

The Mechanism of Copper-Catalyzed Trifunctionalization of Terminal Allenes

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ABSTRACT

A highly selective copper-catalyzed trifunctionalization of allenes has been established based on diborylation/cyanation with *bis*(pinacolato)diboron (B₂pin₂) and *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS). The Cu-catalyzed trifunctionalization of terminal allenes is composed of three catalytic reactions (1st borocupration, electrophilic cyanation and 2nd borocupration) that provide a densely functionalized product with regio-, chemo- and diastereoselectivity. Allene substrates have multiple reaction-sites, and the selectivities are determined by the suitable interactions (e.g. electronic and steric demands) between the catalyst and substrates. We employed density functional theory (DFT) calculations to understand the cascade copper-catalyzed trifunctionalization of terminal allenes, providing densely-functionalized organic molecules with outstanding regio-, chemo- and diastereoselectivity in high yields. Systematic computational studies for the high selectivity levels seen give insight into the design of catalytic multiple-functionalization strategies that address the selectivity challenges presented by cumulated π -systems.

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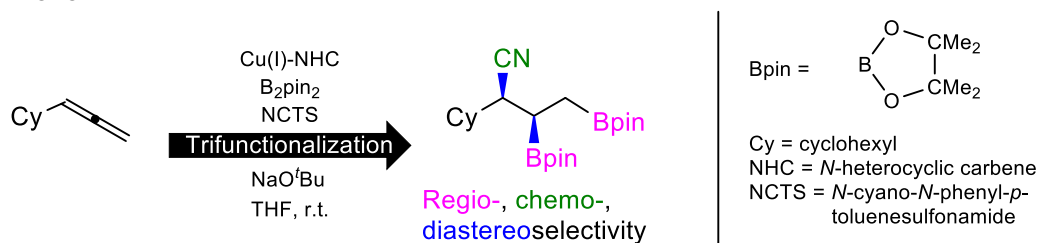
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INTRODUCTION

Transition-metal-catalyzed functionalization of boron-containing σ -bonds to carbon–carbon multiple bonds is an effective strategy for the formation of densely functionalized organic molecules.^[1] In particular, transition-metal boryl complexes play a key role in a range of borylation reactions such as C–H borylation, hydroboration, diboration, and other B–X addition reactions on unsaturated organic substrates.^[1f,2] More specifically, allene substrates have been investigated previously, motivated by the variety of structural motifs and functional value that allenes present for access to natural products, pharmaceuticals, and organic materials.^[2e,2f,3] Trifunctionalization processes have the potential to provide practical and powerful solutions for accessing valuable organic molecules with intriguing selectivities and high yields,^[1b–e,4] but the strategy remains underdeveloped compared to other reaction types that show similar versatility. Recently, Ma and Ito reported the borocupration reaction of allenes with B_2pin_2 based on both experimental and theoretical studies.^[5] Furthermore, although the borometallation processes of substrates that possess two or more unsaturations have considerable potential in this regard, but their application in trifunctionalization processes has seen very limited exploration.

Recently, one of us reported that a copper-catalyzed cascade trifunctionalization of terminal allenes derived from diborylation and cyanation provides a method to efficiently synthesize functionalized products with high degrees of regio-, chemo- and diastereoselectivity, as depicted in **Scheme 1**.^[6] Based on our previous experimental study, a putative mechanism was proposed to involve a series of diborylation and cyanation on the π -systems of the allene substrates. Most importantly, we were able to isolate an alkenyl intermediate, which is proposed to give the trifunctionalized final product. Whereas the overall sequence of the reaction appears to be clear, many important details remain poorly understood. For example, it is not at all clear which features govern the various selectivities that have been observed and that make these reactions synthetically attractive.

Scheme 1. Cascade Copper-Catalyzed Trifunctionalization Process: A Triple-Selective Functionalization of Cyclohexyl Allene.



In this study, we employed density functional theory (DFT) calculations to understand the mechanism for the copper-catalyzed trifunctionalization of cyclohexyl allene in detail. The aim of this study is to explain the observed triple-selectivities as shown in **Scheme 1** and to construct a complete mechanistic framework that will offer mechanistic details to expedite the rational design of the next generation of new catalytic reactions.

