# A Computational Investigation of the Ligand-Controlled Cu-Catalyzed Site-Selective Propargylation and Allenylation of Carbonyl Compounds

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Ⓢ *Supporting Information*
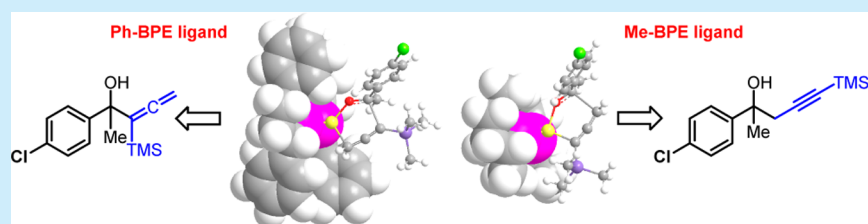
ABSTRACT: A copper-catalyzed site-selective propargylation/allenylation reaction toward carbonyl compounds has been mechanistically investigated using a computational approach. Different reaction pathways and catalytic cycles were investigated. Control of the site selectivity arises from a destabilizing interaction introduced by the phenyl-substituted ligand.

The addition of organometallic reagents to ketones and aldehydes is a highly useful synthetic method for the construction of carbon−carbon bonds.[1] The corresponding propargylation[2] and allenylation[3] reactions have attracted considerable attention, as the functionality in the resulting allenyl and propargyl carbinols is useful for further structural modification.[4] To meet demand, various methods for the direct allenylation of carbonyl compounds have been reported, including those based on B,[5] Al,[6] Si,[7] Cr,[8] Zn,[9] and other Lewis acids[10] with propargyl species. In addition, several systems for the site-selective propargylation of carbonyl systems have been reported.[11] We have shown site-selective propargylation/allenylation of aldehydes[12] and ketones[13] commencing from TMS-propargyl boronates mediated by copper−bis(phosphine) complexes (Figure 1). Herein we describe a detailed study to understand the site selectivity of the propargylation and allenylation processes using DFT calculations, which have pinpointed the competing interactions of this useful transformation.
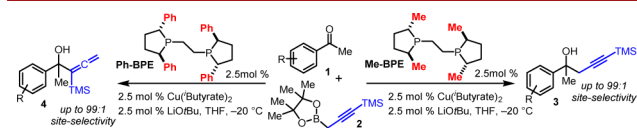
These systems presumably react through Cu−boron exchange (Figure 2) to generate the intermediate allenyl cuprate species **8**, which is then amenable to the propargylation of carbonyl compounds **9**.[14] It has been proposed that the metallic−propargyl/allenyl active intermediates are then dictated by the relative stability of the respective allenyl- or propargylmetal species (e.g., **7** or **8**).[15] Knochel[16] and others[17] have reported that the regioselectivity can be controlled by the substitution pattern
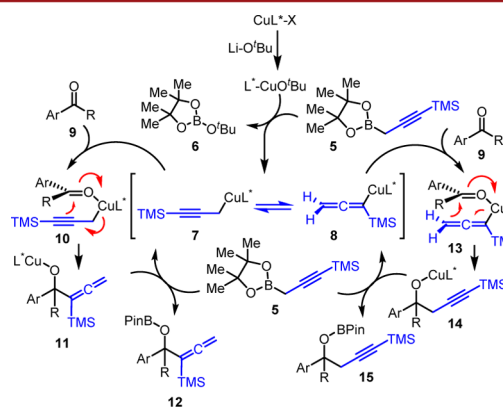

Figure 2. Proposed catalytic cycle for the ligand-controlled Cu-catalyzed allenylation/propargylation.

