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

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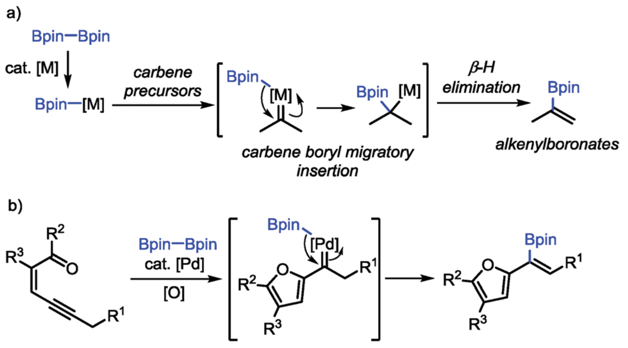
A palladium-catalyzed oxidative borylation reaction of conjugated enynones is developed. This reaction represents a new method for the synthesis of furyl-substituted alkenylboronates. The reaction works well with a series of conjugated enynones. Boryl migratory insertion of the palladium carbene intermediate 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 activation[4] 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 formation[11] 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 reaction[22] 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.

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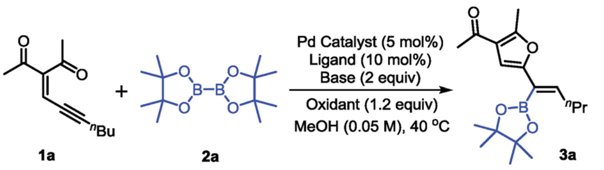
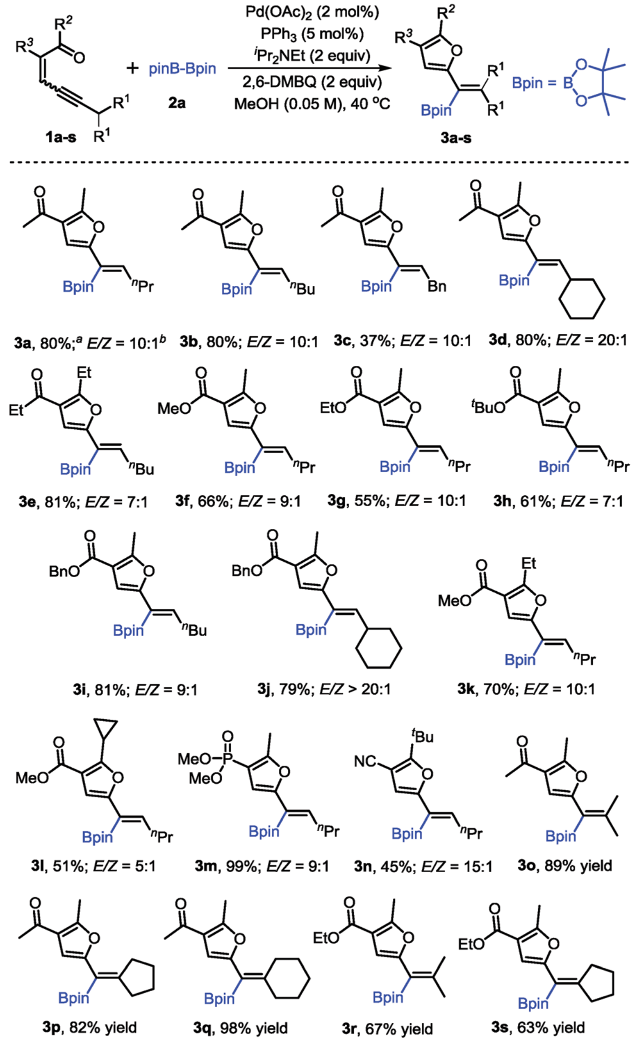
Table 1 Optimization of the reaction conditions[a]