COMPUTATIONAL METHODS

All calculations were performed using density functional theory^[7] (DFT) as implemented in the Jaguar 9.1 suite^[8] of ab initio quantum chemistry programs. Geometry optimizations to the stationary points as well as the transition state (TS) optimization to the saddle points were performed the B3LYP^[9] hybrid exchange and correlation functional including Grimme's D3 dispersion correction.^[10] The 6-31G** basis set^[11] was used for all atoms except for copper, which was represented by the Los Alamos LACVP** basis set^[12] including effective core potentials. The

energies of the optimized structures were reevaluated by single-point calculations on each optimized geometry using Dunning's correlation consistent triple- ζ basis set cc-pVTZ(-f)^[13] that includes a double set of polarization functions. Copper were represented using a triple- ζ version of LACVP**, where the exponent of the basis functions were decontracted to mimic the flexibility of the triple- ζ basis. Analytical vibrational frequencies within the harmonic oscillator approximation were computed with the B3LYP-D3/6-31G** level to confirm proper convergence to well-defined minima and saddle points on the potential energy surface. Solvation energies were evaluated by a self-consistent reaction field (SCRF) approach based on accurate numerical solutions of the Poisson–Boltzmann equation.^[14] These solvation calculations were carried out with the B3LYP-D3/6-31G** level at the optimized gas-phase geometry employing the dielectric constant of $\epsilon = 7.6$ for tetrahydrofuran (THF). As is the case for all continuum models, the solvation energies are subject to empirical parametrization of the atomic radii that are used to generate the solute surface. We employed the standard set of optimized radii in Jaguar for H (1.150 Å), B (2.042 Å), C (1.900 Å), N (1.600 Å), O (1.600 Å), Na (1.491 Å), S (2.070 Å), Cl (1.974 Å) and Cu (1.748 Å).^[15] The free energy in solution-phase $G(\text{sol})$ has been calculated as follows:

$$G(\text{sol}) = G(\text{gas}) + \Delta G(\text{solv}) \quad (1)$$

$$G(\text{gas}) = H(\text{gas}) - TS(\text{gas}) \quad (2)$$

$$H(\text{gas}) = E(\text{SCF}) + \text{ZPE} \quad (3)$$

$$\Delta E(\text{SCF}) = \sum E(\text{SCF}) \text{ for products} - \sum E(\text{SCF}) \text{ for reactants} \quad (4)$$

$$\Delta G(\text{sol}) = \sum G(\text{sol}) \text{ for products} - \sum G(\text{sol}) \text{ for reactants} \quad (5)$$

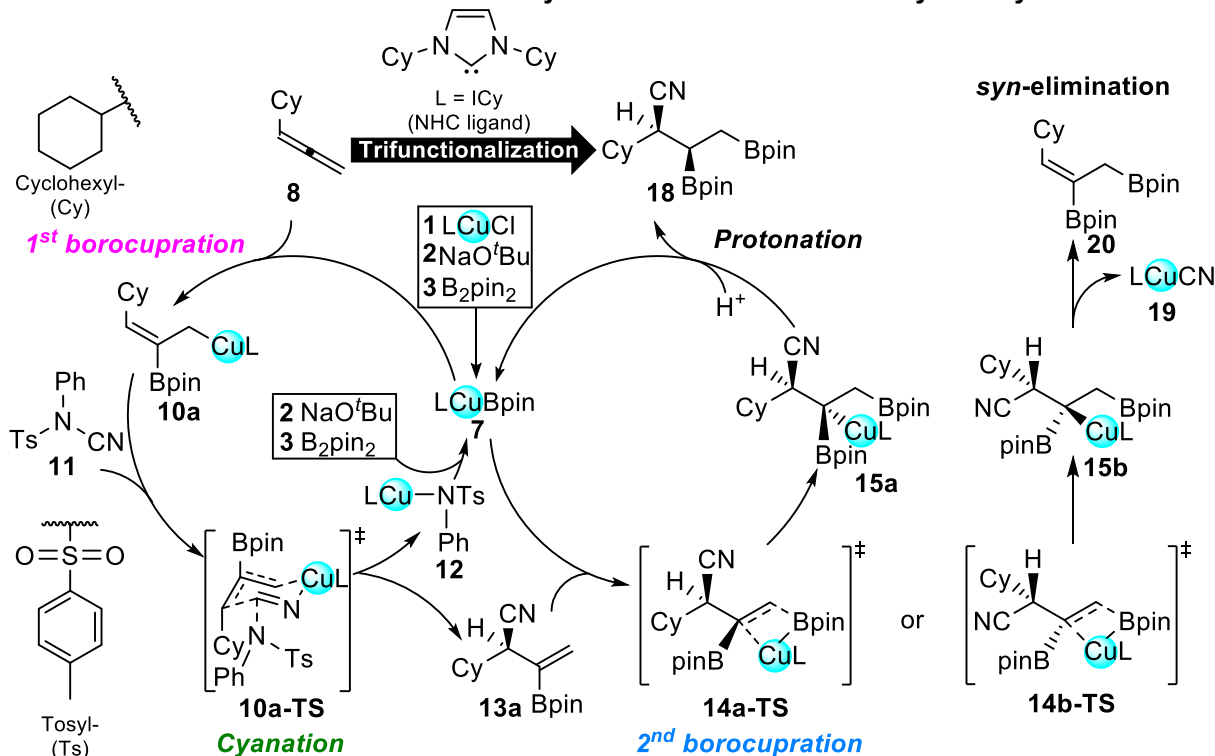
$G(\text{gas})$ is the free energy in the gas-phase; $G(\text{solv})$ is the free energy of solvation as computed using the continuum solvation model; $H(\text{gas})$ is the enthalpy in gas-phase; T is the temperature (298.15 K); $S(\text{gas})$ is the entropy in the gas-phase; $E(\text{SCF})$ is the self-consistent field energy, i.e., raw electronic energy as computed from the SCF procedure; and ZPE is the zero-point energy. Note that by entropy here we refer specifically to the vibrational/rotational/translational entropy of the solute(s); the entropy of the solvent is incorporated implicitly in the continuum solvation model. Transition state structures were obtained from the quadratic synchronous transit (QST) search methods.^[16]

