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Mechanisms of the synthesis of trialkylsubstituted alkenylboronates from unactivated internal alkynes catalyzed by copper: A theoretical study

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The mechanisms of copper-catalyzed trialkylsubstituted alkenylboronates reaction from unactivated internal alkynes were studied by using density functional theory (DFT). Our calculations suggest that the additive KO^{t}Bu plays an important role for the initiation of the precatalyst. The electrophilic addition (**E-A**) mechanism is calculated to be more favorable than the oxidation addition-reductive elimination (**O-R**) one. Through investigating the origin of ligand-controlled regioselectivity, we find that the steric effects rather than electronic effects determine the regioselectivity.

1. Introduction

Tetrasubstituted alkenylboronates are versatile building blocks, e.g. for constructing tetrasubstituted alkenes, thus the development of metal catalyzed transformations to synthesize tetrasubstituted alkenylboronates has gained more and more attention recently [1–9]. Currently, the reported synthesis of tetrasubstituted alkenylboronates often use aromatic-substituted alkynes as substrates. It is rare to use alkyl-substituted alkynes [7–9]. Another challenge for synthesizing trialkylsubstituted alkenylboronates is the regioselectivity controlling.

Recently, Kanai et al. developed the copper-catalyzed borylalkylation of dialkylsubstituted internal alkynes with bis(pinacolato)diboron [$(Bpin)_2$] and benzyl halides (Scheme 1) [10]. In their study, by choosing a proper ligand for the copper catalyst, the regioselectivity could be controlled very well for the borylalkylation of alkynes. The π-accepting ability of the NHC ligand (^{NQ}IMes, **L**) on the copper(I) catalyst was considered to be essential for controlling the high regioselectivity of product **P1** (Scheme 1, **P1**:**P2** = 10:1). However, it remains unclear how the transformation takes place and how the high regioselectivity is achieved. Herein we reported a theoretical mechanistic study to address the issues.

2. Computational details

In our calculations, the geometries of all intermediates and transition states were optimized at the B3LYP [11] level of density functional theory (DFT) in the gas phase. A mixed basis set of SDD for Cu and I atoms, and 6-31G(d,p) for other atoms (BSI) was used, which has been proved to be appropriate for the copper-catalyzed reactions [12–14]. Frequency analyses were carried out to ensure all stationary points to be minima (zero imaginary frequencies) or transition states (one imaginary frequency) at the B3LYP/BSI level. When necessary, intrinsic reaction coordinates (IRC) [15] calculations were applied to confirm a transition state actually connecting the corresponding two minima. To consider solvent effects, we performed single-point energy calculations using the gas-phase optimized structures with SMD [16] solvent model at the M06 [17]/BSII (SDD [18] for Cu and I atoms, and 6−311++G(d,p) for other atoms) level. Natural bond orbital (NBO) analysis were performed at the M06/BSII level on selected structures with the NBO code included in Gaussian 09 [19]. Free energies (kcal/mol) obtained at the M06/BSII//B3LYP/BSI level were used in the following

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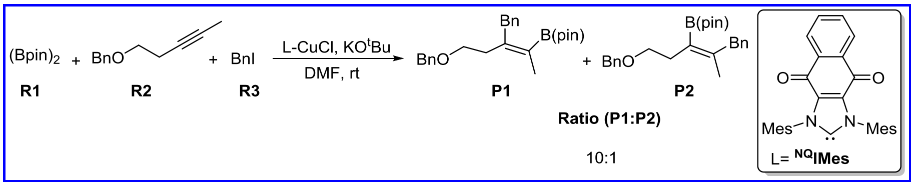

Scheme 1. Synthesis of trialkylsubstituted alkenylboronates from unactivated internal alkynes reported by Kanai's group.

discussion. All the calculations were carried out with the Gaussian 09 packages. Computed structures are illustrated using CYLview [20].

3. Results and discussion

To complete the transformation, we envisioned that the catalytic cycle should involve a borylcopper complex featuring a Cu–B bond. Previously, it has been proposed that LCuCl may react with $(Bpin)_2$ (**R1**) to generate a borylcopper complex [21–23]. We explored the possibility but the high barrier (53.6 kcal/mol) of the reaction excludes the possibility (red pathway Fig. 1). Instead, according to the species involved in the catalytic system, we propose that LCuCl (**1**) first undergoes ligand exchange with the additive KO^{t}Bu, giving LCu-O^{t}Bu (**2**) which then reacts with $(Bpin)_2$, resulting in a borylcopper complex. Supportively, the ligand exchange (LCuCl + $(KO^tBu)_4$ → LCu-O^{t}Bu + $K_4(O^tBu)_3Cl$) [24] is exergonic by 0.2 kcal/mol, and the reaction of LCu-O^{t}Bu (**2**) with $(Bpin)_2$ has a low barrier (13.3 kcal/mol) and is exergonic by 14.5 kcal/mol (Fig. 1).