Entry	Pd catalyst	Ligand	Base	Oxidant	Yield[b] (%)
1	$Pd(OAc)_2$	PPh_3	KOAc	BQ	51
2	$Pd(PPh_3)_4$	—	KOAc	BQ	35
3	$Pd(PPh_3)_2Cl_2$	—	KOAc	BQ	37
4	$Pd(TFA)_2$	PPh_3	KOAc	BQ	48
5	$Pd(OAc)_2$	PPh_3	K_2CO_3	BQ	19
6	$Pd(OAc)_2$	PPh_3	K_3PO_4	BQ	Trace
7	$Pd(OAc)_2$	PPh_3	KOMe	BQ	Trace
8	$Pd(OAc)_2$	PPh_3	KOAc	2,5-DPhBQ	63
9	$Pd(OAc)_2$	PPh_3	KOAc	2,6-DMBQ	65
10	$Pd(OAc)_2$	PPh_3	NEt_3	2,6-DMBQ	67
11	$Pd(OAc)_2$	PPh_3	$^iPr_2NEt$	2,6-DMBQ	78
12[c]	$Pd(OAc)_2$	PPh_3	$^iPr_2NEt$	2,6-DMBQ	78
13[d]	$Pd(OAc)_2$	PPh_3	$^iPr_2NEt$	2,6-DMBQ	80(80)[e]

[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%), PPh_3 (5 mol%). [d] **2a** (2 equiv.), 2,6-DMBQ (2 equiv.). [e] *E*/*Z* = 10 : 1. Isolated yield shown in brackets.



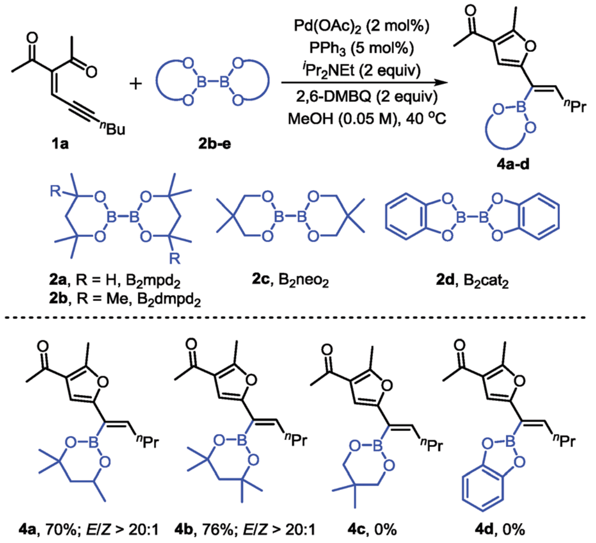
Scheme 2 Scope of the enynones. Reaction conditions: **1a–g** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (2 mol%), PPh_3 (5 mol%), $^iPr_2NEt$ (0.4 mmol), and 2,6-DMBQ (0.4 mmol) in MeOH (4 mL) at 40 °C for 10 h. [a] Isolated yields using column chromatography. [b] The *E*/*Z* ratio was determined by ^1H NMR.

the catalyst, PPh_3 as the ligand, KOAc as the base and benzoquinone (BQ) as the oxidant. Gratifyingly, we could observe the corresponding product **3a** in 51% yield (Table 1, entry 1). Some other palladium catalysts such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$ and $Pd(TFA)_2$ were then examined, however, the yields were slightly diminished with these palladium catalysts (entries 2–4). We also investigated the effect of substituted benzoquinones (entries 8 and 9). The yield could be improved to 65% with sterically-bulky 2,6-dimethylbenzoquinione (2,6-DMBQ) as the oxidant (entry 9). Inorganic bases such as K_2CO_3, K_3PO_4 and KOMe gave inferior results due to the side reactions (entries 5–7). Organic bases such as triethylamine and diisopropyl ethylamine were found to afford better results (entries 10 and 11). With diisopropyl ethylamine as the base, the catalyst loading was further reduced to 2 mol% (entry 12). Finally, increasing the loading of **2a** and oxidant to 2 equiv., the reaction could give 80% yield with 10 : 1 *E*/*Z* ratio (entry 13). The configuration of the double bond of **3a** was confirmed by ^1H NMR analysis of the protodeboronation product of **3a**.[25]

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–l** are all 1 : 1 mixtures of *E*/*Z* isomers. However, the reaction with the mixture of (*E*)- and (*Z*)-enynones afforded the corresponding products through cyclization of the ketone carbonyl oxygen in moderate to good yields (**3f–l**), which indicated that the isomerization of the double bonds occurred easily under the reaction conditions. Functional groups, such as phosphate and cyano groups, were tolerated in this reaction (**3m–n**). Furthermore, several conjugated enynones bearing secondary alkyl groups adjacent to the alkyne moiety were explored, leading to the formation of *tetra*-substituted alkenylboronates. The reaction proceeded smoothly and afforded the acyclic or exocyclic products in good yields (**3o–s**).

