

## Mechanism of Substitution Reaction on $sp^2$ -Carbon Center with Lithium Organocuprate

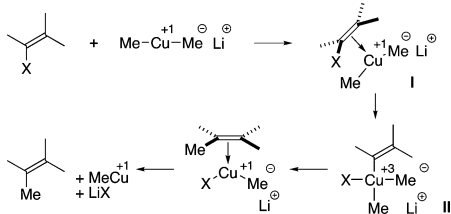
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A report in 1967 that a lithium diorganocuprate ( $R_2CuLi$ ) undergoes substitution reaction with an alkenyl bromide with retention of stereochemistry<sup>1</sup> changed the accepted wisdom that a nucleophilic substitution on an  $sp^2$ -hybridized carbon is synthetically impracticable.<sup>2</sup> The new paradigm is now firmly established in chemistry through subsequent development of catalytic variants.<sup>3,4</sup> A generally accepted mechanism of the cuprate reaction involves an oxidative addition/reductive elimination sequence (Scheme 1).<sup>5–7</sup>

### Scheme 1

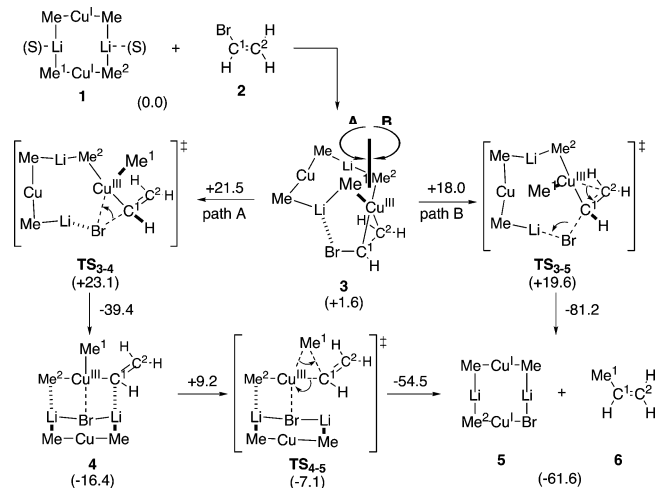


There underlie, however, a few questionable assumptions in such a scheme: The first is the neglect of the polymetallic structure of  $R_2CuLi$  that is essential for the reactivity of organocuprate.<sup>8,9</sup> In addition, the mechanism silently assumes direct insertion of the metal atom into the C–X bond to form the vinyl complex II and, hence, underrates the role of the  $\pi$ -complex I (note that the  $\sigma^*$ - and the  $\pi^*$ -orbitals of the alkenyl bromide responsible for the  $\sigma$ - and the  $\pi$ -complexation are orthogonal to each other). On the basis of theoretical<sup>10</sup> and experimental studies, we propose here a significant mechanistic modification, which is consistent with and adds a new dimension to the modern mechanistic pictures of organocuprate reactions.<sup>8</sup>

Experimental and theoretical studies in recent years have shown that the cyclic dimer **1** (in its solvated form, S = ethereal solvent) exists as a stable species in ethereal solution and reacts with electrophiles (Scheme 2).<sup>8,9</sup> The cuprate **1** undergoes a two-point interaction with vinyl bromide **2** to form a  $\pi$ -complex **3**, as it does with cyclohexenone.<sup>11</sup> This  $\pi$ -complex, however, is less favorable here than in the case of more electrophilic cyclohexenone. This energetics was confirmed by <sup>13</sup>C NMR measurement on a mixture of  $Me_2CuLi \cdot LiI$  and 1-bromocyclooctene in diethyl ether, which did not show any indication of a  $\pi$ -complex at  $-20$  to  $-40$  °C (Supporting Information) and afforded directly the coupling product at  $> -10$  °C (note that conjugate addition usually proceeds below  $-50$  °C).

In the  $\pi$ -complex **3** that may be viewed as an ate complex of a cuprio(III)cyclopropane,<sup>8</sup> the two methyl groups and the vinyl carbon atoms serve as four anionic ligands in this  $d^8$  square-planar complex. Conversion of **3** to the conventional three-centered TS (**TS**<sub>3–4</sub> then to **4**) keeps the Cu–C<sup>1</sup> bond while breaking the Cu–C<sup>2</sup> bond. This process can be viewed as rotation of the  $Me^1CuMe^2$  moiety along Cu–C<sup>1</sup> bond as indicated as rotation A. This motion creates a vacant site on the metal and forms the Cu–Br bond. The