Figure 1. Cu−BPE ligand-controlled site-selective allenylation and propargylation of carbonyl compounds.

on the propargyl/allenyl unit. We have shown that the site selectivity can be controlled completely by modulating the groups of the 1,2-bis(2,5-dimethylphospholano)ethane (Me-BPE) ligand scaffold (Figure 1).[18] For example, high site selectivity is obtained for the propargyl adducts (e.g., **3**) when the less sterically demanding Me-BPE ligand is employed, and this site selectivity is completely inverted with the more sterically crowded Ph-BPE ligand. Furthermore, we showed that a combination of both a sterically demanding ligand (Ph-BPE) and a large substituent on the propargyl unit leads to the allenyl adducts (e.g., **4**). This observation implies that the equilibrium of the allenyl- or propargylcopper species can also be altered by changing the ligand. Hoveyda subsequently showed computationally[19] that the intermediate propargyl or allenyl Cu−NHC complex can undergo a η^1-allyl to η^3-allyl isomerization promoting the equilibrium of the two species. However, a systematic computational study of this transformation has not been performed. Herein we report a computational study[20] of the entire reaction cycle of the site-selective propargylation and allenylation employing the Cu−BPE catalytic system. The proposed reaction pathway can be divided into three main parts: (a) the Cu to boronate transmetalation process, (b) the Cu isomerization process, and (c) the carbonyl addition process (Figure 3). Alternate pathways for each of the unit operations are also investigated.
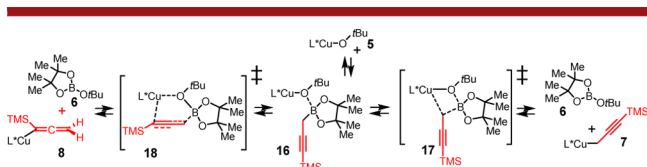

Figure 3. Proposed pathways for the Cu−B exchange with BPE ligands and propargylboronates.

The copper to boronate exchange is a fundamental step of the copper-mediated allenylation/propargylation process. It has been shown that either a copper(I) fluoride[14] or copper(I) alkoxide[12,13,18] precatalyst is required for the chemistry, which has been proposed to facilitate the Cu to B transfer via precomplexation to the Lewis acid−boronate reagent (Figure 3). The complexed boronate−Cu species **16** can then transfer the boronate directly or via an inversion cyclic mechanism with the π system. Considering that each unit operation is in equilibrium, the combination of both pathways, if energetically feasible, would also offer a means for the Cu−propargyl (**7**) to Cu−allenyl (**8**) equilibrium (via reversible Cu−B transfers).

Targeting the first stage, the Cu−propargyl to Cu−allenyl equilibration, which has been the founding premise of site-selective allenylation processes described by us and others,[15] is known to occur at low reaction temperatures (−20 °C)[18] and is hypothesized to occur rapidly. Hoveyda proposed a "slippage" model based on NHC ligands[19] in which the Cu−propargyl species can directly isomerize with the open valence on the copper species via an intermediate η^3 transition state. The way phosphine ligands would affect this process and the stability of the resulting equilibrium species have not been investigated prior to this computational study. The Cu−B transfer could proceed via two different pathways (Figure 4). In the first pathway, complexation of the cuprate (**INT1**) is largely enthalpically favored and slightly endergonic because of the steric congestion from the pinacol boronate substituents, the *tert*-butoxide groups, and the substituent groups on the BPE ligands. Direct Cu−B
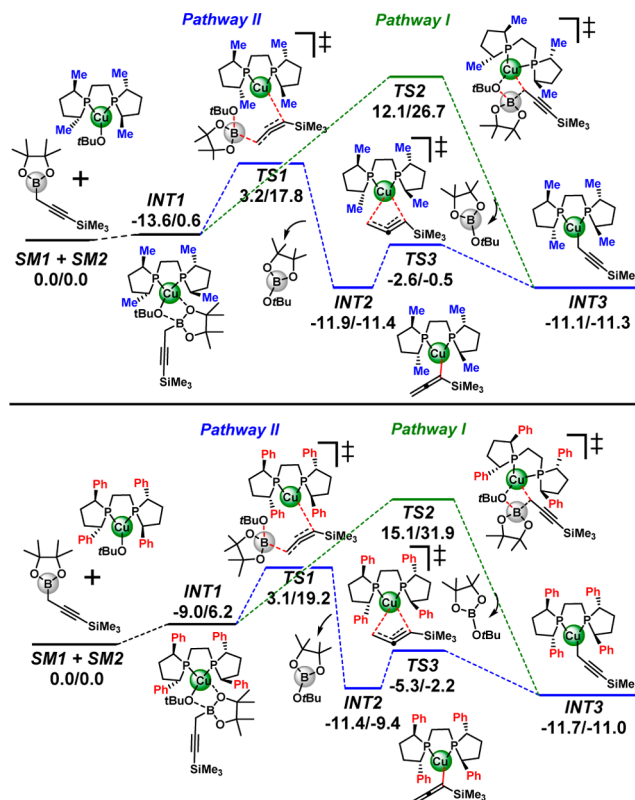

