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Stille Cross-Coupling Reactions of Alkenylstannanes with Alkenyl Iodides Mediated by Copper(I) Thiophene-2-carboxylate: A Density Functional Study

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The detailed reaction mechanism for the Stille cross-coupling reaction of vinylstannane with vinyl iodide mediated by copper(I) thiophene-2-carboxylate (CuTC) was studied with the aid of density functional theory (DFT) calculations. The results of the DFT calculations show that the reaction mechanism involves two major steps: (1) the transmetalation between (NMP)CuTC (NMP = N-methylpyrrolidone, a solvent molecule) and $CH_2{=}CHSnMe_3$ to give the organocopper intermediate (NMP)Cu-CH=CH$_2$ and (2) a one-step process involving both oxidative addition of $CH_2{=}CHI$ to (NMP)Cu-CH=CH$_2$ and reductive elimination of the coupling product $CH_2{=}CH-CH{=}CH_2$. We found that the overall barrier involves the effect of both steps. In this paper, we also examined the role of the thiophene-2-carboxylate ligand in the reaction and discussed the possibility of a catalytic version of the reaction.

Introduction

Stille cross-coupling reactions of organostannanes and organic electrophiles are widely used for carbon–carbon bond formation in organic synthesis.[1] In general, catalysts based on palladium are mostly applied in these reactions.[2] Since palladium is relatively expensive, effort has been directed to search for a substitute made of cheaper materials. The use of catalysts based on copper is particularly attractive because of their relatively low cost. In 1990, Liebeskind et al. found that copper salts could be used as additives to increase the rate of palladium-catalyzed Stille cross-coupling reactions.[3] Subsequently, there was a significant finding that organostannanes and organic iodides could undergo cross-coupling with the action of copper salts alone,[4] shown in eq 1. It was found that 1.5 equiv of copper(I) thiophene-2-carboxylate (CuTC) would mediate rapid and very efficient cross-coupling of aryl-, heteroaryl-, and alkenylstannanes with alkenyl and activated aryl iodides within minutes in N-methylpyrrolidone (NMP) solvent at or below room temperature.[4] With this finding, CuTC-mediated Stille coupling reactions have been applied in a number of synthetic reactions.[5] In addition, CuTC has found applications in aryl and alkenyl amination,[6] Ullmann-like reductive coupling,[7] thiol ester[8] (thioalkyne,[9] as well as aryl and alkenyl iodides[10])

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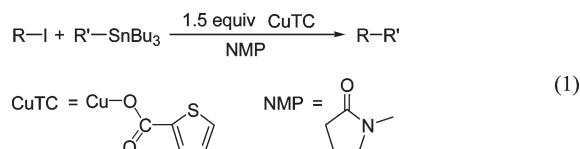
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and boronic acid coupling, and C−O coupling lactonization.[11]

R−I + R'−SnBu$_3$ $\xrightarrow[\text{NMP}]{\text{1.5 equiv CuTC}}$ R−R'

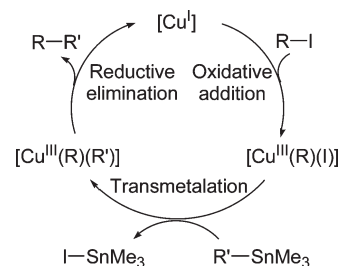CuTC = Cu−O—C(=O)—thiophene   NMP = N-methyl-2-pyrrolidinone   (1)

In this paper, we are interested in knowing how CuTC mediates the cross-coupling reactions shown in eq 1. We employed density functional theory calculations to study the reactions, which allow us to shed light on the possible reaction mechanism. Pd-mediated or -catalyzed cross-coupling reactions have attracted extensive theoretical studies.[12] In contrast, theoretical studies on Cu-mediated or -catalyzed cross-coupling reactions are rather limited. The mechanism of copper(I)-catalyzed cross-coupling of aryl halides and amides has been theoretically studied.[13] It was found that a Cu(I)/Cu(III) catalytic cycle is involved. A copper(I)-catalyzed Kharasch−Sosnovsky C−O cross-coupling reaction has also been reported and theoretically studied.[14] The calculated reaction mechanism supports a process including oxidative addition of the O−O bond from *tert*-butyl perbenzoate to Cu(I), generating a Cu(III) intermediate. Related C−C bond formation reactions such as copper-catalyzed cyclopropanation reactions[15] of olefins with N_2CHCOOMe and addition of stannylcuprates to α,β-acetylenic esters[16] have been reported. Recently, Pd-catalyzed, Cu(I) carboxylate-mediated desulfitative coupling of thioorganics with boronic acids has been theoretically studied.[17]

Computational Details

Molecular geometries of the model complexes were optimized without constraints via DFT calculations using the Becke3LYP (B3LYP)[18] functional. For the basis set, the effective core potentials of Hay and Wadt with double-ξ valence basis sets (LanL2DZ)[19] were chosen to describe I and Sn, while the 6-311G* Wachters−Hay basis set[20] was used for Cu and the 6-31G* basis set for all other atoms. Polarization functions were also added for I ($\zeta_d = 0.266$) and Sn ($\zeta_d = 0.183$).[21] Frequency calculations were carried out at the same level of theory to identify all of the stationary points as minima (zero imaginary frequencies) or transition states (one imaginary frequency) and to provide free energies at 298.15 K, which include entropic contributions by taking into account the vibrational, rotational,

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Scheme 1. Possible Mechanism for the Copper-Mediated Stille Cross-Coupling Reaction

and translational motions of the species under consideration. Intrinsic reaction coordinates[22] were calculated for the transition states to confirm that such structures indeed connect two relevant minima. All calculations were performed with the Gaussian 03 software package.[23] In all of the figures that contain potential energy profiles, calculated relative free energies (kcal/mol) and relative electronic energies (kcal/mol, in parentheses) are presented. Because of the entropic contribution, the relative free energies and relative electronic energies are significantly different in cases where the numbers of reactant and product molecules are not equal. In this paper, relative free energies are used to analyze the reaction mechanism. The steps that are crucial to the conclusions we made do not involve a change in the numbers of species (*vide infra*). Therefore, the possible overestimation of the entropic effect due to our gas-phase calculations should not affect the conclusions made in this paper.

