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Communication

# Mechanism and selectivity of copper-catalyzed borocyanation of 1-aryl-1,3-butadienes: A computational study

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ABSTRACT

Density functional theory calculations have been performed to investigate the copper-catalyzed borocyanation of 1-aryl-1,3-butadienes. The computations show that the regio- and enantioselectivity is determined by the borocupration step. The $\pi$-electron withdrawing aryl group at the $C^1$ atom makes the $C^4$ atom more electrophilic than the other carbon atoms, which together with the steric repulsion around the forming C—B bond, results in the experimentally observed exclusive 4,3-regioselectivity. The origins of the enantioselectivity were attributed to the steric effect and $\pi$-$\pi$ stacking interaction between the butadiene moiety and the ligand.

The boron-containing compounds are widely observed in medicinal chemistry and material science [1], and are key building blocks in a range of organic transformations [2]. The development of the efficient strategies for the synthesis of these compounds is thus of vital importance in modern organic synthesis [3,4]. In this regard, the copper-catalyzed borylative functionalizations of C—C multiple bonds, which represents one of the most efficient and straightforward protocols, have attracted extensive research interest over the past two decades [4,5]. From a mechanistic point of view, the key step of these reactions is the initial borocupration of the C—C multiple bonds to afford the organocopper species, which then can react with the electrophilic coupling partners to produce the final boron-containing compounds [6].

Despite the significant progress has been made in this field, the development of the regio- and enantio-selective reactions remains a key challenge. In this context, Procter and co-workers recently reported an elegant example of the Cu-catalyzed borocyanation of 1-aryl-1,3-butadienes under mild reaction conditions (Scheme 1) [7]. It was found that with the *in situ* generated LCu-Bpin complex, the reactions of the 1-aryl-1,3-butadienes **1** with the *N*-cyano sulfonamide **2** can give the borocyanation products (*S*)-**3** with the complete 4,3-regioselectivity and good enantioselectivity (up to 93% *ee*). The reaction thus represents a rare case of the regio- and enantio-selective borylative functionalization of unsymmetrical 1,3-dienes.

Considering the origins of the selectivity remain unclear and following our continuous research interest in this field [8], we therefore decided to investigate the title reaction by means of density functional theory (DFT) calculations (see Supporting information for the computational details). The results show that the selectivity of the overall reaction is determined by the borocupration step, and the origins of the experimentally observed regio- and enantio-selectivities are attributed to the combination of the electronic and steric effects. The present results, together with our previous work [8a], may provide important implications for a better understanding of related Cu-catalyzed borylative functionalization reactions.

The 1-phenyl-1,3-butadiene **1a** was selected as the model substrate in the current calculations. The calculated energy profile of the 4,3-borocyanation of **1a** is given in Fig. 1. The computations show that the reaction is initiated by the coordination of the $C^3$-$C^4$ double bond of **1a** to the Cu center of active catalyst **A**, leading to the formation of intermediates (*S*)-**INT1** and (*R*)-**INT1**, which was calculated to be exergonic by 2.2 and 1.2 kcal/mol, respectively. Then, the ensuing 4,3-borocupration was found to take place *via* transition states (*S*)-**TS1** and (*R*)-**TS1**, with the energy barriers of 7.2 and 9.5 kcal/mol relative to (*S*)-**INT1**. The borocupration was calculated to be highly exergonic, as evidenced by the resulted allyl copper intermediates (*S*)-**INT2** and (*R*)-**INT2** being much more stable than (*S*)-**INT1** by 22.0 and 24.3 kcal/mol, respectively.

From intermediates (*S*)-**INT2** and (*R*)-**INT2**, the electrophilic cyanation can occur *via* the migratory insertion of the C≡N triple

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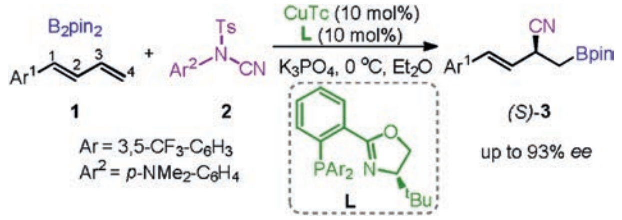


