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Cationic Palladium-Catalyzed [5+2] Annulation: Synthesis of 1-Benzoxepines from 2-Aroylmethoxyarylboronic Acids

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Abstract: The synthesis of 1-benzoxepines from 2-aroylmethoxyarylboronic acids and alkynes in the presence of a catalytic amount of $[Pd(dppp)(H_2O)_2]^{2+}(TfO^-)_2$ was developed. This [5+2] annulation involves the intramolecular nucleophilic addition of a vinylpalladium species to ketones.

Keywords: alkynes; arylboronic acids; benzoxepines; cationic palladium; ketones

The 1-benzoxepine moiety is an important structural unit in many natural products,[1] biologically active molecules,[1b] and natural herbicides.[2] The simple and efficient synthesis of 1-benzoxepine derivatives is attractive in synthetic organic chemistry and medicinal chemistry.[3] We reported herein a new, efficient synthesis of 1-benzoxepines by cationic palladium-catalyzed tandem cyclization of 2-aroylmethoxyarylboronic acids (**1**) and alkynes (**2**) [Eq (1)] involving the addition of vinylpalladium species to ketones.

In general, vinylpalladium species have a relatively low nucleophilicity.[4] There are only a limited number of examples concerning the direct addition of vinylpalladium species to electrophilic carbon-heteroatom multiple bonds, such as ketones.[5] Our group previously reported the Pd(II)-catalyzed cyclization of alkynes containing ketones initiated by the acetoxypalladation[6a] or carbopalladation[6b] of alkynes.

We recently reported the cationic palladium-catalyzed intramolecular addition of arylboronic acids to ketones [Eq (1)].[7] Bearing both a nucleophilic carbon-boron bond and an electrophilic carbonyl bond, the substrate 2-aroylmethoxyarylboronic acids **1** are in fact ambiphilic bifunctional arylboron compounds. In contrast to the seminal studies on the Rh-catalyzed cascade reaction of bifunctional organoborons and alkynes,[8,9] the corresponding palladium-catalyzed reaction has not been seen, perhaps owing to the lower nucleophilicity of the vinylpalladium species.[10]

Inspired by the examples of the addition of vinylpalladium species to ketones,[6,10] we next attempted to extend the application of substrate **1** from simple intramolecular addition reaction to the tandem cyclization with alkynes [Eq (1)]. Unlike most Pd(0)-catalyzed nucleophilic addition reaction in which a Pd(0)/Pd(II) redox system must be involved,[5] using Pd(II) as the catalyst for this type of reaction may be advantageous regarding the maintenance of Pd(II) throughout the catalytic cycle.

Initially, we chose **1a** (1 equiv.) as a model substrate in combination with alkyne **2a** (2 equivs.) to test the possibility of the tandem reaction (Table 1). This cascade reaction would be obviously unfavorable due to the facility of intramolecular cyclization[7] and the generation of a seven-membered ring which occurred uncommonly. In spite of these obstacles, the cascade cyclization of **1a** and **2a** did take place with a catalytic amount of $[Pd(dppp)(H_2O)_2]^{2+}(TfO^-)_2$[11] in dioxane at 60 °C. Although only a trace of the desired product **3aa** was produced, the dehydrated product **4aa** was isolated in moderate yield (72%, Table 1, entry 1). To prevent the dehydration of the normal product, the

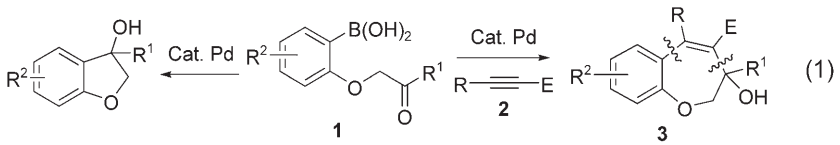
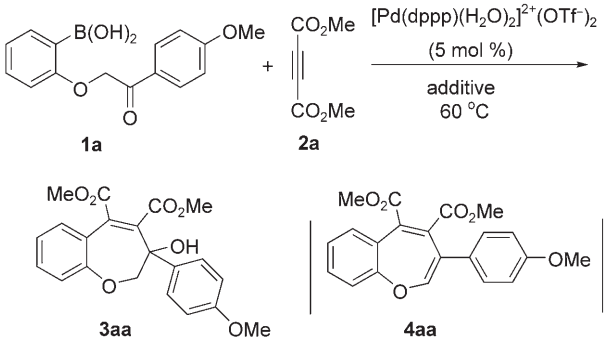