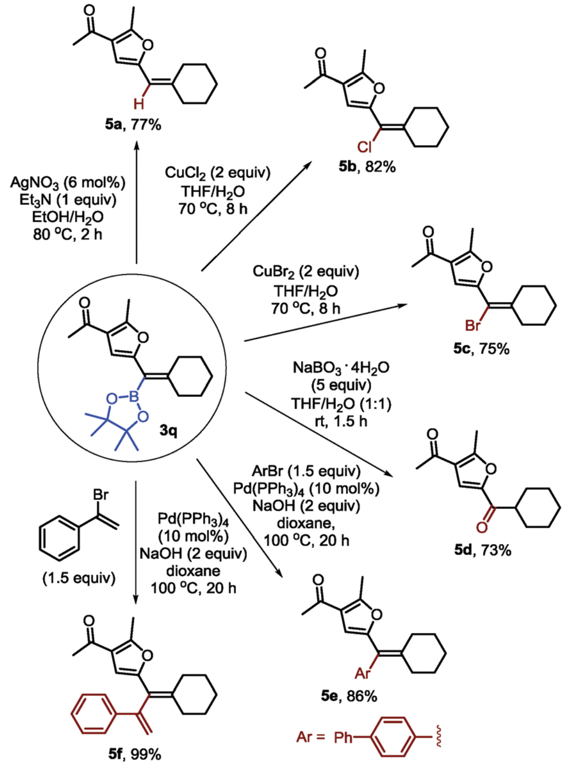
We also evaluated other diboron compounds, which are typically used in borylation reactions (Scheme 3). The use of B_2mpd_2 and B_2dmpd_2 gave the corresponding alkenylboronates in good yields and good stereoselectivities (**4a–b**). However, for the diboron compounds B_2neo_2 and B_2cat_2, no desired products were observed (**4c**, **4d**).

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

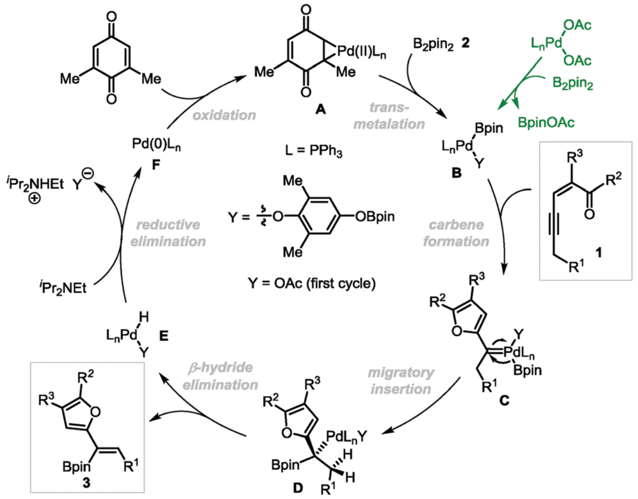


Scheme 3 Scope of the diboron compounds. Reaction conditions: **1a** (0.2 mmol), **2b–e** (0.4 mmol), $Pd(OAc)_2$ (2 mol%), PPh_3 (5 mol%), $^iPr_2NEt$ (0.4 mmol), and 2,6-DMBQ (0.4 mmol) in MeOH (4 mL) at 40 °C for 10 h. Isolated yields. The *E*/*Z* ratio was determined by ^1H NMR.

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



Scheme 4 The transformations of furyl-substituted alkenylboronates.



Scheme 5 The proposed reaction mechanism.

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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