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Palladium-catalyzed oxidative borylation of conjugated enynones through carbene migratory insertion: synthesis of furyl-substituted alkenylboronates†

Yifan Ping,^a Taiwei Chang,^{ib} Kang Wang,^a Jingfeng Huo^a and Jianbo Wang^{id} *^{ab}

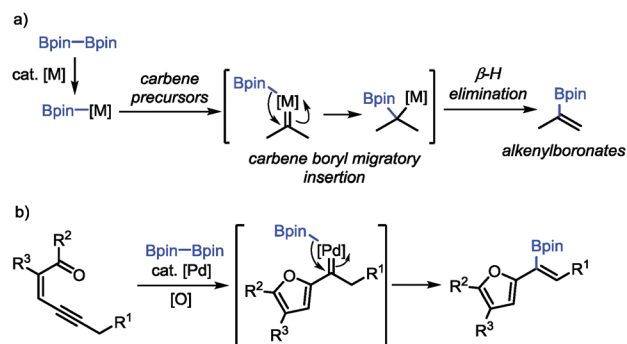
A palladium-catalyzed oxidative borylation reaction of conjugated enynones is developed. This reaction represents a new method for the synthesis of furyl-substituted alkenylboronates. The reaction works well with a series of conjugated enynones. Boryl migratory insertion of the palladium carbene intermediate is proposed as the key step in these transformations.

Transition-metal-catalyzed carbene-based cross-coupling reactions have emerged as powerful synthetic methods for C–C and C=C bond formation.¹ In these transformations, the organometallic species, which can be generated from oxidative addition,² transmetalation,³ C–H activation⁴ or other processes,⁵ reacts with a carbene precursor to form a metal carbene intermediate. Then, carbene migratory insertion occurs to generate a new organometallic species that undergoes further transformation to afford various coupling products. Diazo compounds are the most common carbene precursors, which can be decomposed by transition-metal catalysts to generate a metal carbene species with the release of nitrogen gas.⁶ Recently, we have explored other carbene precursors for this type of coupling reaction.⁷ In particular, we have previously focused on the carbene coupling with conjugated enynones, which have been used as furyl carbene precursors in traditional carbene transformations,⁸ such as X–H insertion,⁹ cyclopropanation,¹⁰ ylide formation¹¹ and other transformations.¹² We have developed a series of transition-metal-catalyzed cross-coupling reactions between conjugated enynones and various coupling partners, demonstrating that the migratory insertion can also be applied to these non-diazo carbene precursors.¹³ These reactions constitute efficient approaches for the synthesis of furan derivatives, which are

important frameworks of many bioactive compounds and pharmaceuticals.¹⁴

As a continuation of our interest in carbene-based coupling reactions, we have envisioned that a boron–metal species generated from transmetalation between diboron compounds and transition-metal catalysts may also participate in carbene migratory insertion to form C–B bonds followed by β -H elimination, which may provide a new method for the synthesis of alkenylboronates (Scheme 1a).^{15,16} Alkenylboronates are versatile building blocks in transition-metal-catalyzed cross-coupling reactions and other functional group transformations.¹⁷ The established methods for their synthesis include alkyne borylation,¹⁸ alkene cross-metathesis,¹⁹ Miyaura borylation,²⁰ alkene C–H borylation,²¹ Boryl–Heck reaction²² and Boron–Wittig reaction.²³ Nevertheless, the methods for the synthesis of furyl-substituted alkenylboronates are still rather limited.²⁴ Herein, we reported a palladium-catalyzed oxidative cross-coupling reaction between conjugated enynones and diboron compounds for the synthesis of furyl-substituted alkenylboronates (Scheme 1b). We have also demonstrated the transformations of the furyl-substituted alkenylboronates.

The investigation was initiated with conjugated enynone **1a** and bis(pinacolato)diboron **2a** as the model substrates. The reaction was carried out in methanol at 40 °C with Pd(OAc)₂ as



Scheme 1 Carbene boryl migratory insertion for the synthesis of alkenylboronates.