Results and Discussion

On the basis of the limited theoretical studies of the above-mentioned copper-mediated or -catalyzed organic reactions, a Cu(I)/Cu(III) cycle (Scheme 1) analogous to the well-known Pd(0)/Pd(II) cycle could be proposed to account for the Cu-mediated cross-coupling reactions shown in eq 1. The mechanism involves oxidative addition of R−I to Cu(I), transmetalation between the resulting complex formed and R'−SnMe$_3$, and reductive elimination to give the final coupling product R−R'. It should be noted that the reaction studied here is a stoichiometric reaction because 1.5 equiv of CuTC was experimentally used to mediate the reaction.[4] A catalytic cycle (Scheme 1) is calculated and studied for convenience of our discussion.

The Active Species (NMP)CuTC. On the basis of the reported experiments[4] that the reactions were mediated by CuTC in the NMP solvent, we considered the model complex (NMP)CuTC as the active species, in which a solvent molecule NMP was seen as a ligand. The vinylstannane CH_2=CHSnMe$_3$ and vinyl iodide CH_2=CHI were used as the models for the alkenylstannanes and alkenyl iodides used in the experiments.[4]

For the model complex (NMP)CuTC, there are a number of possible isomers (Chart 1, relative energies given in kcal/mol) considering the relative orientations of the NMP and TC ligands around the Cu center as well as the relative orientations of the thiophene ring in the TC ligand. Our calculations show that the thiophene group of the TC ligand has a significant steric effect on the relative stabilities of the isomers. Those isomers with the thiophene group being away

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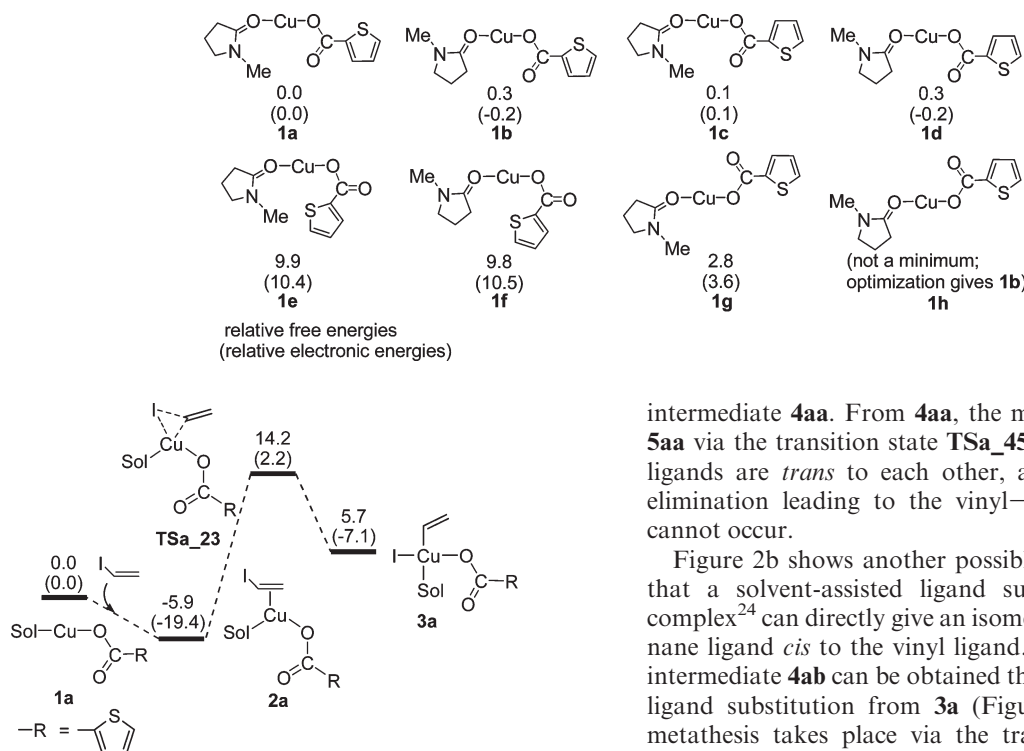
Chart 1

relative free energies
(relative electronic energies)

Figure 1. Energy profile calculated for the oxidative addition of CH$_2$=CHI to Sol-Cu-OCOR ((NMP)CuTC) (Sol = NMP, R = 2-thienyl). The calculated relative free energies and electronic energies (in parentheses) are given in kcal/mol.

from the metal center to prevent ligand−ligand repulsion are clearly more stable. For example, the isomers **1e** and **1f** experience significant ligand−ligand repulsive interactions and are the least stable among the isomers calculated. For all of the isomers calculated, we do not see any significant coordination interaction between the S atom of the TC ligand and the Cu center. The experiments also suggested an S-coordination is not essential because certain Cu(I) carboxylates without a TC ligand can also induce Ullmann-like reductive coupling reactions.[7a] The isomers **1a**, **1b**, **1c**, and **1d** have similar stability, and their relative energies are within 0.3 kcal/mol. In our calculations, the isomer **1a** was chosen considering that it provides a sterically less hindered open coordination site for substrate molecules.

