Computational study of regiodivergent pathways in the copper-catalyzed borocyanation of 1,3-dienes: Mechanism and origin of regioselectivity

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Abstract

Regioselective control in the Cu-catalyzed borylcyanation of non symmetrically substituted 1,3-dienes remains challenging. In this study, we used density functional theory calculations to elucidate the origins of ligand- and substrate-controlled regioselectivity. The mechanism rationalizes why ligand PCy3 favors 1,2-borocupration while ligand XantPhos favors 4,3-borocupration for 2-substituted 1,3-dienes, and why 1-substituted, 1,2-disubstituted, and 1,3-disubstituted 1,3-dienes afford 4,3-borocupration, irrespective of the presence of bidentate or monodentate ligands. Based on established experiments and stimulated by other relevant reactions, we attempted to enrich ligands and substrates computationally. The different regioselectivities for different substrates and ligands were attributed to different electronic and steric factors.

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1. Introduction

In the last few decades, transition-metal-catalyzed multifunctionalization reactions of C–C multiple bonds have proven to be important because they allow molecular complexity to be rapidly generated from simple precursors [1]. With increasing interest in sustainable catalysis, the use of relatively inexpensive copper catalysts, which can act as Lewis acids, π-acids, single-electron mediators, and two-electron mediators, has attracted considerable attention [2]. In recent years, Cu-catalyzed borylative transformations of nonpolar C–C unsaturated compounds, such as alkenes [3], 1,3-dienes [4], allenes [5], alkynes [6], 1,3-enediynes [7], and 1,3-dienes [8], have been recognized as important approaches to accessing organoboron compounds. These processes generally form an allyl organocopper intermediate that can be then captured by various electrophiles for further chemical manipulation [9].

The cyano group is a core chemical structure found in a broad range of biologically active agents and functional materials [10]. Owing to their important biological properties and unique structural characteristics, considerable research effort has been directed toward the development of new methods for the synthesis of cyano-containing compounds. N-Cyano-N-phenyl-p-methylbenzenesulfonamide (NCTS) [11], which is an electrophilic cyanation reagent with low reactivity but low toxicity, has emerged as a promising reagent for nitrile synthesis. Studies on Cu-catalyzed borylcyanation using NCTS to introduce a cyano group onto styrene and allene have been reported [12]. More recently, the Procter [13] and Meng groups [14] reported Cu-catalyzed three-component coupling reactions of 1,3-dienes and diboranes using NCTS. The challenge for Cu-catalyzed borylcyanation of non-symmetrically substituted 1,3-dienes is the control of regioselectivity.

The pioneering work of Procter developed ligand-controlled catalytic methods to bias the desired regioselectivity [13]. Using different ligands (such as XantPhos and tricyclohexyl phosphine) on the copper catalyst allowed either 4,1- or 1,4-borocupration of 2-substituted 1,3-dienes, resulting in either 4,3- or 1,2-borocyanation products (Scheme 1a). However, using different ligands with 1-substituted 1,3-dienes resulted in the formation of only 4,3-borocyanation products (Scheme 1b) [14].

The number of potential reaction pathways and complexity of these processes makes detailed elucidation of the reaction mechanism challenging. Although the ligand and substrate are widely accepted to affect the reaction pathway, the details and origins of...
PCy3 and XanthPhos ligands to elucidate the overall catalytic cycle of the borylation reaction of 2-substituted 1,3-dienes using Multiwfn 3.6 program package [25].

The whole energy profiles for 2-substituted 1,3-diene 1a with PCy3 as ligand are shown in Fig. 1.

The calculations showed that electrophilic cyanation is exergonic, and that resulting intermediate 1-5A is 15.4 kcal/mol lower in energy than 1-4A. Consequently, C–N bond cleavage occurs via transition state 1-TS4A to give 1,2-borocyanation product 3a with amine liberation, which has an activation energy barrier of 10.7 kcal/mol relative to 1-5A. Therefore, the calculations were in agreement with the experimental regioselectivity for 1,2-borocyanation over 4,3-borocyanation [13].