Figure 4. Reaction coordinates for two transmetalation pathways with the (top) Me-BPE and (bottom) Ph-BPE ligands. Relative enthalpy/Gibbs free energy values (in kcal/mol) were calculated at the B3LYP/LANL2DZ/PCM(THF) level with thermal corrections to 253 K.

transfer (**TS2** in pathway I, shown in green) led to significant increases in both enthalpy (12.1 kcal/mol for the Me-BPE ligand and 15.1 kcal/mol for the Ph-BPE ligand) and Gibbs free energy (26.7 kcal/mol for the Me-BPE ligand and 31.9 kcal/mol for the Ph-BPE ligand), which then resulted in low-energy propargyl cuprate intermediate **INT3**. The alternative pathway (pathway II, shown in blue in Figure 4) via addition of the copper to the π system of the propargyl boronate (**TS1**) is energetically favored over the direct Cu−B transfer by 8.9 and 12.7 kcal/mol in Gibbs free energy for the Me-BPE and Ph-BPE ligands, respectively. In both cases, the resulting allenyl cuprate (**INT2**) is in rapid equilibration with the propargyl cuprate (**INT3**) via a low barrier the η^3 transition state (**TS3**).

Having elucidated the initial Cu−B exchange pathway, we then focused on computing the barriers for the cuprate addition to the carbonyl. A systematic computational study was carried out that started with direct addition of the allenyl cuprate (**INT2**) to the carbonyl (Figure 5). This transformation (pathway I, shown in green in Figure 5) entailed the high-energy four-membered transition state **TS7** (31.4 kcal/mol