Mechanism Based on Scheme 1. We first examined the possible mechanism shown in Scheme 1. The potential energy profile calculated for the oxidative addition of vinyl iodide CH$_2$=CHI to (NMP)CuTC (**1a**) is presented in Figure 1. Coordination of CH$_2$=CHI to (NMP)CuTC (**1a**) forms the η^2 intermediate **2a**, and the oxidative addition takes place via the transition state **TSa_23** with a free energy barrier of 20.1 kcal/mol to generate the d^8 square-planar Cu(III) complex **3a**. From complex **3a**, the reverse energy barrier of 8.5 kcal/mol is small, suggesting that the oxidative addition of CH$_2$=CHI to (NMP)CuTC is a reversible process.

Following Scheme 1, transmetalation occurs through metathesis between the Cu−I bond in **3a** and the vinyl−Sn bond in CH$_2$=CHSnMe$_3$ to give the Cu−vinyl and Sn−I bonds. The energy profile for this transmetalation is presented in Figure 2a. First, substitution of the vinylstannane CH$_2$=CHSnMe$_3$ for the solvent ligand NMP in **3a** gives the

intermediate **4aa**. From **4aa**, the metathesis occurs to give **5aa** via the transition state **TSa_45a**. In **5aa**, the two vinyl ligands are *trans* to each other, and therefore, reductive elimination leading to the vinyl−vinyl coupling product cannot occur.

Figure 2b shows another possible pathway. It is known that a solvent-assisted ligand substitution in a square complex[24] can directly give an isomer that has the vinylstannane ligand *cis* to the vinyl ligand. In other words, the *cis* intermediate **4ab** can be obtained through a solvent-assisted ligand substitution from **3a** (Figure 2b). From **4ab**, the metathesis takes place via the transition state **TSa_45b**. Interestingly, the metathesis from **4ab** does not give a transmetalation product that contains two *cis* vinyl ligands. Instead, a C−C coupling of the two vinyl ligands is directly resulted from the transition state **TSa_45b** to give the η^2 complex **5ab** with the coupling product diene as a π ligand (Figure 2b). In the process **4ab → 5ab** (Figure 2b), metathesis and reductive elimination proceed in one step. These results are understandable if we consider that the reductive elimination from a *cis* bis(vinyl)Cu(III) species is barrierless. From **5ab**, release of diene product CH$_2$=CH−CH=CH$_2$ gives **6ab**, from which substitution of the solvent ligand NMP for Me$_3$SnI regenerates the active complex (NMP)CuTC, **1a**.

In Figure 2a,b, **TSa_45a** is higher in energy than **TSa_45b** by 7.8 kcal/mol. To analyze the different stabilities between the two transition states, the structures calculated for **TSa_45a** and **TSa_45b** are presented in Figure 3 together with selected geometrical parameters (bond distances). In the two transition states, the vinyl−Sn bonds (2.142 Å in free CH$_2$=CHSnMe$_3$) are almost cleaved, having bond distances of 2.722 and 2.694 Å in **TSa_45a** and **TSa_45b**, respectively. The Cu−vinyl bonds in **TSa_45a** (1.931 and 2.000 Å) are longer than those in **TSa_45b** (1.905 and 1.924 Å). This is a result of the strong *trans* influence properties of the vinyl ligands, which in turn destabilizes the *trans* arrangement in **TSa_45a** when compared with the *cis* arrangement in **TSa_45b**.

Mechanism with (NMP)Cu-I as the Active Species. As we will see later, in the stoichiometric reactions studied in this paper, copper(I) iodide could be produced when the TC ligand in CuTC, instead of the iodide ligand derived from the oxidative addition of vinyl iodide substrate, forms the by-product R$_3$SnTC in the transmetalation process. Therefore, for the purpose of comparison, we also considered the possibility of having a mechanism with (NMP)Cu-I, **1i**, as