**Scheme 1.** Copper-catalyzed borocyanation of 1-aryl-1,3-butadienes **1**.

bond of *N*-cyano sulfonamide **2** into the Cu-$C^3$ bond. However, this possible pathway was calculated to be kinetically infeasible, requiring energy barriers of higher than 30 kcal/mol (see Supporting information for details). Instead, we found that (*S*)-**INT2** and (*R*)-**INT2** can first undergo an $\eta^1$-allyl isomerization *via* transition states (*S*)-**TS2** and (*R*)-**TS2** to give intermediates (*S*)-**INT3** and (*R*)-**INT3** [9]. Subsequently, the electrophilic cyanation at $C^3$ position takes place *via* six-membered transition states (*S*)-**TS3** and (*R*)-**TS3**, giving the intermediates (*S*)-**INT4** and (*R*)-**INT4**, respectively. The computations show that the electrophilic cyanation *via* the six-membered transition states is much more favorable than that *via* the four-membered migratory insertion transition states (see Supporting information for other possibilities), being in accordance with the previous computational studies [6c].

Instead of the $\eta^1$-allyl isomerization, the electrophilic cyanation at $C^1$ position can occur directly from (*S*)-**INT2** and (*R*)-**INT2** *via* transition states (*S*)-**TS3′** and (*R*)-**TS3′** (Scheme 2). However, this possibility can be ruled due to the high energy barriers required compared with those of (*R*)-**TS3** and (*R*)-**TS3**, being in line with our previous study [8a]. The results are thus in accordance with the experimental results that no cyanation at $C^1$ position was observed [7]. The origins are probably due the steric repulsion around the forming C—C bond in (*S*)-**TS3′** and (*R*)-**TS3′** is larger than that in (*S*)-**TS3** and (*R*)-**TS3**.

The next step of the reaction is the 1,2-elimiantion of the copper tosylamide **INT5**, which was calculated to proceed *via* transition states (*S*)-**TS3** and (*R*)-**TS3**, leading to the 4,3-borocyanation products (*S*)-**3a** and (*R*)-**3a**, respectively.

The catalytic cycle is finally completed by the regeneration of the active catalyst **A** with the assistance of $K_3PO_4$. The computations show that the ligand exchange between **INT5** and $K_3PO_4$ to give intermediates **INT6** and **INT7** is exergonic by 7.9 kcal/mol. Then, the incoming $B_2pin_2$ binds to intermediate **INT7** to generate intermediate **INT8**, from which the transmentallation *via* transition state **TS5** is quite facile, with an energy barrier of only 2.8 kcal/mol relative to **INT8**. The transmentallation process was calculated to be highly exergonic, and the resulting intermediate **INT9** is more stable than **INT8** by as much as 19.1 kcal/mol. The active catalyst **A** can be regenerated *via* the release of $K_2PO_4$-Bpin from **INT9**.

The results show that the borocupration constitutes the rate-and selectivity-determining step of the overall reaction. The overall energy barrier of the reaction is 21.7 kcal/mol, which was calculated by the energy difference between **INT9** and **A** (16.7 kcal/mol) and the energy difference between **A** and (*S*)-**TS1** (5.0 kcal/mol). The calculated energy difference of 2.3 kcal/mol (5.0 kcal/mol of (*S*)-**TS1** *versus* 7.3 kcal/mol of (*R*)-**TS1**) corresponds to a calculated enantioselectivity of around 97% *ee* at 0 °C, which is in agreement with the experimentally observed 91% *ee* [7].

The origins of the enantioselectivity are attributed to both electronic and steric effects. Fig. 2 shows the optimized geometries of the enantioselectivity-determining transition structures (*S*)-**TS1** and (*R*)-**TS1**. It was found that in transition state (*R*)-**TS1**, the butadiene moiety is oriented toward to the bulky *t*Bu group of the oxazoline ring. As such, the steric repulsion between the butadiene moiety and the oxazoline ring can be expected, whereas no such steric repulsion exists in (*S*)-**TS1**. To minimize the steric