The calculated free-energy profile for borocyanation of 2-substituted 1,3-diene 1a with bidentate phosphine XanthPhos as ligand is shown in Fig. 3. First, we evaluated the two borocyanation modes. The free energy of transition state 1-TS1D (–6.2 kcal/mol) for 1,2-borocyanation was higher than that of 1-TS1C (–8.5 kcal/mol) for 4,3-borocyanation, resulting in a regioselectivity switch from 1,2-borocyanation to 4,3-borocyanation. 1–1C then undergoes ligand exchange by spanning a barrier of 17.6 kcal/mol (1-TS2C) relative to 1–1C, which generates 4,1-borocyanation complex 1–2C. Subsequent coordination of 2a with the Cu center leads to the formation of Cu–cyano complex 1–3C. Finally, amine is liberated from cyanide via transition state 1-TS4C, with an energy barrier of 5.8 kcal/mol, to give 4,3-borocyanation product 4a.

To probe the origins of the regioselectivity for 2-substituted 1,3-diene 1a, we analyzed the frontier molecular orbitals for both the borylcopper catalyst and substrate 1a. Fig. 4 shows spatial plots and orbital energies of the relevant frontier molecular orbitals. The energy gap between the LUMO of 1a and HOMO of the catalyst was much smaller than that between the LUMO of the catalyst and HOMO of 1a, suggesting that substrate 1a received electrons and acted as an electrophile in the reactions. The HOMO of the borylcopper catalyst was the Cu–B σ molecular orbital, while the LUMO of 1a was the π* molecular orbital [27]. Therefore, the LUMO of 1a played a key role in the regioselectivity. For 1a, there were two electrophilic sites, namely, the terminal C1 and C4 atoms. As shown in Fig. 4, orbital population analysis found that the 2p orbital of the C1 atom (314) made a significantly larger contribution than that of the C4 atom (137). Therefore, it is reasonable that borocyanation takes place at the C1=C2 bond when PCy3 is used as ligand. When bidentate phosphine ligand XanthPhos is used, the dissociation of XanthPhos to the monodentate coordination mode is highly endergonic, which accordingly increases the energy barrier of the borocyanation step [28]. Therefore, the borocyanation steps occurred with the XanthPhos ligand in bidentate coordination mode. Transition state 1-TS1D in the 1,2-borocyanation using the bidentate XanthPhos ligand experienced greater steric repulsion than 1-TS1C in the 4,3-borocyanation. The optimized geometries indeed show that the phenyl group of 1a and the phenyl group of XanthPhos are shorter than the sum of the van der Waals radii of the relevant elements (2.90 Å for C–H) [29]. However, no such steric repulsion

Scheme 1. Cu-catalyzed borylation reaction of 1,3-dienes.
Fig. 1. Calculated energy profiles for Cu-catalyzed borylation reaction of 2-substituted 1,3-diene 1a with PCy3 as ligand (black and red lines indicate 1,2-borocupration and 4,3-borocupration, respectively). Values shown are relative free energies calculated by M06/BS2 and B3LYP/BS1 (in parentheses) in kcal/mol. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 2. Optimized structures of key species labeled in Figs. 1 and 3. Key bond lengths are given in Å; trivial H atoms are omitted for clarity.
exists in 1-TS1c, which thus results in 1-TS1c being more favored than 1-TS1d. This result can be further supported by the RDG analysis (Scheme S5). Therefore, steric factors were dominant in determining the regioselectivity of the reaction using the bidentate XantPhos ligand.

To further verify that steric factors were dominant in determining the regioselectivity of the reaction using the bidentate XantPhos ligand, we replaced the hydrogen atom at C4 in 1a with a methyl group and computed the 4,3- and 1,2-borocupration steps. For 2,4-disubstituted 1,3-diene 1b, the bulky methyl group still effectively promoted 1,2-borocupration, and induced the barrier difference (4.6 kcal/mol) between 4,3- and 1,2-borocupration for Fig. 3.

Fig. 3. Calculated energy profiles for Cu-catalyzed borylation reaction of 2-substituted 1,3-diene 1a with XantPhos as ligand (black and red lines indicate 4,3-borocyanation and 1,2-borocyanation, respectively). Values shown are relative free energies calculated by M06/BS2 and B3LYP/BS1 (in parentheses) in kcal/mol. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 4. Frontier molecular orbitals calculated for the borylcopper catalyst, and 2-substituted (1a) and 2,4-disubstituted (1b) 1,3-diienes. Orbital energies are given in eV.

the reaction using PCy₃ as ligand (Fig. 5a). For the reaction using the bidentate XantPhos ligand (Figs. 5b), 1,2-borocupration (II-TS1C, −5.1 kcal/mol) was able to override 4,3-borocupration (II-TS1D, −3.9 kcal/mol) of 1b. Therefore, both electronic and steric effects favored 1,2-borocupration for 2,4-disubstituted 1,3-dienes, regardless of the ligand used.