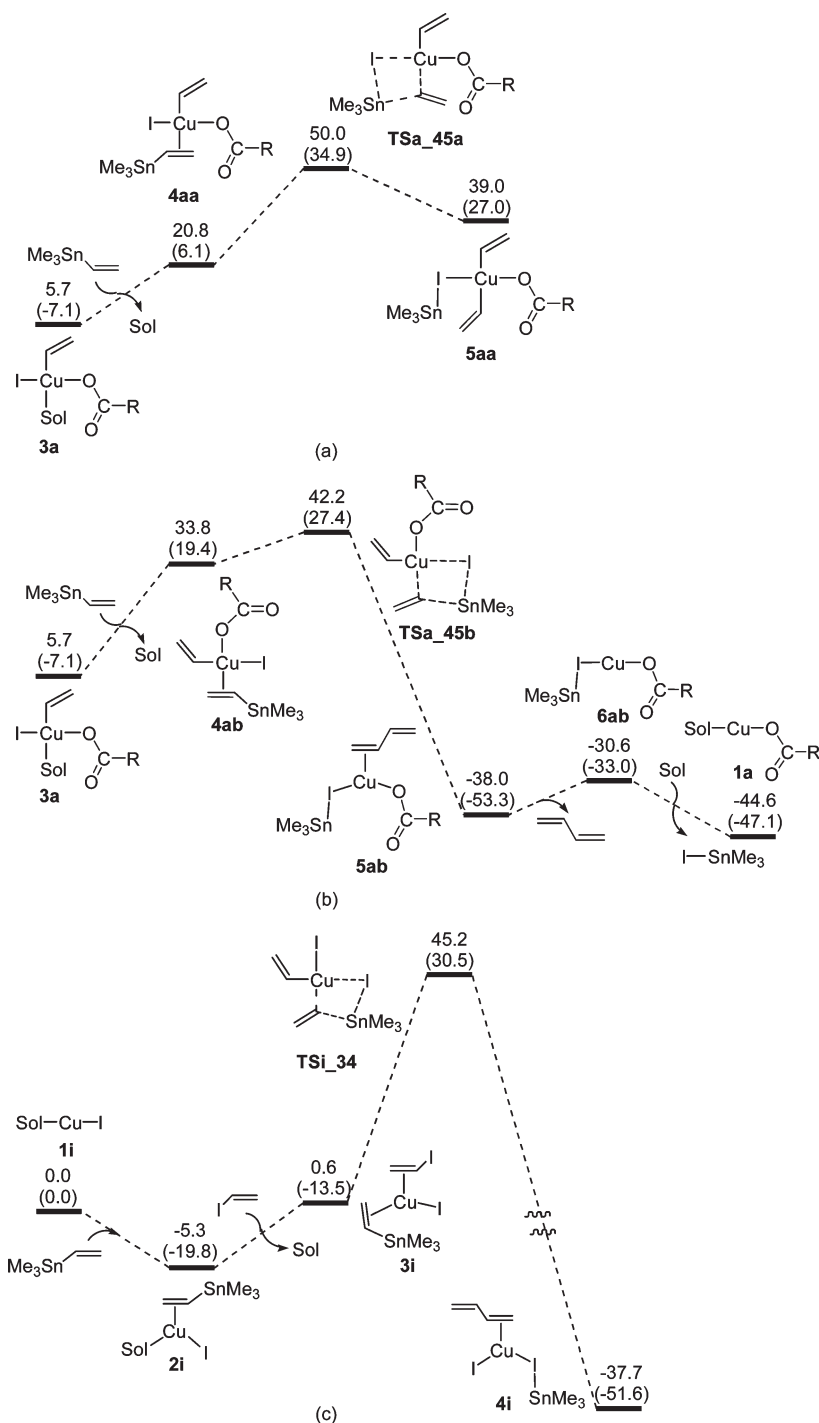(24) Braga, A. A. C.; Ujaque, G.; Maseras, F. *Organometallics* **2006**, *25*, 3647.

Figure 2. Energy profiles calculated for transmetalation from complex **3a** through metathesis between the Cu−I bond in **3a** and the vinyl−Sn bond in CH$_2$=CHSnMe$_3$ via the *trans* intermediate **4aa** (a), the *cis* intermediate **4ab** (b), and the reaction path mediated by the species (NMP)Cu-I, **1i** (c). The calculated relative free energies and electronic energies (in parentheses) are given in kcal/mol.

the active species. Figure 2c shows the calculated energy profile. This energy profile was obtained as follows. We took **TSa_45b** (Figure 2b) as our reference structure by replacing the TC ligand with an iodide ligand; the transition state **TSi_34** (Figure 2c) was then obtained. Interestingly, the intrinsic reaction coordinate calculations show that the transition state **TSi_34** connects the precursor complex **3i**, a Cu(I) complex containing both the vinylstannane CH$_2$=CHSnMe$_3$ and the vinyl iodide CH$_2$=CHI as the ligands, and **4i**, the complex having the coupling product diene as a ligand (Figure 2c). The CH$_2$=CHSnMe$_3$ coordinated complex similar to **4ab** but

replacing the TC ligand with the iodide ligand cannot be located, likely due to the instability of the relevant Cu(III) species. From the energy profile shown in Figure 2c, the complex **3i** can be derived from substitution of the vinyl iodide for the coordinated solvent NMP in **2i**, which was formed by a simple coordination of the vinylstannane CH$_2$=CHSnMe$_3$ to the active species (NMP)Cu-I, **1i**. **TSi_34** is the highest point in the potential energy profile, and **2i** is the lowest point. A free energy barrier of 50.5 kcal/mol is calculated. Clearly, (NMP)Cu-I cannot easily mediate the reaction considering the high reaction barrier. The structure calculated for **TSi_34** is
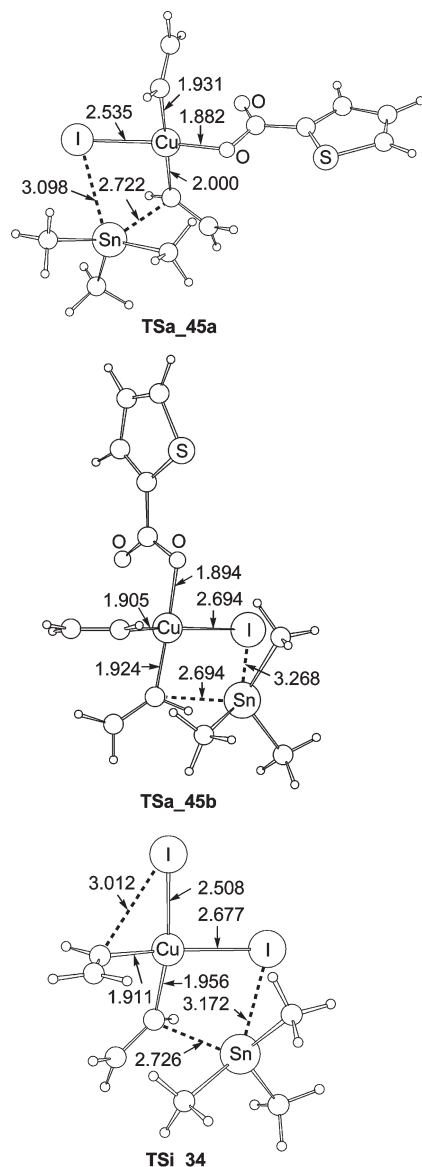
Figure 3. Structures calculated for the transmetalation transition states **TSa_45a**, **TSa_45b**, and **TSi_34**. Bond distances are given in Å.

also presented in Figure 3, whose geometrical parameters are similar to those in **TSa_45b**.