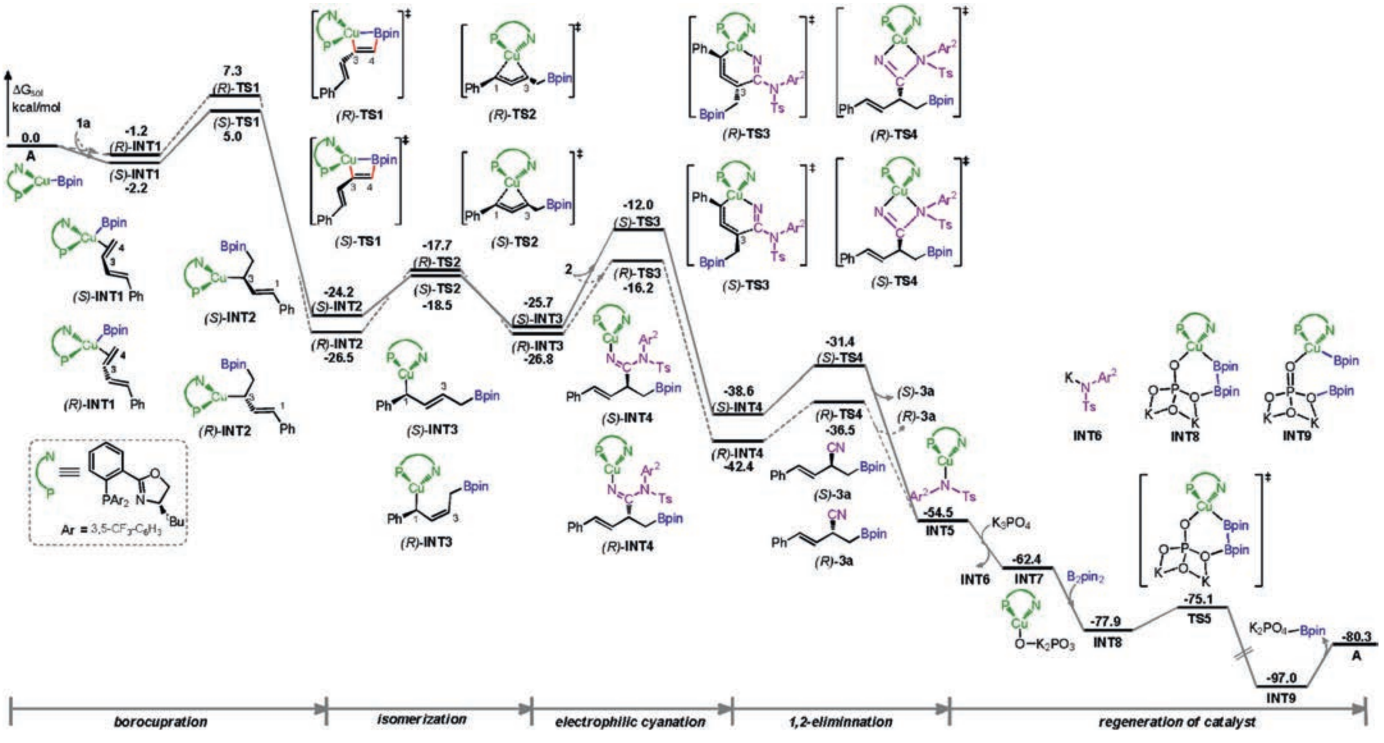
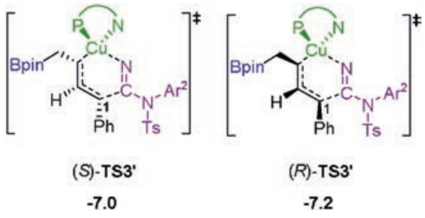


**Fig. 1.** Calculated energy profile of the Cu-catalyzed 4,3-borocyanation of **1a**.



**Scheme 2.** Electrophilic cyanation at $C^1$ position.

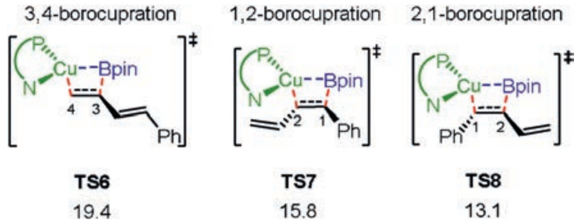


**Fig. 3.** Other possibilities of the borocupration. Energies are given in kcal/mol.

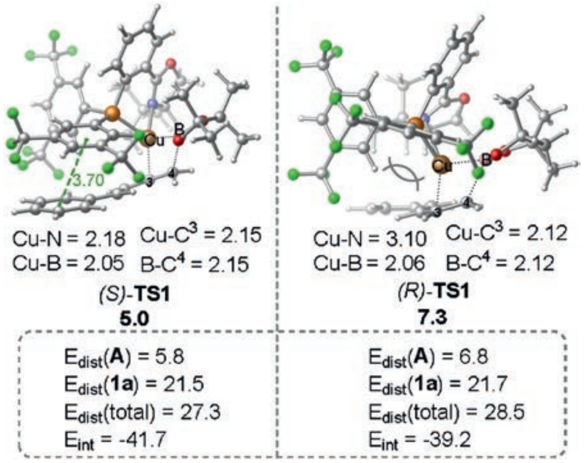


**Fig. 2.** Optimized geometric structures of (*S*)-**TS1** and (*R*)-**TS1**. The distortion/interaction energies were calculated at the level of ωB97XD-SMD($Et_2O$)/6-311+G(d, p)-SDD. The energies and selected bond distances are given in kcal/mol and Å, respectively.