Table 1. Optimizing the tandem cyclization conditions.[a]



Entry	Additive (equivs.)	Product	Yield [%][b]
1	none	**4aa**	72
2	K_3PO_4 (2), H_2O (2)	-	-
3	$Ba(OH)_2$ (1.5)	**3aa**	90
4	Amberlite IRA-400 (OH) (1.5)	**3aa**	86
5[c]	Amberlite IRA-400 (OH) (1.5)	**3aa**	94
6[c,d]	Amberlite IRA-400 (OH) (1.5)	**3aa**	88

[a] Unless otherwise indicated, all reactions were performed at 60 °C using **1a** (0.1 mmol), **2a** (0.2 mmol) and [Pd(dppp)$(H_2O)_2]^{2+}(TfO^-)_2$ (5 mol %) in dioxane (0.5 mL) under N_2.
[b] Isolated yield.
[c] DME was used as the solvent.
[d] 1.2 equivs. of **1a** and 1 equiv. of **2a** was used.

effect of base was examined. Adding K_3PO_4 (2 equivs.) and H_2O (2 equivs.) resulted in the rapid decomposition of **2a** and none of the annulation product was detected. However, the use of insoluble bases, such as $Ba(OH)_2$ or Amberlite IRA-400 (OH), was found to give high yield of the normal product **3aa** (90 % and 86 %, respectively, Table 1, entries 3 and 4). The yield of **3aa** was also affected by the solvent. Reaction in DME led to the best result (94 % yield, Table 1, entry 5), while in DCE and toluene large amounts of deboronated product of **1a** was obtained. The use of 1.2 equivs. of **1a** combined with 1 equiv. of **2a** still gave an 88 % yield of desired product **3aa**. Furthermore, the [5+2] annulation was not catalyzed by $Pd(OAc)_2$/dppp or $Pd(TFA)_2$/dppp under the same reaction conditions. This indicated that the cationic palladium complex has great advantages over the neutral one in this reaction.

As shown in Table 2, the cascade cyclization could be carried out with a variety of substrate combinations of **1** and **2** to furnish a series of 1-benzoxpines. Arylboronic acids **1a–e** containing either electron-donating or electron-withdrawing aromatic ketones reacted smoothly with substitued propynoic acid methyl esters **2a–c** to afford the corresponding 1-benzoxepines in moderate to good yields (57–94 % yield, Table 2). When the arylboronic acid **1c** bearing an *ortho*-substituted aryl ketone was subjected to the reaction conditions, a good yield (89 %) was still achieved (Table 2, entry 3). Alphatic ketone **1f** was able to react with **2a** at 80 °C to produce **3fa** in 41 % yield (Table 2, entry 7). We then investigated the effect of substituents on the aromatic ring of the boronic acids. The reaction of Cl- and CH_3-substituted phenylboronic acids **1g** and **1h** with methyl-2-butynoate (**2b**) led to good yields of the desired products (90 and 81 %, respectively, Table 2, entries 10 and 11). Thus, the substitution on ketone or phenylboronic acid did not play a pronounced role in this tandem cyclization. In spite of the successful results above, the reaction of substrates **1i–k** with butynedioic acid dimethyl ester (**2a**) under the optimized conditions resulted in the recovery of the starting materials (Figure 1).