We attempted to computationally expand the ligand scope for 2-substituted 1,3-diene 1a to further verify the factors that determine regioselectivity. The energy profiles in the presence of monodentate Sphos and bidentate dppe ligands (Fig. 6), which have been used in the borocupration of 1-substituted 1,3-diene 1c [14], were examined. For the monodentate Sphos ligand (Fig. 6a), the barrier for the 4,3-borocupration step (4.3 kcal/mol) was higher than that for the 1,2-borocupration step (1.1 kcal/mol). In contrast, for bidentate ligand dppe, the free energy of transition state I-TS1H (5.4 kcal/mol) for 1,2-borocupration is higher than that of I-TS1G (−0.3 kcal/mol) for 4,3-borocupration, meaning that the regioselectivity could still be switched (Fig. 6b). Therefore, a bidentate ligand, such as XantPhos or dppe, does not provide the convenience of ligand dissociation, resulting in instability in the transition state for 1,2-borocupration of 1a. When monodentate ligands PCy₃ and Sphos were used in the calculations, 1,2-borocupration was preferred over 4,3-borocupration for 1a.

We further elucidated the origin of substrate-controlled regioselectivity by investigating the Cu-catalyzed borylation reaction in the presence of 1-substituted, 1,2-disubstituted, and 1,3-disubstituted 1,3-dienes, which were used in experiments reported by Meng and coworkers [14]. The calculated overall energy profile is shown in Fig. 7. In agreement with experimental observations, the calculations indicated that 1,2-borocupration was less favorable than 4,3-borocupration for the three substrates, regardless of the ligand (PCy₃ or XantPhos). These results were consistent with the relative orbital percentage contribution of the two carbon atoms, C1 and C4, in the LUMO of the three substrates (Fig. 8).

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**Fig. 5.** Calculated energy profiles for regioselectivity-determining steps of 2,4-disubstituted 1,3-diene 1b with XantPhos and PCy₃ ligands. Values shown are relative free energies calculated by M06/BS2 and B3LYP/BS1 (in parentheses) in kcal/mol.

**Fig. 6.** Calculated energy profiles for regioselectivity-determining steps with Sphos and dppe ligands for 2-substituted 1,3-diene 1a. Values shown are relative free energies calculated by M06/BS2 and B3LYP/BS1 (in parentheses) in kcal/mol.
Furthermore, the steric effects also favored 4,3-borocupration.

4. Conclusions

The regioselectivity of the Cu-catalyzed borylcyanation of non-symmetrically substituted 1,3-dienes was theoretically studied using DFT calculations at the B3LYP level. The computational results showed that monodentate ligands PCy3 and SPhos can favor 1,2-borocupration over 4,3-borocupration in 2-substituted 1,3-dienes. However, 4,3-borocupration can be avoided when large bidentate ligands, such as XantPhos and dppe, are present. The 1-substituted, 1,2-disubstituted, and 1,3-disubstituted 1,3-dienes.

Fig. 7. Calculated energy profiles for regioselectivity-determining steps with PCy3 and XantPhos ligands for 1-substituted (1c), 1,2-disubstituted (1d), and 1,3-disubstituted (1e) 1,3-dienes. Values shown are relative free energies calculated by M06/BS2 and B3LYP/BS1 (in parentheses) in kcal/mol.
disubstituted 1,3-dienes enabled 4,3-borocupration, while 2,4-disubstituted 1,3-dienes favored 1,2-borocupration, irrespective of the presence of bidentate or monodentate ligands. Analysis of the frontier molecular orbitals suggested that the borylcyanation step was a nucleophilic attack of the Cu–B σ bond at the coordinated 1,3-diene. The different regioselectivities for different substrates and ligands can be attributed to different electronic and steric factors. These theoretical results will aid understanding of other borocupration reactions in a wide range of substrates and could be used for ligand design. We believe these theoretical results are inspiring for future ligand design of other borocupration reactions.

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 data to this article can be found online at https://doi.org/10.1016/j.jorganchem.2019.121014.

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For selected examples, see (a) L. Dang, Z. Wu, G. Huang, J. Org. Chem. 84 (2019) 5514–5523.