^a Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China.

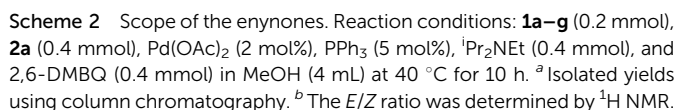
E-mail: wangjb@pku.edu.cn

^b The State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

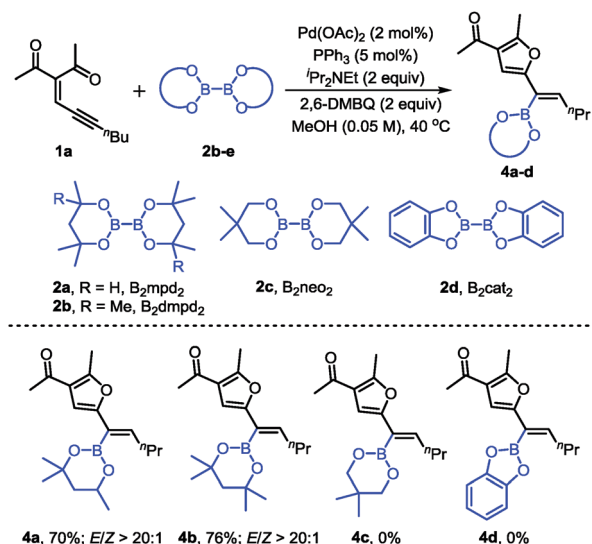
† Electronic supplementary information (ESI) available: Experimental details, and characterization data. See DOI: 10.1039/c8cc09024f

^a Reaction conditions are the following if not otherwise noted: **1a** (0.1 mmol), **2a** (0.12 mmol), Pd catalyst (5 mol%), ligand (10 mol%), base (2 equiv.) and oxidant (1.2 equiv.) in methanol (2 mL) at 40 °C for 10 h.
^b Determined by ¹H NMR using nitromethane as the internal standard if not otherwise noted. ^c Pd(OAc)₂ (2 mol%), PPh₃ (5 mol%). ^d **2a** (2 equiv.), 2,6-DMBO (2 equiv.). ^e E/Z = 10:1. Isolated yield shown in brackets.

With the optimized conditions in hand, the scope of conjugated enynones was evaluated (Scheme 2). It should be mentioned that the hydrogens on the carbon adjacent to the alkyne moiety of the enynone substrates are required. Thus, a β -hydride elimination process can occur to complete the catalytic cycle. We first investigated the conjugated enynones bearing the primary alkyl group adjacent to the alkyne moiety (Scheme 2). The coupling reaction worked smoothly in all cases, affording a series of trisubstituted alkenylboronates in moderate to good yields and high stereoselectivities (**3a-n**). Notably, the enynone substrates **1f-i** are all 1:1 mixtures of *E/Z* isomers. However, the reaction with the mixture of (*E*)- and (*Z*)-enynones afforded the corresponding

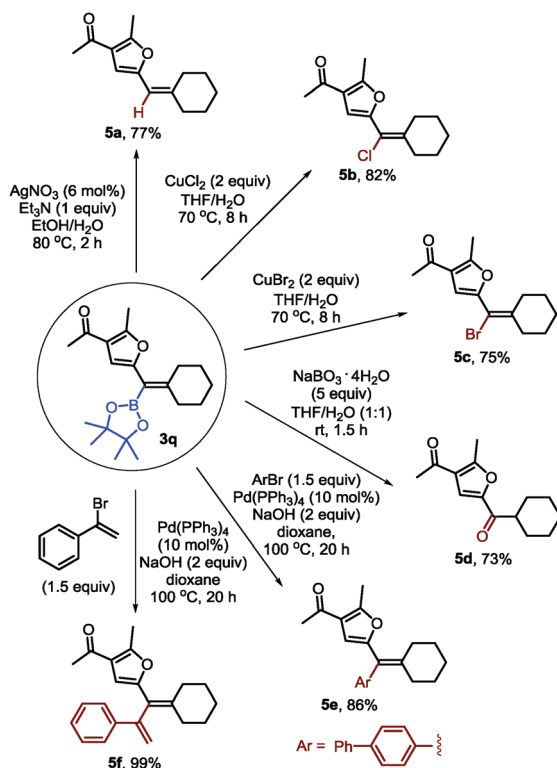


To demonstrate the synthetic utility of furyl-substituted alkenylboronates, further transformations of **3q** were carried