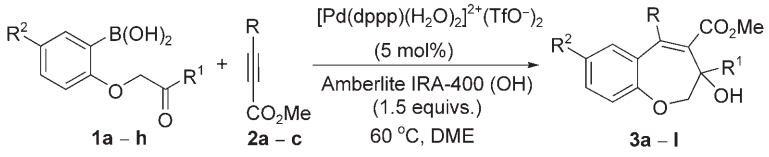
When substrate **1l**, bearing a cylic ketone moiety, was treated with **2b** in the presence of 5 mol % of $[Pd(dppp)(H_2O)_2]^{2+}(TfO^-)_2$ in DME at room temperature, a tricyclic product **3lb** was formed in moderated yield (Scheme 1). Encouraged by the good results obtained for alkynes featuring an electron-withdrawing ester group, alkoxymethyl-substituted alkyne **2d** was also examined for our [5+2] annulation. The reaction of **2d** and **1a** under the optimized conditions gave a complicated mixture of products. If the anion exchange resin was subtracted from the reaction, **2d** reacted with **1a** at 90 °C for two days to produce a 30 % yield of the dehydrated product **3ad** (Scheme 1). The relatively high temperature and low yield suggested that the alkoxymethyl-substituted alkyne is less active than ester-substituted alkynes.

Premilinary results on the asymmetric version of this protocol are shown in Scheme 2. The annulation of **1a** and **2a** proceeded very slowly catalyzed by $[Pd((R)\text{-binap})(H_2O)_2]^{2+}(TfO^-)_2$[12] and after three to four days a moderate asymmetric induction was observed. We then turned our efforts to the ligand (*S,S*)-bdpp, which has a similar skeleton as dppp. The use of *in situ* prepared $[Pd((S,S)\text{-bdpp})(H_2O)_2]^{2+}(TfO^-)_2$ from $Pd(OTf)_2{\cdot}2H_2O$[13] and (*S,S*)-bdpp improved the reaction rate and the yield of product **3aa**, whereas the *ee* value was still 50 %. Other chiral bisphosphine ligands such as Segphos and DIOP turned out to be ineffective ligand for this [5+2] annulation reaction.

As we have mentioned aboved, the substrate **1** could undergo intramolecular addition efficiently catalyzed by $[Pd(dppp)(H_2O)_2]^{2+}(TfO^-)_2$. Interestingly, the intramolecular reaction of **1** did not occur in the presence of alkynes implying that the stoichiometric amount of alkynes tuned the chemoselectivity of the substrates **1**, which will be explained from the catalytic cycle.

A plausible mechanism of this [5+2] annulation reaction is shown in Scheme 3. The mono-hydroxo cat-

Table 2. $[Pd(dppp)(H_2O)_2]^{2+}(TfO^-)_2$-catalyzed [5+2] annulation of 2-aroylmethoxyarylboronic acids with alkynes.[a]



1a: R^1 = *p*-MeO-C_6H_4, R^2 = H
1b: R^1 = C_6H_5, R^2 = H
1c: R^1 = *o*-MeO-C_6H_4, R^2 = H
1d: R^1 = *p*-Cl-C_6H_4, R^2 = H
1e: R^1 = *p*-CF_3-C_6H_4, R^2 = H
1f: R^1 = CH_3, R^2 = H
1g: R^1 = C_6H_5, R^2 = Cl
1h: R^1 = C_6H_5, R^2 = CH_3
2a: R = CO_2Me
2b: R = CH_3
2c: R = C_6H_5

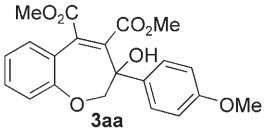
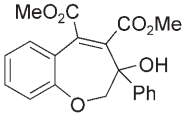
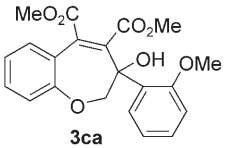
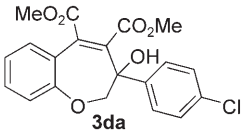
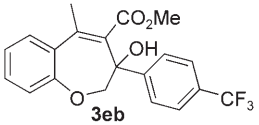
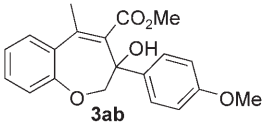
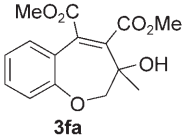
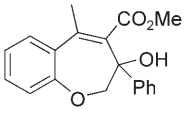
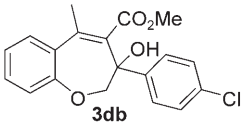
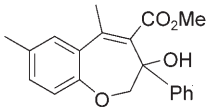
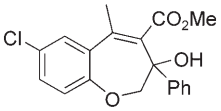
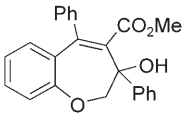
Entry	Substrate **1**	**2**	*t* [h]	Product	Yield [%][b]
1	**1a**	**2a**	33	 **3aa**	94
2[c]	**1b**	**2a**	16	 **3ba**	57
3	**1c**	**2a**	18	 **3ca**	89
4	**1d**	**2a**	4	 **3da**	82
5	**1e**	**2b**	4	 **3eb**	87
6	**1a**	**2b**	12	 **3ab**	59
7[c]	**1f**	**2a**	36	 **3fa**	41
8	**1b**	**2b**	72	 **3bb**	75
9[d]	**1d**	**2b**	12	 **3db**	87

