf{TS_{CM}}'$ (Figure 2c vs 2d).

To probe the effect of the Li cation, we next examined a model of the heterocuprate where the Me^1 or Me^2 ligand of the [Me$_2$CuLi]$_2$ model (Scheme 1) was replaced by a cyano ligand (box in Scheme 2; the entire reaction pathways are given in Supporting Information). We found that the $\mathbf{TS_{MC}}$ that is equivalent to the lithium-free one ($\mathbf{TS_{MC}}'$) is even more favored (7.8 kcal/mol) because of the Li^2 coordination on the leaving acetate group.

The structures of $\mathbf{TS_{MC}}$ and $\mathbf{TS_{CM}}$ are shown in Figure 1b and 1c, respectively, and can be compared with that of **TS** (Figure 1a). The geometries of the cuprate clusters in these TSs are strongly influenced by the presence of the cyano ligand, which coordinates to the Li^1 cation, leaving the Me^1 (or Me^2) group free.[14] In $\mathbf{TS_{MC}}$, the CN ligand and the acetate group are positioned on the same side and serve as a bidentate ligand to the Lewis acidic Me$_2$CuLi$_2^+$ moiety (note the ideal linear Cu—CN—Li geometry).[16,20] On the other hand, such bidentate coordination is far from ideal in the regioisomeric structure $\mathbf{TS_{CM}}$ where the acetate group is located on the opposite side of the CN group. Note also the significant difference between $\mathbf{TS}/\mathbf{TS_{MC}}$ and $\mathbf{TS_{CM}}$ in the geometry of the Cu/allyl moiety, which probably reflects the mismatched HOMO/LUMO overlap in $\mathbf{TS_{CM}}$ (vide supra).

In conclusion, we found that the anti and the γ-selectivities in the allylic substitution of a heterocuprate MeCu(CN)Li are determined in the initial oxidative addition step of the reaction. The difference of the trans effect of the ligands on the Cu $3d_{xz}$ orbital is the most important factor, and the coordination of Li atoms on the CN and the leaving acetate groups causes an additional effect. The coordination effect examined in the gas phase may, however, be overestimated. On the other hand, the regioselectivity of the

symmetric Me$_2$CuLi is not determined in the oxidative additive step. We note in passing that the oxidative addition step for MeCuCN$^-$ is slower than that of the more electron-rich Me$_2$Cu$^-$, while the reductive elimination step of the former is faster because the electron-withdrawing CN group destabilizes the Cu(III) intermediate.[16] We found that other heterocuprates MeCuX$^-$ (X = Cl, SMe, or NMe$_2$) were also predicted to be γ-selective for the same reasons (Supporting Information). We therefore suspect that such heterocuprates are responsible for the γ-selectivity widely observed for catalytic copper reagents generated from organomagnesium,[1f,h,i] zinc,[1e] and titanium[1g] reagents. The Cu/Li bimetallic mode of the oxidative addition will stimulate further mechanistic experiments[5] and will inspire the design of new ligands[21] for the allylation reactions.

Supporting Information Available: Computational details, energies, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Attachment of solvent molecules (Me$_2$O) on the lithium atoms gave essentially the same results (Supporting Information).
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