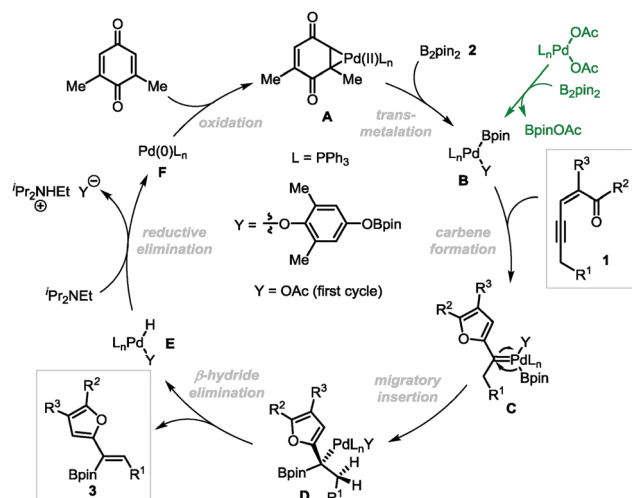


Scheme 3 Scope of the diboron compounds. Reaction conditions: **1a** (0.2 mmol), **2b-e** (0.4 mmol), Pd(OAc)₂ (2 mol%), PPh₃ (5 mol%), ⁱPr₂NEt (0.4 mmol), and 2,6-DMBQ (0.4 mmol) in MeOH (4 mL) at 40 °C for 10 h. Isolated yields. The *E/Z* ratio was determined by ¹H NMR.

out (Scheme 4). First, protodeboronation could occur in the presence of a silver catalyst (**5a**). Alkenyl chloride or bromide could be formed with stoichiometric copper halides (**5b-c**). Besides, the alkenylboronate could be easily oxidized into a ketone with sodium perborate as a mild oxidant (**5d**). Finally, Suzuki-Miyaura coupling of **3q** with 4-bromo-1,1'-biphenyl or



Scheme 4 The transformations of furyl-substituted alkenylboronates.



Scheme 5 The proposed reaction mechanism.

(1-bromovinyl)benzene could afford the furyl-substituted alkene and 1,3-diene in good yields (**5e-f**).

On the basis of our previous studies,¹³ a plausible mechanism has been proposed for the Pd-catalyzed oxidative borylation reaction (Scheme 5). First, palladium acetate reacts with diboron compound **2** through transmetalation to generate the palladium(II)-boron species **B**,²⁰ which activates the alkyne moiety of conjugated enynones **1** to form palladium-carbene complexes **C**. Then boryl-migratory insertion occurs to generate intermediate **D**, followed by β-H elimination to produce the final product **3**. The intermediate **E** undergoes reductive elimination in the presence of a base to produce Pd(0), which can be oxidized by 2,6-DMBQ to regenerate catalytically reactive Pd(II) species **A** to complete the catalytic cycle. The *E* selectivity is presumably attributed to the different steric hindrances of the furyl and boryl groups in the *cis* β-H elimination step.

In summary, we have developed a Pd-catalyzed oxidative borylation reaction of conjugated enynones as the carbene precursors. A wide range of substrates were tolerated in this reaction, and various furyl-substituted alkenylboronates were obtained in good yields. The products could be converted into various furan derivatives, demonstrating the synthetic utility of this reaction. The strategy by using carbene boryl migratory insertion to form C-B bonds may open a new door for the synthesis of organoboron compounds.

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Conflicts of interest

There are no conflicts to declare.

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