Results and Discussion

Mechanism. The proposed reaction pathway for the Cu(I)-catalyzed trifunctionalization of the allene substrate is outlined in **Scheme 2** and consists of three major steps that govern the regio-, chemo- and diastereoselectivities. For the purpose of constructing a model reaction energy profile, which is shown in **Figure 2**, we chose to employ the cyclohexyl allene substrate, which was experimentally shown to selectively form the 1,2,3-trifunctionalized product **18** in high yields. In general, borocupration reactions are thought to involve *N*-heterocyclic carbene (NHC) copper-boryl complex **7** as the active species with a range of reported NHC ligands such as 1,3-*bis*(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes), 1,3-*bis*(2,4,6-trimethylphenyl)- 4,5-dihydroimidazol-2-ylidene

(SiMes), 1,3-*bis*(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr), and 1,3-dicyclohexylimidazol-2-ylidene (ICy).^[17] Among them, ICy was found to offer the best combination of high yields and triple-selectivities for the product **18**. The catalytic cycles proceed as summarized in **Scheme 2**, with the pre-catalyst ICyCu–Cl, B₂pin₂, and NaO^tBu reacting to generate ICyCu–Bpin species **7** in tetrahydrofuran (THF) as a solvent.

Scheme 2. Overview of Mechanism for Cu-Catalyzed Trifunctionalization of Cyclohexyl Allene.



The formation of the catalytically active species **7** deserves some attention, as it is the key intermediate that starts the catalytic cycle and is responsible for two different borylation cycles during the reaction cascade. It is generated from the pre-catalyst LCu–Cl with NaO^tBu and B₂Pin₂, as illustrated in **Figure 1**.^[18] Starting from reactants **1** and **2**, ligand exchange gives a thermodynamically stable LCu–O^tBu complex **5** and sodium chloride, which can undergo a σ -bond metathesis reaction where the Cu–O and B–B bonds are cleaved and Cu–B and O–B bonds are formed through a typical four-membered transition state **3-TS** at a relative energy of 16.2 kcal/mol to afford the stable intermediate complex **7** at –15.6 kcal/mol. We expect this reaction to be irreversible and rapid given the low barrier and large exothermic driving force.

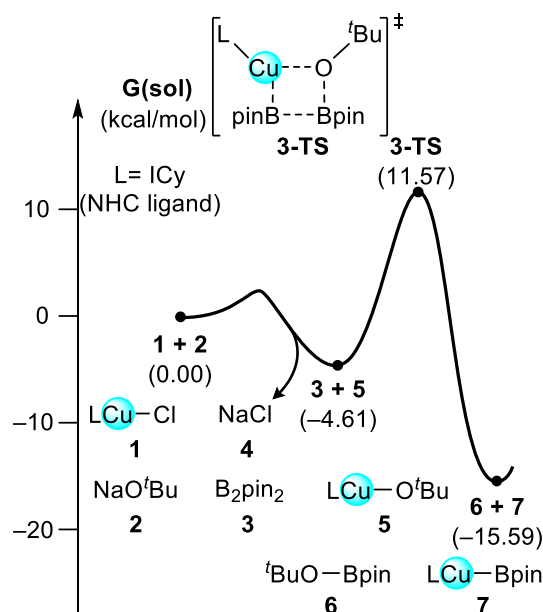


Figure 1. Energy profiles for pre-catalyst activation.