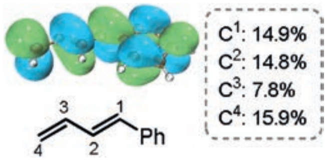


**Fig. 4.** LUMO analysis of **1a**. The numbers shown in box are the orbital percentage contributions of the carbon atoms.

repulsion, the oxazoline ring in (*R*)-**TS1** was found to be distorted (Cu-N = 3.10 Å in (*R*)-**TS1** *versus* Cu-N = 2.18 Å in (*S*)-**TS1**). Furthermore, since that the butadiene moiety is oriented toward to the phosphorus moiety of the ligand in (*S*)-**TS1**, the $\pi$-$\pi$ stacking interaction between the phenyl group of **1a** and the aryl ring on the phosphorus atom was observed (3.70 Å). Therefore, the combination of the steric and electronic effects makes transition state (*S*)-**TS1** being more favorable than transition state (*R*)-**TS1**, enabling the experimentally observed enantioselectivity. The distortion/interaction analysis [10] of (*S*)-**TS1** and (*R*)-**TS1** also shows that the distortion energy of active catalyst **A** ($E_{\text{dist}}$(**A**)) and interaction energy ($E_{\text{int}}$) in (*S*)-**TS1** are both more favorable than those in (*R*)-**TS1**, providing thus further support for our argument.

Finally, apart from the 4,3-borocupration, the other possible modes of the borocupration, namely 3,4-, 1,2- and 2,1- borocupration, were considered in order to investigate the regioselectivity of the reaction (see Supporting information for other possibilities). As depicted in Fig. 3, the computations indeed show that the energies of the other possibilities of the borocupration are much higher than that of the 4,3-borocupration by at least 5 kcal/mol, which is in consistent with the fact that only 4,3-borocyanation products were observed in the experiments [7,11].

Previous studies have demonstrated that the nature of the borocupration is the nucleophilic attack of the boryl group on the alkenes, and the orbital percentage contributions of the carbon atoms in the lowest unoccupied molecular orbital (LUMO) of alkene play an important role in determining the regioselectivity [6a,b]. The LUMO analysis of **1a** indeed correlates quite well with this finding, showing that the contribution of the $C^4$ atom is among the highest (Fig. 4). This is due to the presence of the $\pi$-electron withdrawing phenyl group at the $C^1$ atom makes the $C^4$ atom being more electrophilic than the other carbon atoms, which thus results in the addition of the Bpin group to the $C^4$ atom being favorable. Further to this, the steric repulsion around the forming C—B bond in the 4,3-borocupration transition state should be smaller than that in the other transition states (see Supporting information for the optimized geometries), which also contributes to the experimentally observed exclusive 4,3-regioselectivity.

To summarize, we have herein presented a mechanistic study on the copper-catalyzed borocyanation of 1-aryl-1,3-butadienes by means of DFT calculations. The computations show that the overall catalytic cycle consists of five major steps, including (1) the borocupration of the C=C double bond, (2) the $\eta^1$-allyl isomerization of the allyl copper intermediate, (3) the electrophilic cyanation *via* the six-membered transition state, (4) the 1,2-elimiantion of the copper tosylamide, and (5) the regeneration of the active catalyst. The borocupration was found to be the rate- and selectivity-determining step of the overall reaction. The presence of the $\pi$-electron withdrawing phenyl group at the $C^1$ atom makes the $C^4$ atom being more electrophilic than the other carbon atoms, which coupled with the steric repulsion around the forming C—B in the borocupration transition states, leading to the experimentally observed exclusive 4,3-borocyantion. The origins of the enantioselectivity are due to the combination of both steric and electronic effects. The steric repulsion between the butadiene moiety and the oxazoline ring of the ligand and the $\pi$-$\pi$ stacking interaction between the phenyl group of the butadiene and the aryl ring of the ligand results in the *S*-transition state being more favorable than the *R*-transition state, enabling the experimentally observed good enantioselectivity.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.11.045.

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