From Figures 1 and 2, we can clearly see that the three reaction paths discussed above have inaccessible barriers. Because of the inaccessible barriers, we did not spend the effort in locating the transition state structures for the substitution steps of the vinylstannane $CH_2=CHSnMe_3$ for the solvent ligand NMP in **3a** (Figure 2a,b) and that of $CH_2=CHI$ for NMP in **2i** (Figure 2c).

Mechanism with the TC Ligand Involved in the Metathesis. As shown in eq 1, 1.5 equiv of CuTC was used in the reactions. Therefore, we thought that metathesis might occur between the Cu−O(TC) bond in **3a** and the vinyl−Sn bond in $CH_2=CHSnMe_3$ to form the Sn−O(TC) bond. Figure 4a shows the potential energy profile calculated for this case. From the *trans* intermediate **4ac**, the metathesis takes place through a six-membered transition state, **TSa_45c**, to give complex **5ac**. The reductive elimination leading to the vinyl−vinyl coupling product again cannot occur from **5ac**,

an intermediate whose structure is similar to that in **5aa** (Figure 2a), because of the *trans* arrangement of the two vinyl ligands. Despite the *trans* arrangement that prevents the C−C coupling, the much higher stability of the related transision state **TSa_45c** with respect to **TSa_45a** and **TSa_45b** shown in Figure 2 suggests that involvement of the TC ligand promotes the metathesis step significantly. The structure calculated for **TSa_45c** is presented in Figure 5 together with selected bond distances. In **TSa_45c**, the vinyl−Sn bonds (2.142 Å in free $CH_2=CHSnMe_3$) are almost cleaved, having bond distance of 2.690 Å, similar to the cases in **TSa_45a** and **TSa_45b**, with bond distances of 2.722 and 2.694 Å (Figure 3), respectively. **TSa_45c** shows strong interaction between Sn and O with a Sn−O distance of 2.210 Å.

In view of the very strong interaction between Sn and O and the strong *trans* influence properties of vinyl ligands, we then consider a transition state having both a Sn−O interaction and a *cis* arrangement of the two vinyl ligands. We expect a much more stable transition state when compared with the isomeric transition states **TSa_45a**, **TSa_45b**, and **TSa_45c**. The transition state **TSa_45d** calculated and shown in Figure 4b possesses both the structural features and is indeed more stable by 9.1 kcal/mol than **TSa_45c** (Figure 4a).

The intrinsic reaction coordinate calculations show that the transition state **TSa_45d** connects the precursor complex **4ad**, a Cu(I) complex containing both the vinylstannane $CH_2=CHSnMe_3$ and the vinyl iodide $CH_2=CHI$ as the ligands, and **5ad**, the complex having the coupling product diene as a ligand (Figure 4b). The $CH_2=CHSnMe_3$ coordinated complex similar to **4ac** but having the iodide and vinyl ligands switched cannot be located. The reaction pathways shown in Figures 4b and 2c are similar. Coordination of $CH_2=CHSnMe_3$ to (NMP)CuTC (**1a**) generates the η^2 complex **3ad**, and ligand substitution gives the coordinated complex **4ad**, having both $CH_2=CHI$ and $CH_2=CHSnMe_3$ as ligands. From **4ad**, metathesis takes place via **TSa_45d**, generating the coordinated complex **5ad** with diene as a ligand. From **5ad**, release of the diene product $CH_2=CH−CH=CH_2$ gives **6ad**, from which substitution of the solvent ligand NMP for Me_3SnTC generates the complex (NMP)Cu-I, **1i**. Assuming that a stoichiometric amount of free TC ligand in the form of NaTC was provided, one could regenerate the active species (NMP)CuTC (**1a**) via substitution of the TC ligand for the iodide ligand.

For the reaction path shown in Figure 4b, **TSa_45d** corresponds to the highest point in the potential energy profile and **3ad** is the lowest point. Therefore, a free energy barrier of 35.2 kcal/mol is calculated. The structure calculated for **TSa_45d** is presented in Figure 5 together with selected bond distances. The relatively long Sn−O distance (2.440 Å) and the relatively short vinyl−Sn distance (2.257 Å) in the transition-state structure indicate that **TSa_45d** is an early transition state, making this reaction path a relatively favorable one among the four paths discussed above.