As illustrated in **Figure 2**, the catalytic cycle starts with species **7** adding across a terminal double bond of the allene to form an intermediate **9a**, a Cu- η^2 -allene π -complex, at a relative energy of 4.6 kcal/mol, making this step endergonic by 11.0 kcal/mol. The insertion of the allene into the Cu-B bond is surprisingly easy from this π -adduct only requiring an additional 7.7 kcal/mol to afford an overall barrier 18.7 kcal/mol for the insertion from intermediate **7**. The inserted species is the olefin intermediate **10a**, which we were able to locate at -45.4 kcal/mol, rendering this insertion step highly irreversible. Note that the regiochemical outcome of which double bond of the allene is functionalized is determined at this step, as will be discussed in greater detail below. Our calculations suggest that intermediate **10a** should not be experimentally observable, because the next step, which is the cyanation, is associated with a very low barrier of only 13.9 kcal/mol traversing the transition state **10a-TS**. *Ortho*-cyanation of a benzyl copper species by reagent **11** was first described by Buchwald^[19] and was computationally studies by Liu.^[20] Given that the cyanating reagent is offered in sufficient quantities, this step is expected to be fast, preventing the accumulation of **10a** in the reaction mixture. The product of the cyanation is intermediate **13a**, located at a free energy of -83.5 kcal/mol, rendering the cyanation step also irreversible with an energetic driving force of **10a** $\rightarrow$ **13a** to be 38.1 kcal/mol. For the final step of the cascade reaction, intermediate **13a** must be re-engaged by the catalytically active species **7** to facilitate the second borocupration reaction. Our calculations suggest that this step is also facile with a step barrier of only 11.4 kcal/mol associated with the transition state **14a-TS** to give the product complex **15a**, but since the concentration of **7** is low, the rate of this step is expected to be low compared to the other steps with similar or even slightly higher barriers. As a consequence, the alkenyl intermediate **13a** may accumulate during the catalytic reaction and become amenable for isolation, as was previously found. Furthermore, we observed independently-prepared compound **13a** is converted to the expected product **18** experimentally, and suggested that **13a** is not the final product because 2nd borocupration is a highly exothermic reaction with an energetic driving force of 15.7 kcal/mol and the lowest activation barrier of about 11 kcal/mol in the copper-catalyzed trifunctionalization reaction based on DFT calculations. Finally, protonation of **15a** gives the trifunctionalized cyanation/diborylation product **18**. **Figure 2** also indicates which step is responsible for the regio-, chemo- and

diastereoselectivity, namely, the first borylation, the cyanation and the second borylation steps, respectively. These features are discussed in detail below.

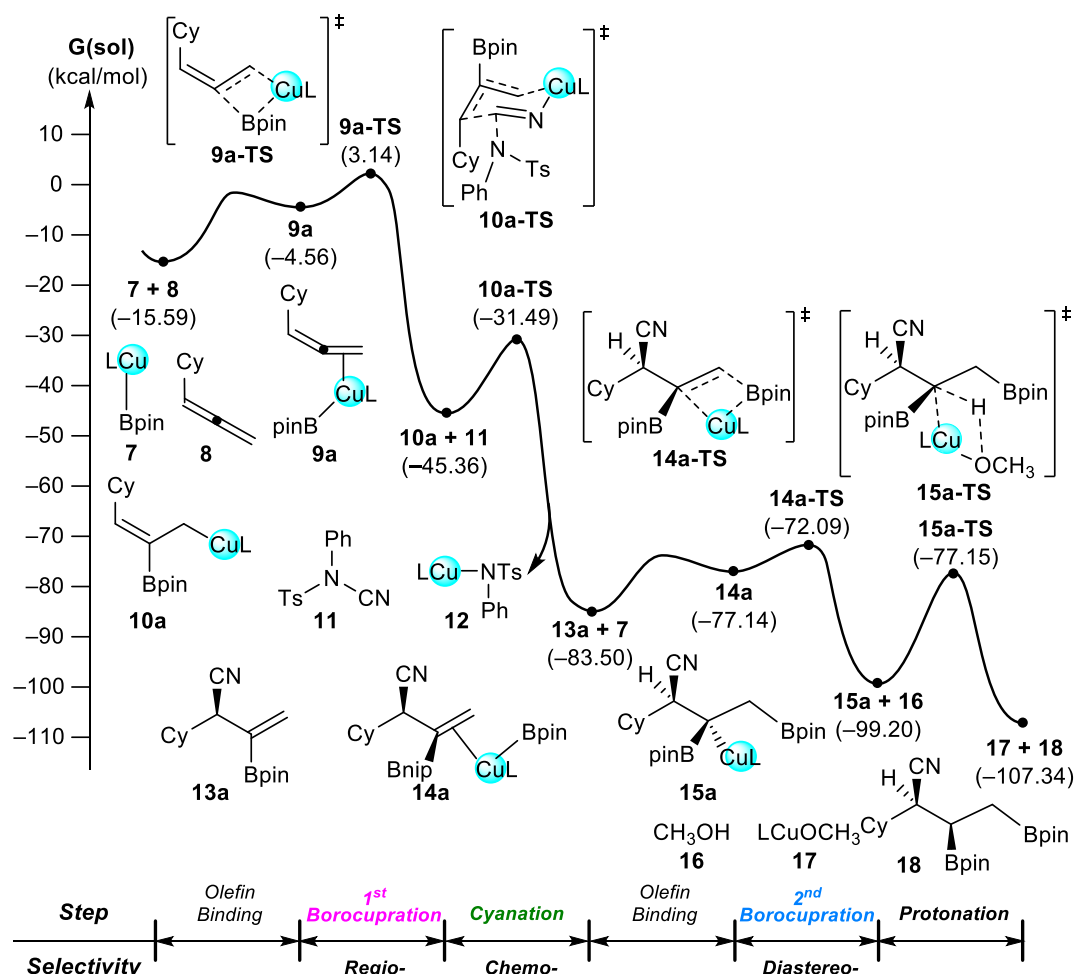


Figure 2. Overall energy profiles for Cu-catalyzed trifunctionalization of terminal allenes.