for the Me-BPE ligand and 33.0 kcal/mol for the Ph-BPE ligand, due to steric congestion from the TMS group and the substituents on the BPE ligands) that eventually led to the allenyl boronate product **P1** after Cu−B exchange. In contrast, pathway II (shown in blue in Figure 5) proceeded via the six-membered cyclic transition state **TS6** with significantly lower Gibbs free energy barriers (16.3 kcal/mol for the Me-BPE ligand and 17.0 kcal/mol for the Ph-BPE ligand) that instead resulted in propargyl boronate product **P2**. Likewise, starting with the propargyl cuprate (**INT3**), the six-membered transition state (**TS4**) is largely favored over the four-membered
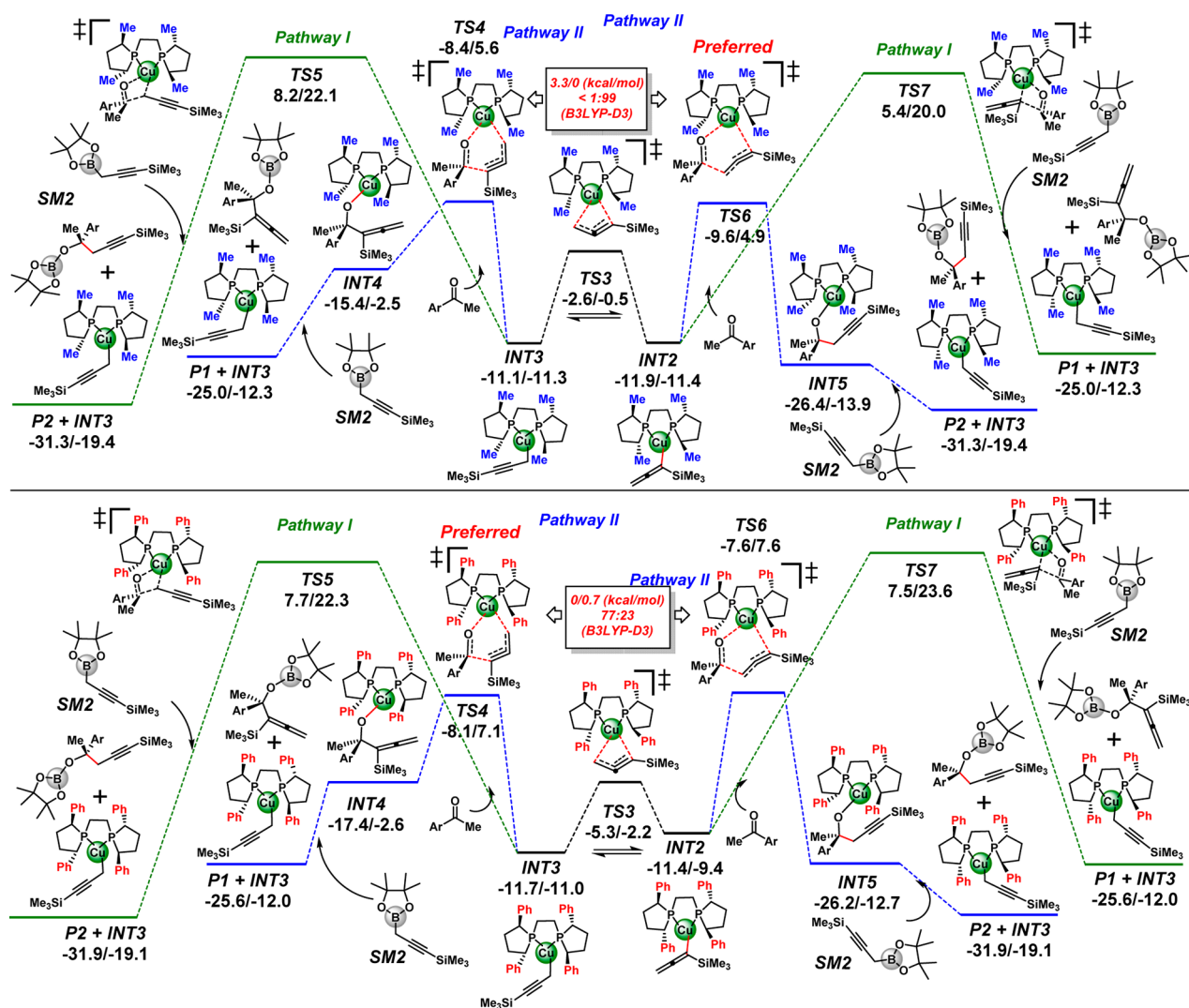
Figure 5. Reaction coordinates for two addition pathways with the (top) Me-BPE and (bottom) Ph-BPE ligands. Relative enthalpy/Gibbs free energy values (in kcal/mol) were calculated at the B3LYP/LANL2DZ/PCM(THF) level with thermal corrections to 253 K. Ar = 4-chlorophenyl.

transition state (**TS5**) by 16.5 kcal/mol for the Me-BPE ligand and 15.2 kcal/mol for the Ph-BPE ligand and results in allenyl boronate product **P1**. In regard to the energy barriers, both addition steps to the carbonyl are under kinetic control at low temperature (−20 °C). The entire reaction pathways reveal a process that is downhill overall. The propargyl cuprate species **INT3** is finally regenerated in position for a subsequent boronate transfer, thus completing the catalytic cycle.