### Scheme 2. Two Pathways of the Reaction of Cuprate **1** with Vinyl Bromide **2** To Give Propene<sup>a</sup>

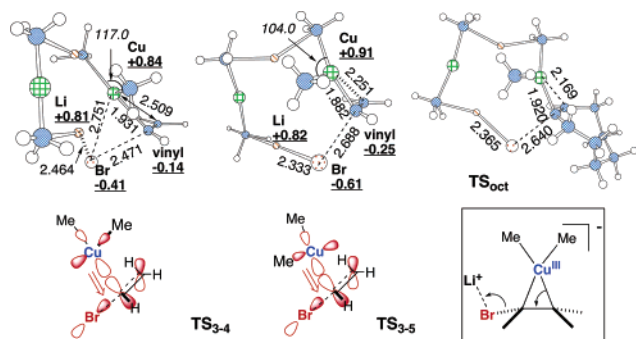


<sup>a</sup> A and B rotations refer to rotation along the Cu–C<sup>1</sup> axis. Energies (in kilocalories per mole) are relative to [**1** + **2**]. Energy changes are shown together with arrows.

vinylcopper(III) complex **4** undergoes quick reductive elimination via **TS**<sub>4–5</sub> to give the mixed cuprate **5** and propene **6**.<sup>12</sup>

There is another alternative rotational mode that has thus far escaped attention (rotation B), wherein the Cu–C<sup>2</sup> bond is retained until the C–Br bond cleaving TS (**TS**<sub>3–5</sub>). Here the Br atom eliminates by itself without interaction with the Cu atom, which may look rather surprising but is quite good since the leaving Br anion keeps strong interaction with the Li atom. The tetracoordination that still exists in **TS**<sub>3–5</sub> becomes disrupted as the Cu–C<sup>1</sup> bond becomes fully formed after the TS (Supporting Information), and the resulting tricoordinated Cu<sup>III</sup> complex undergoes spontaneous reductive elimination of the vinyl and the Me<sup>1</sup> groups without giving a discrete Cu<sup>III</sup> intermediate.<sup>13</sup> The activation energies of paths A and B are ( $\Delta E^\ddagger$ ) 21.5 and 18.0 kcal/mol, respectively, and comparable to that for the  $S_N2$  alkylation reaction of methyl bromide with **1**.<sup>14</sup> These values decrease by ca. 4 and 1 kcal/mol by inclusion of solvent coordination (S =  $Me_2O$ ) to Li atoms and by consideration of solvent polarity (PCM method,  $\epsilon = 4.335$  for  $Et_2O$ ), respectively (see Supporting Information). With inclusion of solvent effects, path B is still favored by 3–4 kcal/mol over path A (data in Table S1, Supporting Information).

Structure and orbital analysis shows the similarity and the difference between the two TSs of the C–Br bond cleavage, **TS**<sub>3–4</sub> and **TS**<sub>3–5</sub> (Figure 1). In both TSs, the  $Me^1-Cu-Me^2$  moiety is bent ( $117.0^\circ$  and  $104.0^\circ$ ), and the C<sup>1</sup> atom becomes nearly  $sp^3$  hybridized (C<sup>2</sup> becomes closer to  $sp^2$ ). The  $Me^1-Cu-Me^2$  bending pushes up the energy level of the Cu  $3d_{xz}$  orbital,<sup>15</sup> and the deformation of the C<sup>1</sup> center lowers the LUMO level of vinyl bromide through mixing of the  $C^1=C^2$   $\pi^*$  and the  $C^1-Br$   $\sigma^*$  orbitals



**Figure 1.** Structures of C–Br bond cleavage TSs ( $\text{TS}_{3-4}$ ,  $\text{TS}_{3-5}$ , and  $\text{TS}_{\text{oct}}$ ) with schematic representations of orbital interaction based on the analysis of fragment orbitals (Supporting Information). The red arrow indicates back-donative interaction. The numbers refer to bond length (Å), bond angles (italic), and natural charges (bold and underlined).