The Most Favorable Mechanism. As discussed above, the transition state **TSa_45d** is relatively favorable for transmetalation (Figure 4b) because it has a relative orientation of the Sn and O atoms to form the strong Sn−O bond and a *cis* arrangement of the two strong *trans* influence vinyl ligands, both of which stabilize the relevant transition-state structures. We can envision an alternative pathway in which the sequential transition-state structures possess a relative
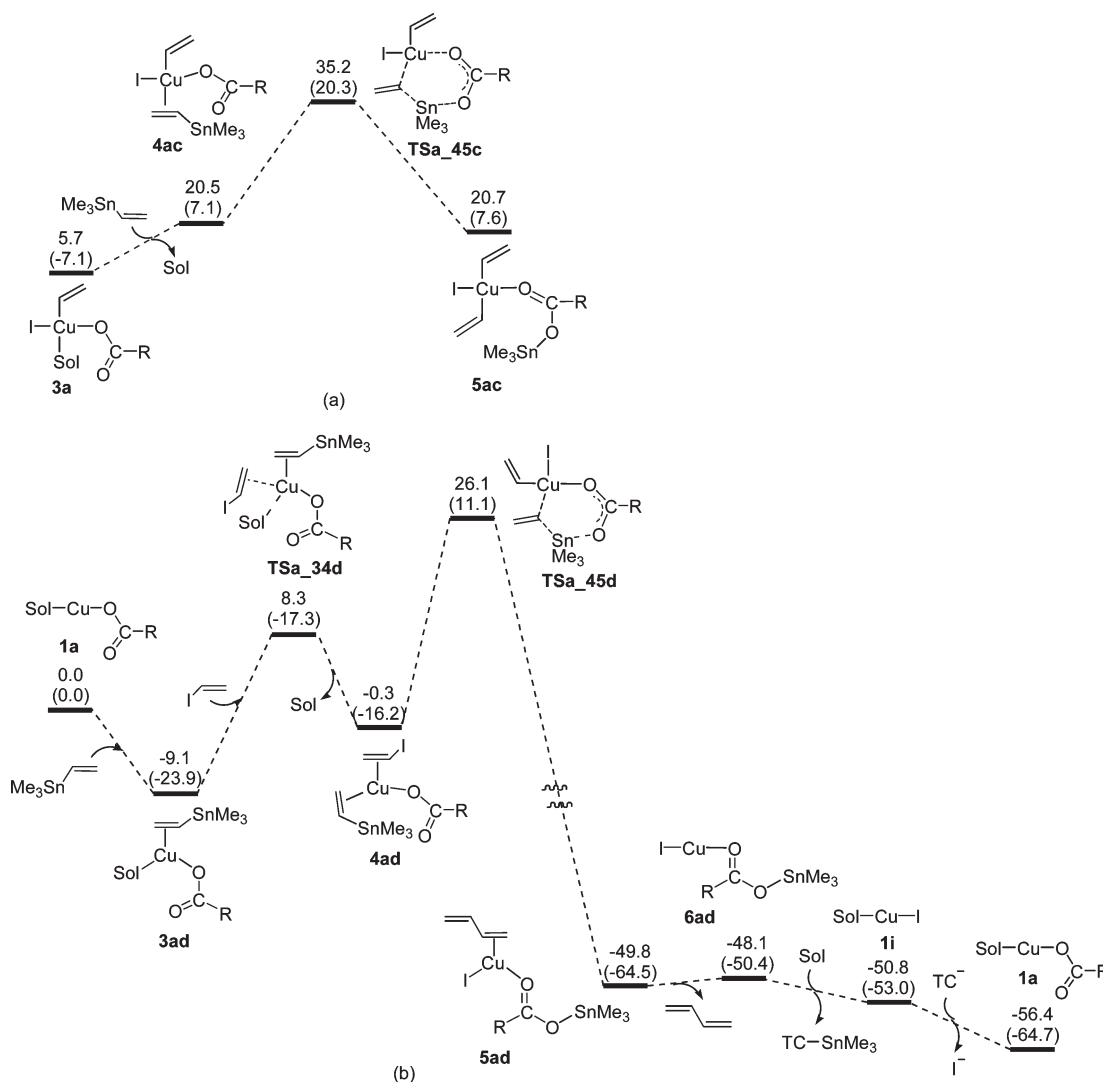
Figure 4. Energy profiles calculated for transmetalation through the transition states **TSa_45c** (a) and **TSa_45d** (b). The substitution of the TC ligand for the iodide ligand in the last step is given by assuming that a stoichiometric amount of free TC ligand is present. The calculated relative free energies and electronic energies (in parentheses) are given in kcal/mol.

orientation to form the strong Sn−O bond and a *cis* arrangement of the two vinyl ligands, respectively. Figure 6 shows the energy profile for such an alternative pathway.

From **3ad**, transmetalation occurs through metathesis between the Cu−O(TC) bond and the vinyl−Sn bond via the transition state **TS_a** to give the copper(I) vinyl complex (NMP)Cu-CH=CH$_2$ (**7**) by releasing Me$_3$SnTC. Then, a one-step process involving oxidative addition of CH$_2$=CHI followed by reductive elimination takes place via transition state **TS_89** to give **9**, having the diene product as a ligand. From **9**, release of the diene product CH$_2$=CH-CH=CH$_2$ gives **1i**, from which the ligand substitution would regenerate the active species **1a** if we again assume that a stoichiometric amount of free TC ligand was provided. **TS_89** is the highest point in the potential energy profile, and **3ad** is the lowest point. The overall free energy barrier calculated for this reaction pathway is 30.0 kcal/mol, 5.2 kcal/mol lower than that (35.2 kcal/mol) corresponding to the reaction path through **TSa_45d** (Figure 4b). In other words, the reaction path **1a → 3ad → 7 → 8 → 9 → 1i → 1a** (Figure 6) is much more favorable when compared with **1a → 3ad → 4ad → 5ad → 6ad → 1i → 1a** (Figure 4b).

The structures calculated for **TS_a** and **TS_89** are presented in Figure 7 together with selected bond distances. In **TS_a**, the Sn−O and Cu−Sn distances are relatively long (3.746 Å) and short (2.704 Å), respectively, when compared with those in **TSa_45d**, indicating that the transmetalation step through **TS_a** occurs via a one-step process involving oxidative addition of CH$_2$=CHSnMe$_3$ to the Cu center to cleave the vinyl−Sn bond followed by an immediate migration of the SnMe$_3$ group to one O atom of the TC ligand to form the strong Sn−O bond. The complex **7** is higher in energy than **3ad**, suggesting that **3ad → TS_a → 7** is reversible, consistent with an early proposal that transmetalation is reversible.[4] In a reported Cu(I)-catalyzed Stille cross-coupling reactions of (*E*)-2,3-difluoro-3-stannylacrylic ester with acid chlorides, an organocopper complex was observed spectroscopically, which was derived from a direct transmetalation between the organostannane reagent and CuI.[25] The observation of the organocopper intermediate provides experimental support to the mechanistic possibility