Table 2. (Continued)

Entry	Substrate 1	Substrate 2	*t* [h]	Product	Yield [%][b]
10	**1g**	**2b**	5	 **3gb**	90
11	**1h**	**2b**	4	 **3hb**	81
12	**1b**	**2c**	12	 **3bc**	68

[a] Unless otherwise indicated, all reactions were performed using **1** (0.1 mmol), **2** (0.2 mmol), Amberlite IRA-400 (OH) (1.5 equivs.) and $[Pddppp(H_2O)_2]^{2+}(TfO^-)_2$ (5 mol%) in DME (0.5 mL) at 60 °C under N_2.
[b] Isolated yield.
[c] The reaction temperature was 80 °C.
[d] The reaction temperature was 40 °C.

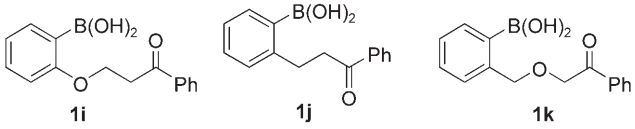
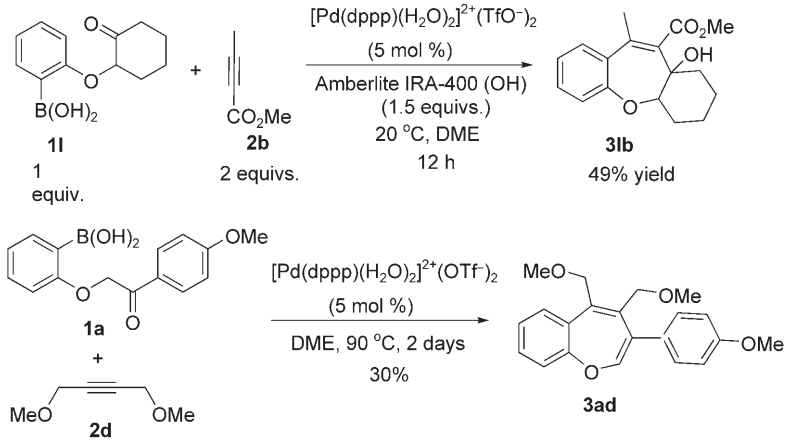


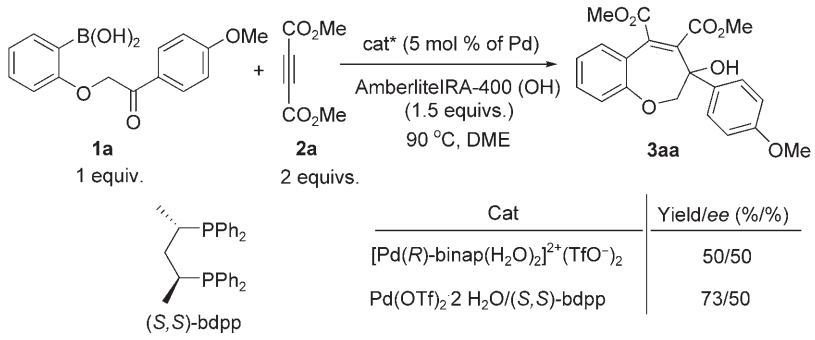
Figure 1. The limitation of substrates.