Regioselective First Borocupration. As discussed above, the first borocupration of the allene substrate determines the regioselectivity in the cascade reaction. In principle, there are four possible ways of inserting the cyclohexyl allene substrate **8** into the Cu–B bond, as summarized in **Figure 3**. Within an energy range of ~3 kcal/mol, we were able to locate four structural isomers of the reactant π -complex, where **9a** and **9b** have the copper-catalyst bound at the distal double bond from the cyclohexyl group adopting two different orientations of the NHC-ligand. Intermediates **9c** and **9d** are the analogous π -complexes where the Cu engages the proximal double bond. These four structural isomers offer entries into the four different regiochemical reaction channels that will produce regioisomeric borocupration products **10(a–d)**, as illustrated in **Figure 3**. The barriers associated with these four channels and the transition states **9(a–d)-TS** are remarkably different at 18.7, 21.0, 23.3 and 50.3 kcal/mol, respectively. The trajectory with the lowest barrier associated with **9a-TS** gives intermediate **10a**, which is also the lowest in energy by ~8–11 kcal/mol among all regioisomers at –45.4 kcal/mol.

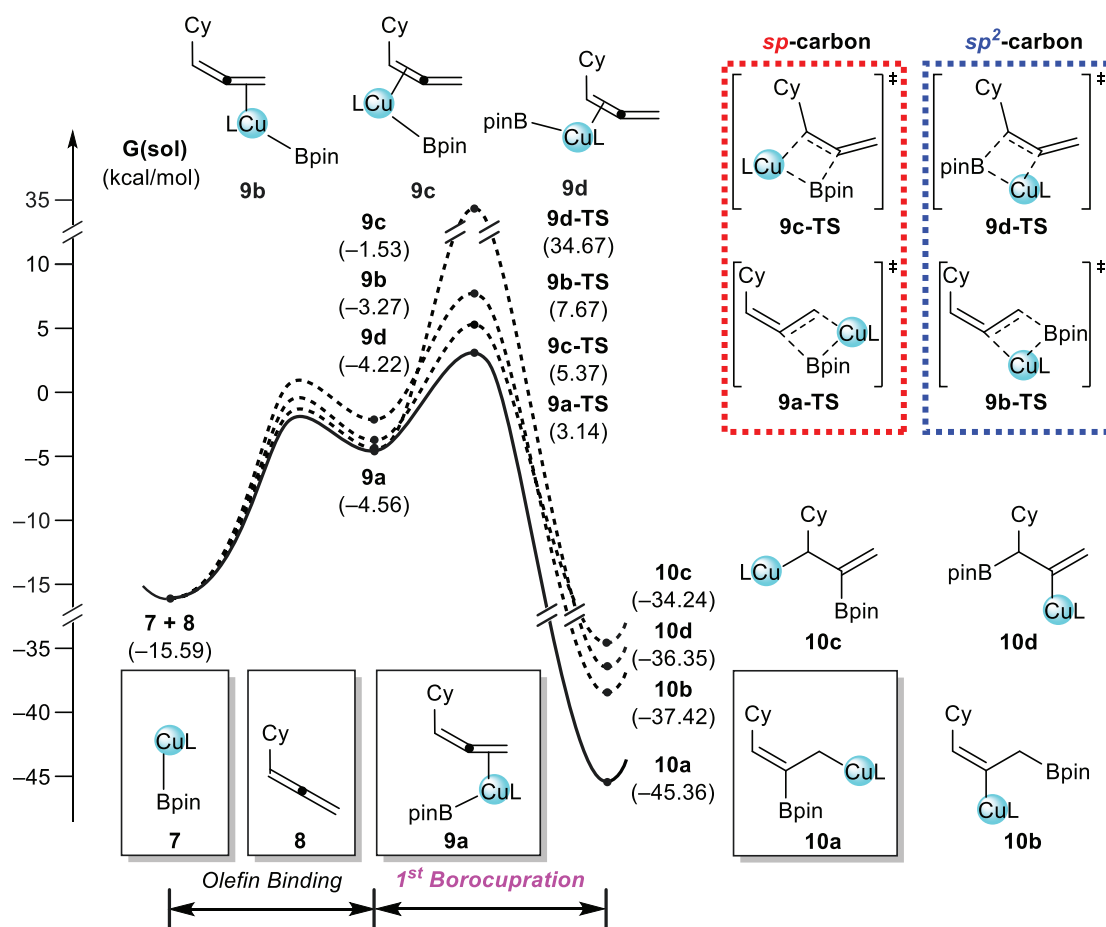


Figure 3. Energy profiles for four possible regioisomeric pathways of the first borocupration related to regioselectivity.