Subsequent to the production of the boroylcopper intermediate **4**, alkyne insertion proceeds. Fig. 2 illustrates the pathway for the insertion. First, dialkylsubstituted alkyne **R2** coordinates to Cu center, giving the coordination complexes **5** and **7**, respectively, depending on the two coordination modes, as shown by black and blue pathways. The two coordination modes lead to **P1** and **P2** products, respectively. Subsequent to alkyne coordination, the alkyne group inserts to the Cu–B bond by crossing the transition states (**TS5** and **TS7**), affording the intermediates (**6** and **8**), respectively. Relative to **4**, the insertions overcome barriers of 22.4 and 23.2 kcal/mol and are exergonic by 24.6 and 23.6 kcal/mol, respectively. Thus, the insertions are feasible in terms of both kinetics and thermodynamics.

When **6** and **8** are available, benzyl halide BnI begins to participate in the transformation. For the convenience of description, we use the reaction of **6** as an example to describe the reaction mechanisms. As shown in Fig. 3, we have considered two possible pathways for the reaction. Along the red pathway (termed as **O-R** hereafter), BnI first undergoes oxidative addition via **TS8**, giving an intermediate **9**. Subsequently, **9** undergoes reductive elimination to form C–C bond, giving the product **P1** and liberating the copper species L-Cu-I. The copper specie can serve as the catalyst precursor for the next catalytic cycle. Note that initially, the metal precursor is L-Cu-Cl, but the difference does not influence our predicted energetics, because the active species L-Cu-O^{t}Bu is used as energy reference. Along the black pathway (termed as **E-A** pathway hereafter), the reaction takes place via concerted electrophilic addition, C–C and Cu–I bond formations and product release occurring simultaneously. As compared, the **O-R** pathway is much less favorable than the **E-A** one; **TS10** is 24.1 kcal/mol lower than **TS8**. We attribute the disfavor of the **O-R** mechanism to the resistance of copper to achieve a high +3 oxidation state [25]. Similarly, **8** also prefers the **E-A** mechanism to afford the product **P2** (blue pathway in Fig. 4).

The possible pathway of borycopper **4** reacting with BnI prior to **R2** was also calculated and precluded due to the high free energy barrier (Fig. S1 in the Supporting Information). In Kanai's experiment [10], **4** reacted preferentially to benzyl bromide than to alkyne

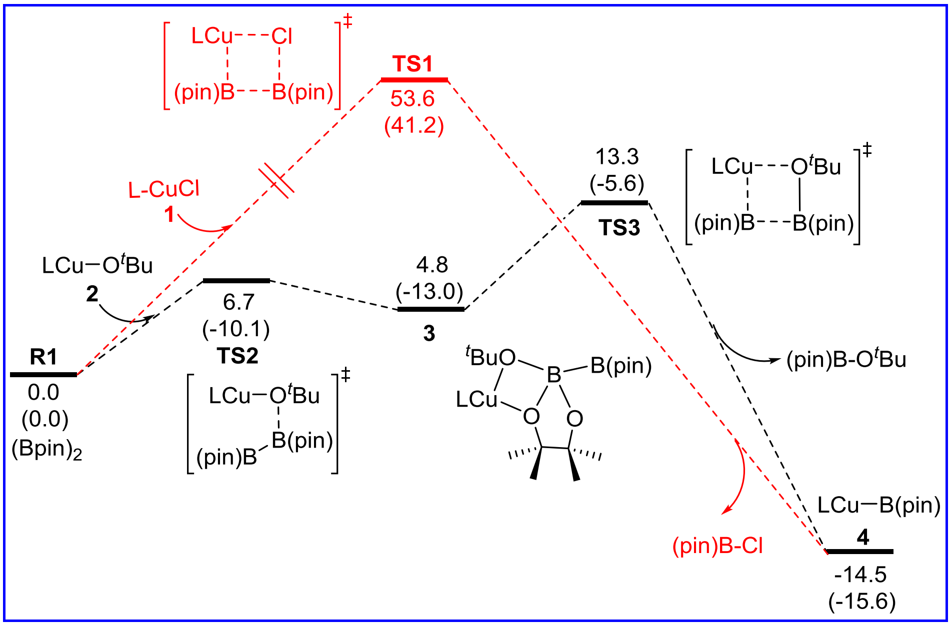

Fig. 1. Free energy diagram for the formation of borylcopper complex **4**. The relative free energies and relative enthalpic energies (in parentheses) are given in kcal/mol.