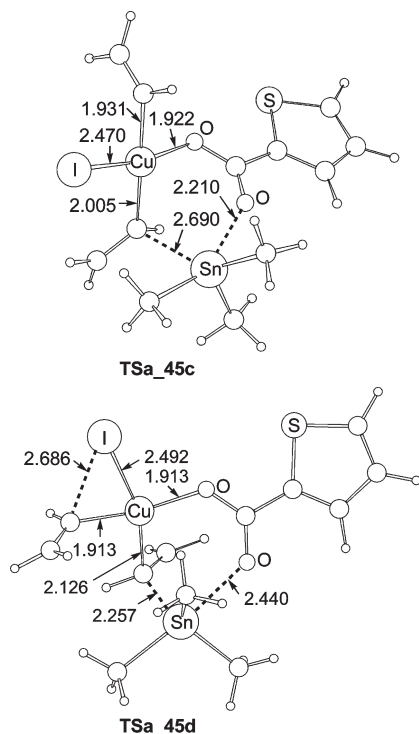(25) Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 1109.

Figure 5. Structures calculated for the transmetalation transition states **TSa_45c** and **TSa_45d**. Bond distances are given in Å.

of having transmetalation as the first step in the reaction process.

Scheme 2 summarizes the reaction mechanism for the CuTC-mediated Stille cross-coupling of vinylstannane with vinyl iodide. The first step is the transmetalation between (NMP)CuTC (**1a**) and R′-SnMe$_3$, forming the organocopper intermediate (NMP)Cu-vinyl (**7**). The second step is a one-step process involving both the oxidative addition of vinyl-I to (NMP)Cu-vinyl and the reductive elimination of the coupling product, giving (NMP)Cu-I, **1i**. The overall barrier for the coupling reaction involves the effect of both the first and second steps. A catalytic cycle can be completed when the TC ligand, if present in a stoichiometric amount, substitutes the iodide ligand in **1i** to regenerate the active species **1a**. These results show that the stoichiometric amount of CuTC used in the reactions studied here could be replaced by a catalytic amount of the copper(I) source and a stoichiometric amount of the TC ligand. Indeed, as reported by Liebeskind and his co-workers, in some cases, the cross-coupling could also be effected with catalytic quantities of Cu(I) salts in the presence of stoichiometric carboxylate salts.[4] Another tiny shred of evidence, although not exactly the same, in support of this conclusion can also be found from the reported cross-coupling of (alkenyl)SnBu$_3$ with alkenyl/aryl iodides in which a catalytic amount of CuI (10 mol %) and a stoichiometric amount of sodium chloride additive are employed.[26] These reactions were carried out at 100−120 °C with a reaction time of 10−16 h. The elevated temperature and prolonged reaction time are consistent with the relatively high overall reaction barrier (30.0 kcal/mol) and the low concentration of the copper(I) source (catalytic amount).

(26) (a) Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* **1997**, *62*, 4208. (b) Kang, S.-K.; Kim, J.-S.; Yoon, S.-K.; Lim, K.-H.; Yoon, S. S. *Tetrahedron Lett.* **1998**, *39*, 3011.

Comments on the Role of the TC Ligand. The role of the TC ligand is apparently related to its involvement in the transmetalation step **3ad** → **7** (Figure 6). The high stability of the byproduct Me$_3$SnTC due to the strong Sn−O interaction promotes the transmetalation process significantly. In an early study on the mechanism of Pd-catalyzed, Cu(I) carboxylate-mediated thioorganic−boronic acid desulfitative coupling reactions, the carboxylate ligand has been found to play a similar role in the transmetalation step, leading to the formation of a B−O bond.[17] Similarly, in the CuOP(O)Ph$_2$-mediated palladium-catalyzed coupling reaction of thiol esters with organostannanes,[27] Bu$_3$SnOP(O)Ph$_2$ with a strong Sn−O bond was formed.

Comments on the Oxidation State of the Cu Center. Throughout the study, we found that there are many one-step processes in which the transition states involve oxidative addition and reductive elimination simultaneously. For example, the transition state **TSa_45d** (Figure 4b) involves the oxidative addition of the vinyl iodide substrate followed by the reductive elimination of the coupling product. The transition state **TS_89** (Figure 6) also shows a similar structural feature. **TS_a** (Figure 6) is a transition state for the transmetalation between (NMP)CuTC and the vinylstannane CH$_2$=CHSnMe$_3$, which also involves a one-step process of oxidative addition of the vinylstannane followed by reductive elimination of Me$_3$SnTC. When two vinyl ligands are *cis* to each other, the corresponding bis(vinyl)Cu-(III) intermediates are not local minima in the potential energy surface, indicating the instability of a Cu(III) species. In contrast, the theoretical study of Cu(I)-catalyzed C−N coupling between aryl halides and amides showed that a pentacoordinated Cu(III) intermediate with NHAc, NH$_2$CH$_2$CH$_2$NH$_2$, Br, and phenyl as ligands is a local minimum.[13] An allyl-Cu(III) intermediate was also located as a local minimum in the mechanistic study of the Kharasch−Sosnovsky reaction.[14] The instability of the bis(vinyl)Cu(III) intermediates studied here can be related to the following two factors. (1) Reductive elimination involving coupling of sp^2 carbons is normally much easier than that involving sp^3 carbons because of the involvement of π electrons (orbitals) during the C−C coupling.[12] (2) A Cu(III) metal center is relatively unstable. This is quite different from other metal centers. For example, a recent computational study on the vinyl−vinyl coupling at other late transition metals showed that the relevant intermediates having Pd(IV), Pd(II), Pt(IV), Pt(II), Rh(III), Ir(III), Ru(II), and Os(II) centers were found to be local minima.[28]