To understand the origin of the regioselectivity during the first borocupration, we examined each transition state **9(a-d)-TS** on the four different regiochemical reaction channels. This analysis illustrated that there are two features that determine the energies of these transition states. First, the insertion of the boryl moiety to form the C–B bond favors the stronger Lewis basic sp -carbon of the allene over the weaker Lewis basic sp^2 -carbon as highlighted in **Figure 3**. This finding is easy to understand since the boryl group acts as a Lewis acid in this bond formation. Thus, the transition states **9a-TS** and **9c-TS** are electronically favored over transition states **9b-TS** and **9d-TS**. The second determining factor is the steric demand enforced by the cyclohexyl functionalities flanking the *N*-heterocyclic ligand and the terminal cyclohexyl groups of the allene substrate. As depicted in **Figure 4**, these sterically demanding groups are oriented away from each other in **9a-TS** and **9b-TS**. In the other two transition states, the cyclohexyl groups cause a steric clash, giving rise to higher energies. Consequently, **9a-TS** is lowest in energy. For similar reasons, intermediate **10a** is about 8 kcal/mol lower in energy than **10b**. Therefore, the formation of the σ -allyl complex **10a** is kinetically and thermodynamically most affordable.

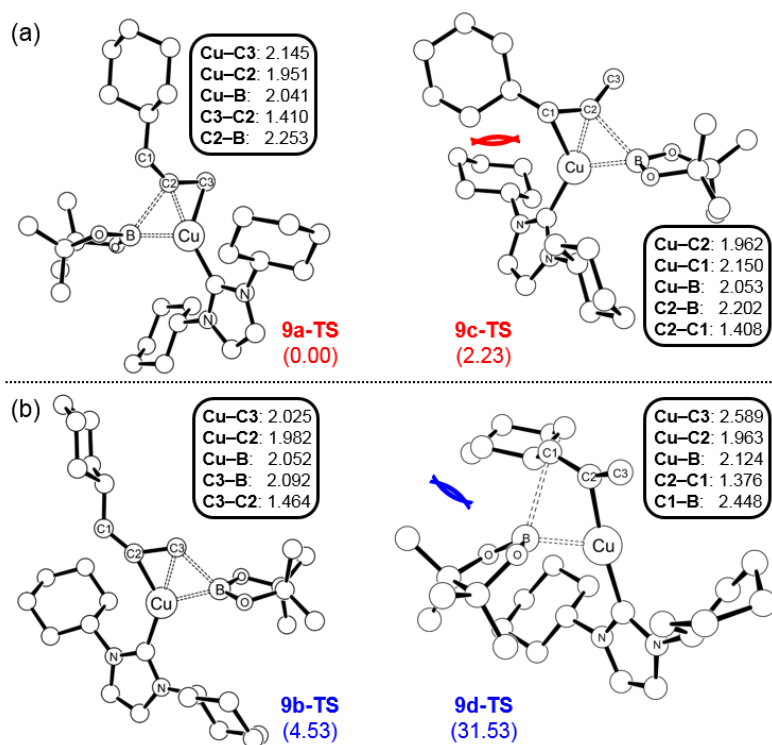


Figure 4. For the first borocupration, four possible transition state structures forming the C–B bond related to sp-carbon (a) and sp²-carbon (b). Hydrogen atoms bound to carbon atoms are omitted for the sake of clarity. All bond lengths are in Å. Relative free energy differences (kcal/mol) are in parenthesis.

Stereoselective Cyanation. After undergoing the borocupration, the NCTS substrate can act as an electrophilic cyanating agent to afford cyanation products in high yield with excellent selectivity.^[19–21] As shown in **Figure 5**, the step barrier associated with **10a-TS** is only 14.0 kcal/mol that is expected to be fast in realistic reaction conditions, and the transition state adopts a six-membered ring conformation as the copper center coordinates to the terminal nitrogen atom of the cyano group. Consequently, placing the cyclohexyl group in the axial position allows for a relaxed geometry via six-membered without steric stress. Furthermore, we found the two possible conformational isomers **13a** and **13b** that may be formed from intermediate **11** via transition state **10a-TS**. The rotamers **13a** and **13b** were transferable to the experimentally observed stereoselectivity in the second borocupration step.