To address our central question, namely, the origin of the experimentally observed site selectivity, we focused on **TS4** and **TS6**. Additional calculations were conducted for these two key transition states using the dispersion-corrected B3LYP-D3 method on each low-energy conformation (see the Supporting Information). From comparison of the energy differences of **TS4** and **TS6** that would determine the site selectivity, the calculated data for the Me-BPE case show excellent agreement (<1:99) with the experimentally observed site selectivity (1:99). For the Ph-BPE case, the calculated site selectivity (77:23) is not as high as the experimental value (94:6), and this difference might result from multiple rotamers from the phenyl substitutions on the BPE ligand, which complicated the computational investigation. In fact, the experimentally observed site selectivity fluctuates from 83:17 to 99:1 and is sensitive to various factors such as reaction

temperature and substrate.[18] Nevertheless, **TS-4**, leading to the experimentally observed product **P1**, was energetically preferred (Figure 5, bottom blue).

The computational models of **Me-** and **Ph-TS4** and **Me-** and **Ph-TS6** indicate mainly two destabilizing interactions involving the bulky TMS group with (1) the aryl group of the ketone segment and (2) the phenyl substituents of the Ph-BPE ligand (Figure 6). The first destabilizing interaction is observed in both **Me-** and **Ph-TS4** species. To avoid this interaction, **Me-TS6** is thereby preferred, leading to the propargyl product **3**. However, this preference is overturned by the second destabilizing interaction, which is observed only in **Ph-TS6**. **Ph-TS4** thus becomes *less disfavored*, leading to the allenyl product **4** instead. This model would explain another observation, namely, that the unsubstituted allenyl- or propargylboronate (with H in the place of the TMS group) reagent favors the propargyl carbonyl adducts (i.e., **3**) in the presence of the Ph-BPE ligand.[18] In this case, because of the lack of the second interaction due to the absence of the TMS group, the system provides the propargyl adduct with high selectivity, i.e., **Ph-TS6**. Furthermore, this model would also explain why the *i*Pr-BPE ligand favors the propargyl adduct (i.e., **3**), but to a lesser degree (43:1) compared with Me-BPE (99:1).[18] This may result from the existence of the second
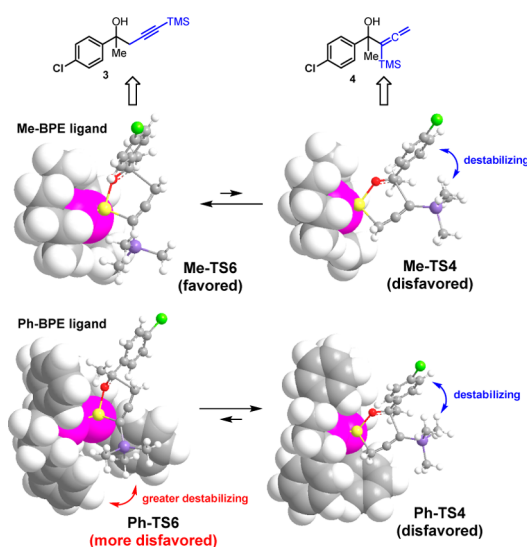
Figure 6. Models of the two key transitions states **TS4** and **TS6** indicating the two main destabilizing interactions.

interaction in which the bulkier ^{i}Pr groups experience repulsion by the TMS group, in a lesser but similar fashion to **Ph-TS6**, to reduce the degree of site selectivity. It is therefore the steric interaction between the substituents on the BPE ligand and a bulky group such as TMS on the substrate that determines the site selectivity.

In conclusion, multiple alternate pathways for the Cu−BPE catalytic cycle have been explored. The lowest-energy pathway for the Cu−BPE system involves a mechanism where the propargyl/allenyl fragment is initially inverted during the Cu−B transfer and inverted again during the carbonyl addition. The key question of the origin of the site selectivity has been elucidated as controlled by the destabilizing interaction between the phenyl substituents on the ligand and the substrates.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02845.

Full computational details and complete ref 20 (PDF)

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Notes

The authors declare no competing financial interest.

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