Conclusions

The detailed reaction mechanism for the CuTC-mediated Stille cross-coupling of vinylstannane and vinyl iodide has been investigated with the aid of DFT calculations. The computational results show that the reaction occurs through (1) the transmetalation between (NMP)CuTC and CH$_2$=CHSnMe$_3$ to give the organocopper intermediate (NMP)Cu-CH=CH$_2$ and (2) a one-step process involving oxidative addition of vinyl iodide to (NMP)Cu-CH=CH$_2$ and reductive elimination of the coupling product. Our

(27) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033.
(28) Ananikov, V. P.; Musaev, D. G.; Morokuma, K. *J. Am. Chem. Soc.* **2002**, *124*, 2839.
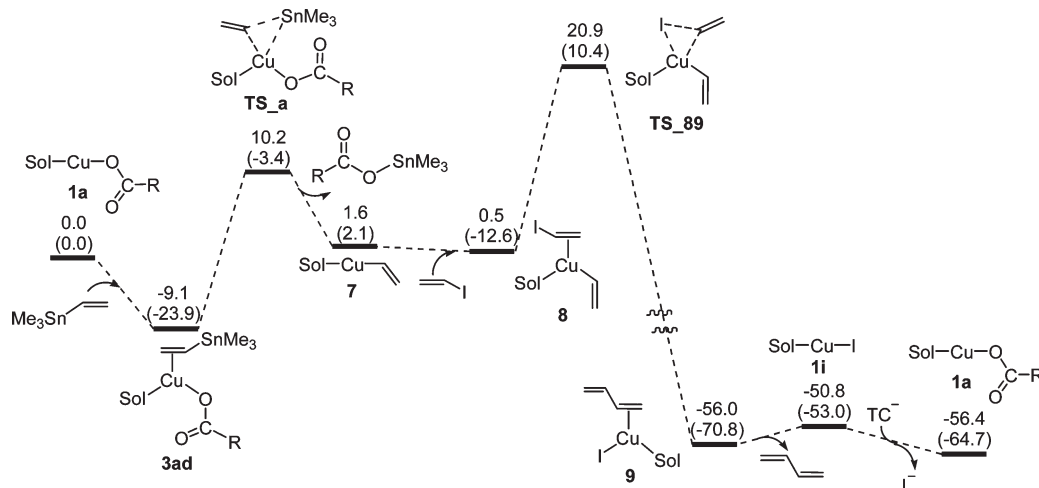
Figure 6. Energy profile calculated for the favorable mechanism involving transmetalation as the first step. The substitution of the TC ligand for the iodide ligand in the last step is given by assuming that a stoichiometric amount of free TC ligand is present. The calculated relative free energies and electronic energies (in parentheses) are given in kcal/mol.
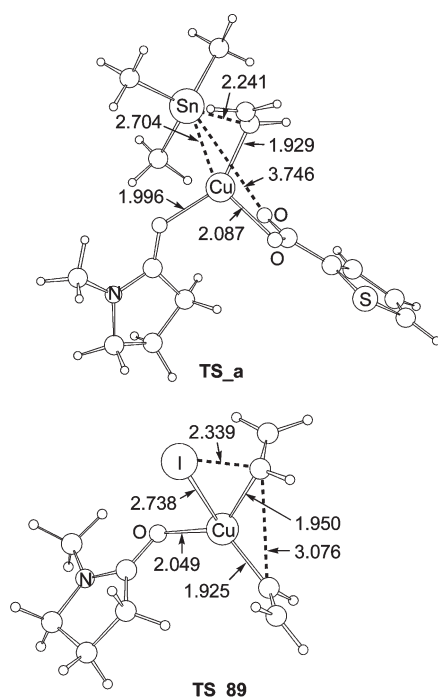

Figure 7. Structures calculated for the transition states **TS_a** and **TS_89**. Bond distances are given in Å.

calculations show that regeneration of the active species (NMP)CuTC via a ligand substitution is favorable when a stoichiometric amount of free TC ligand is given, suggesting that a process using a catalytic amount of copper(I) source together with a stoichiometric amount of free TC ligand is possible. However, such a catalytic process is expected to require elevated temperature and prolonged reaction time because of low concentration of the Cu(I) species (catalytic amount) and the high overall barrier of 30.0 kcal/mol involving the effect of the two important steps.

Scheme 2
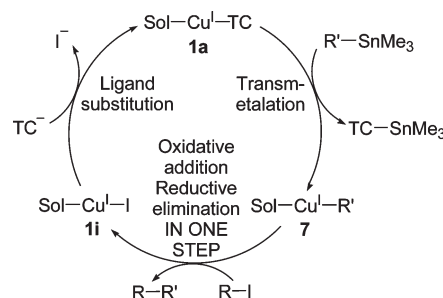
The role of the TC ligand is significant in the transmetalation step. The very stable byproduct Me_3SnTC, which has a strong $Sn-O$ bond, promotes the transmetalation. Throughout the study, we found that there are several one-step processes in which the transition states involve oxidative addition and reductive elimination simultaneously. This is because the bis(vinyl)Cu(III) intermediates are relatively unstable, a result that can be related to the easier reductive elimination involving coupling of sp^2 carbons as well as the instability of the Cu(III) metal center.

A final note on this study is that the mechanism for the Cu-mediated Stille coupling reaction is very different from that of the traditional Pd-mediated/catalyzed Stille coupling reaction, which normally involves three fundamental steps: oxidative addition, transmetalation, and reductive elimination.