**Table 1.** Calculated and Experimental  $^{12}\text{C}/^{13}\text{C}$  KIE Values for the Reaction between  $\text{Me}_2\text{CuLi}$  and Vinyl Bromide/1-Bromocyclooctene

	calcd (A) <sup>a</sup>	calcd (B) <sup>a</sup>	calcd (B) <sup>b</sup>	run 1 <sup>c</sup>	run 2 <sup>c</sup>
C <sup>1</sup>	1.039	1.026	1.024	1.023(3)	1.020(4)
C <sup>2</sup>	1.015	1.018	1.016	1.015(2)	1.017(3)
C <sup>3</sup>			1.003	0.999(1)	1.000(1)
C <sup>4</sup>			1.000	1.003(2)	1.001(1)
C <sup>5</sup>			1.000	1.000	1.000
C <sup>6</sup>			1.000	0.997(2)	0.999(2)
C <sup>7</sup>			1.001	0.997(2)	0.998(2)
C <sup>8</sup>			1.007	1.004(1)	1.006(2)

<sup>a</sup> KIEs calculated for vinyl bromide. <sup>b</sup> KIEs calculated for 1-bromocyclooctene. <sup>c</sup> Experiments 1 and 2 are reactions carried out to 80.4 and 72.6% completion, respectively. The C<sup>5</sup> atom was taken as an “internal standard”. Standard deviations in the last digit are shown in parentheses.

(Supporting Information). Thus, essentially the same frontier orbital interactions (HOMO: Cu 3d<sub>xy</sub>, LUMO: C=C π\*/C–Br σ\*) give  $\text{TS}_{3-4}$  and  $\text{TS}_{3-5}$ . The copper atom is in the T-shaped coordination geometry indigenous to Cu<sup>III</sup> oxidation state.<sup>13</sup> The T-geometry, however, is oriented in an opposite way as to the vinyl bromide moiety and so is the vacant orbital of the Cu<sup>III</sup> center (Figure 1): In  $\text{TS}_{3-4}$ , the vacant site can readily interact with the Br atom, while in  $\text{TS}_{3-5}$ , it can keep the interaction with the C<sup>2</sup> atom as long as it is possible. As one can immediately notice the similarity between  $\text{TS}_{3-5}$  and β-elimination reaction (Figure 1 inset); or also α-elimination of the metallacyclopropane, we may call the  $\text{TS}_{3-5}$  “eliminative TS” as opposed to the “three-centered”  $\text{TS}_{3-4}$ .

Taking place via either path A or B, the rate-limiting step of the reaction is the C–Br bond cleavage, and therefore, we should be able to probe the reaction experimentally through kinetic isotope effect (KIE). The  $^{12}\text{C}/^{13}\text{C}$  KIE values were calculated for  $\text{TS}_{3-4}$  and  $\text{TS}_{3-5}$  by taking **1** and **2** as starting materials. As shown in the first and the second columns of Table 1, the KIE values for C<sup>1</sup> (1.039 and 1.026 for paths A and B, respectively) are significantly different from each other, reflecting the mechanistic difference and indicating that the KIE serves as a measure to probe the mechanism.

Therefore, we compared experimental measurement (based on quantitative  $^{13}\text{C}$  NMR measurement)<sup>16</sup> and theoretical prediction of KIE for the reaction between  $\text{Me}_2\text{CuLi}$  and 1-bromocyclooctene.<sup>17</sup> The calculated KIEs for path B (see  $\text{TS}_{\text{oct}}$  in Figure 1) in column 3 show significant KIEs on C<sup>1</sup> (1.024) and C<sup>2</sup> (1.016),

which agree very well with the experimental data in columns 4 and 5. For 1-bromocyclooctene, the conventional three-centered TS was higher in energy and could not be located as a stationary point. As one can surmise from  $\text{TS}_{\text{oct}}$  in Figure 1, the counterclockwise rotation of the  $\text{Me}_2\text{Cu}$  moiety in path A suffers from steric repulsion between the ring structure and the Me<sup>1</sup> group.

In summary, we have proposed a new mechanism of “oxidative” addition between a cuprate and an alkenyl halide on the basis of theory and experiments. It is first necessary to note that the initially formed π-complex is not a simple Cu<sup>I</sup>/alkenyl halide complex but behaves as a cuprio(III)cyclopropane,<sup>8</sup> where charge transfer is taking place from the 3d orbital of the bent  $\text{Me}_2\text{Cu}$  moiety to the π\*/σ\*-mixed orbital of the deformed alkenyl halide. The subsequent C–Br bond cleavage in this complex may go through the “three-centered” or the “eliminative” way, of which the latter is preferred. The overall mechanistic framework and the cooperation of various components in the cuprate cluster strongly suggest kinship between this and the conjugate addition reaction (and the carbocation reaction as well).<sup>18</sup> We expect that the present mechanistic framework applies not only to the stoichiometric cuprate(I) reaction but also to reactions involving d<sup>10</sup>/d<sup>8</sup> transition metal catalytic cycles<sup>3</sup> and that useful new designs of reactions will result.

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**Supporting Information Available:** Details of computation and experiments (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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