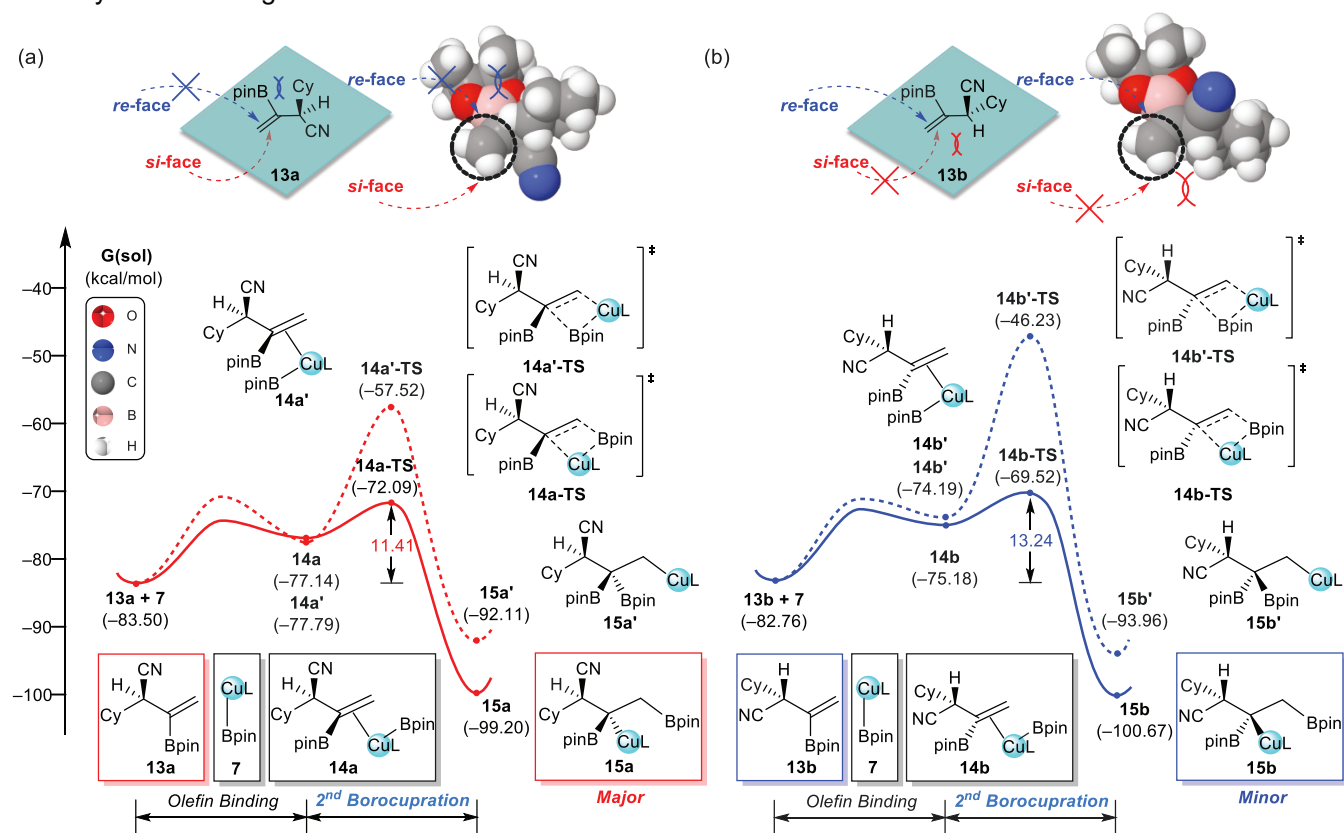
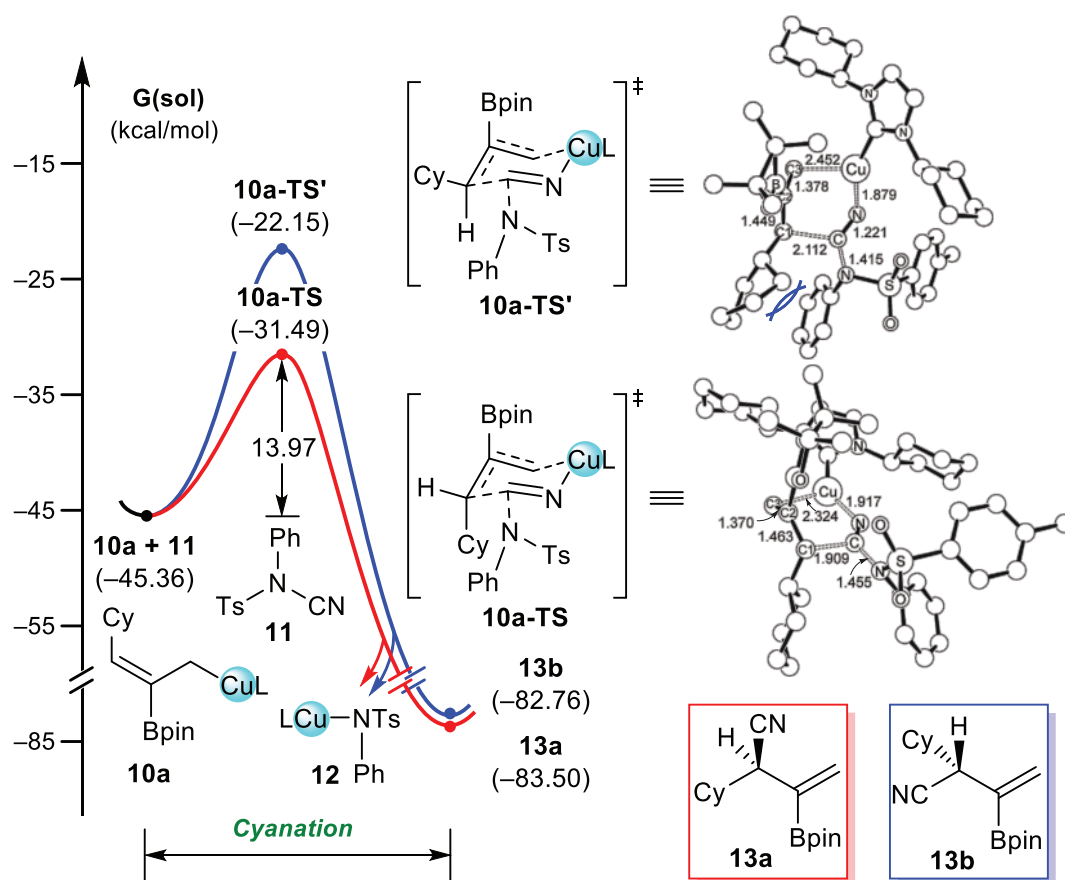