ionic palladium species **A**[12c,14] is believed to be the active catalyst, which enables smooth transmetalation with the substrate **1** without any assistance of additive bases.[7,15] Meanwhile, the alkyne will coordinate to the palladium center followed by regioselective carbopalladation giving intermediate **C**, in which the palladium is proposed to coordinate with the oxygen atom of the internal ketone. The high Lewis acidity of the cationic palladium center in species **C** may activate the carbonyl group by coordination resulting in facile 1,2-addition of vinylpalladium to ketone to furnish the seven-membered ring intermediate **D** which, upon hydrolysis, forms product **3** and regenerates the catalytically active species **A.** Thus, the presence of a vacant coodination site and high Lewis acidity of cationic palladium[16] are cricial for the the addition of vinylpalldium to ketones.

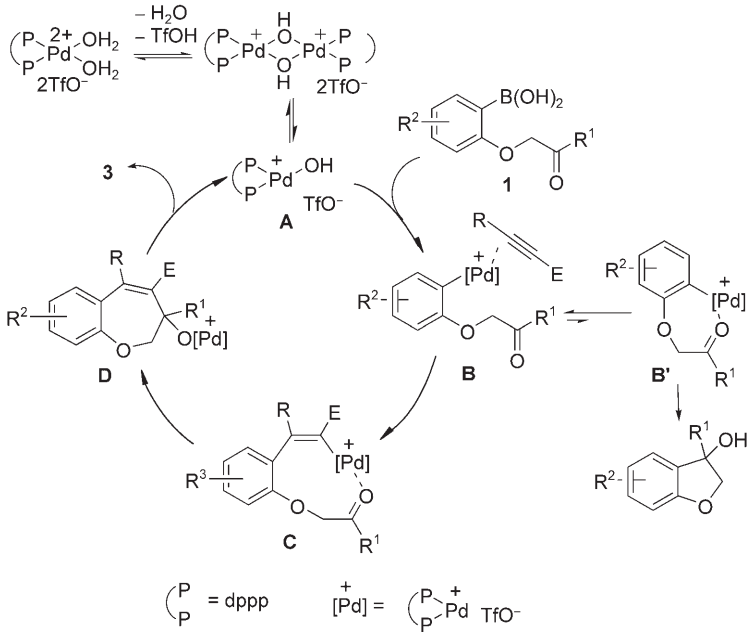
It is supposed that the tuneable role of alkynes may arise from the stronger affinity of the late transition metal palladium with the carbon-carbon triple bond rather than with the intramolecular carbonyl group in intermediate **B**, facilitating the insertion of alkynes into the carbon-palladium bond to form intermediate



Scheme 1.



Scheme 2. Preliminary results of the asymmetric version of the reaction.



Scheme 3. Plausible mechanism of the [5+2] annulation.

C. Otherwise, intermediate **B′** will be formed favoring the intramolecular reaction.[7]

In summary, we have achieved the synthesis of 1-benzoxepines from 2-aroylmethoxyarylboronic acids (**1**) and alkynes in the presence of a catalytic amount of $[Pd(dppp)(H_2O)_2]^{2+}(TfO^-)_2$. This [5+2] annulation involves the intramolecular nucleophilic addition of a vinylpalladium species to ketones and no redox reagent for the Pd(II)/Pd(0) system is involved. Further studies on the asymmetric version of this reaction are underway in our laboratory.

Experimental Section

Typical Procedure

Under nitrogen, Amberlite IRA(OH) (30 mg, 1.5 equivs.) was added to a solution of **1a** (28.6 mg, 0.1 mmol), **2a** (28.4 mg, 0.2 mmol) and $[Pd(dppp)(H_2O)_2]^{2+}(TfO^-)_2$ (4.3 mg, 5 mol%) in DME (0.5 mL). The reaction mixture was stirred at 60 °C for 33 h. After the reaction was completed as monitored by TLC, the reaction mixture was cooled to room tempretrue, filtered and concentrated. The residue was purified by flash column chromatography to afford the **3aa**; yield: 36 mg (94%).

For full experiemntal details and characterization data of all new compounds, see Supporting Information.

Acknowledgements

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