Figure 6. Energy profiles for the second borocupration pathways related to regio- and diastereoselectivity derived from two conformational isomers 13a and 13b.

Regio- and Diastereoselective Second Borocupration. The addition of boryl copper **7** to the olefin occurs in a regio- and stereoselective manner. The stereocontrol is imposed by the sterically demanding interaction between the cyclohexyl group of the alkene substrate and species **7**. As illustrated in **Figure 6a**, the boryl copper complex **7** reacts with **13a** on the *si*-face because the cyclohexyl group effectively blocks the *re*-face. Conversely, in **13b** the *re*-face is blocked by the cyclohexyl moiety, forcing the borocupration to proceed through the *si*-face depicted in **Figure 6b**. Four borocuprated products **15a**, **15b**, **15a'** and **15b'** are possible, as shown in **Figures 6** and **Figure S1**. The intermediate **13a** first forms the π -complex with **7**, which is ~ 6 kcal/mol uphill to afford the two conformers **14a** and **14a'**. The borocupration is exceedingly facile and reaching **14a-TS** only requires an addition 5 kcal/mol to give a total barrier of only 11.4 kcal/mol and form product **15a**. The reaction leading to the alternative regioisomer **15a'** is much more difficult and associated with a barrier of 19.6 kcal/mol. This regiochemical outcome is easy to understand, as the double-bond is likely cleaved in a heterolytic fashion with the terminal carbon becoming negatively polarized, which is well matched with the boryl functionality, which acts as a Lewis acid. The regiocontrol is also operative for the intermediates **14b** and **14b'**, thus, favoring the formation of **15b** with a barrier of 13.2 kcal/mol. Comparing the diastereoisomers **15a** and **15b**, our calculations predict a nearly 2 kcal/mol kinetic preference for the formation of **15a**, which is again in excellent agreement with experimental observations. As discussed above, protonation of **15a** affords the final trifunctionalized product **18**.

Conclusions

In summary, our calculations have revealed a detailed mechanism for the Cu-catalyzed trifunctionalization of cyclohexyl allene employing B₂pin₂ and NCTS as the borylation and cyanation source. We present for the first time how this fascinating, efficient cascade reaction that generated the cyanation/diborylation product with exceptional regio-, chemo- and diastereoselectivity can be understood in detail. Although the sequence of the three reactions occurs in a highly orchestrated fashion, the regio- and stereoselectivities determined in each of the reaction steps are easily rationalized by this study. Specifically, the regiocontrol of the two borocupration steps is determined by significantly different effects. The first borocupration employs mostly sterical demands, but the second borocupration utilizes mainly electronic effects. The diastereoselectivity follows a classical strategy of sterical blocking one of the reactive faces of the olefin by placing the cyclohexyl functionality in that molecular face. This detailed mechanistic investigation offers a precise mechanistic blueprint and serves as a platform for future explorations and rational catalyst design efforts. Applications of these design concepts will be pursued in our laboratories and reported in due course.

Supporting Information

For computed energy components, Cartesian coordinates, vibrational frequencies of all of the DFT-optimized structures, see Supporting Information.

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Conflicts of interest

The authors declare no competing financial interest.

Keywords: density functional theory · trifunctionalization · borylation · cyanation · copper catalysis · selectivities

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