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Cationic Palladium Complex Catalyzed Diastereo- and Enantioselective Tandem Annulation of 2-Formylarylboronic Acids with Allenoates

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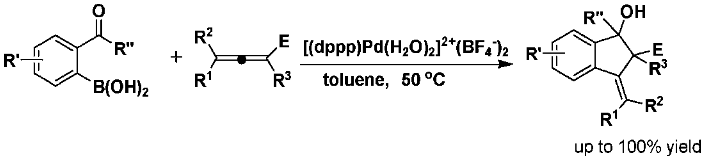
ABSTRACT



Cationic palladium complex $[(dppp)Pd(H_2O)_2]^{2+}(BF_4^-)_2$ catalyzed tandem annulation reactions of 2-formylarylboronic acids and allenoates produce the indenol derivatives diastereo- and enantioselectively in a highly efficient way.

Allenes are a class of compounds with unique reactivities, and they are very useful intermediates in organic synthesis.[1] Transition-metal-catalyzed reactions of allenes have attracted increasing interest due to the existence of two orthogonal π-bonds.[2] Organoboronic acids are widely used reagents in organic synthesis because of their commercial availability, stability, and nontoxicity. Various kinds of reactions using organoboronic acids and transition metals have been developed to construct carbon−carbon bonds.[3]

Recently, our group has developed a series of addition reactions of carbon−heteroatom multiple bonds catalyzed by Pd(II) species.[4−6] In all of these systems, the Pd(II) species was used as catalyst without the use of any redox system.

All of these reactions have similar intermediates, arylpalladium species or vinylpalladium species, which undergo nucleophilic addition to the carbonyl or nitrile groups followed by protonolysis to yield the corresponding products.

Inspired by these reactions, we investigate the tandem reactions of 2-formylarylboronic acids with allenoates. According to the literature, an allene can insert rapidly into a palladium−carbon bond to give π-allylpalladium species (Scheme 1).[7] This is a challenging task since it is known that a π-allylpalladium complex is electrophilic and will react with nuclephiles.[8] In the previous reports of Pd-catalyzed

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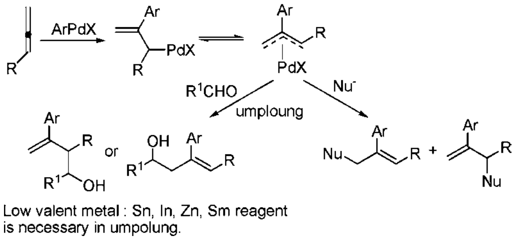
10.1021/ol901714d CCC: $40.75

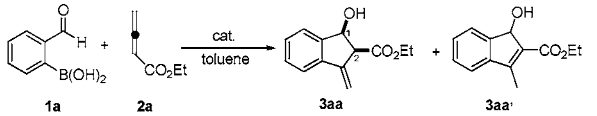
Scheme 1. Reaction of the π-Allylpalladium Complex



allylation of the carbonyl groups, a process called "umpolung" was generally used to change the electrophilicity of the π-allypalladium species by adding some reducing agents making the addition reaction possible.[9,10] Unfortunately, this umploung process is not suitable for the Pd(II)-initiated reactions because Pd(0) will be formed in the presence of reducing agents making the regeneration of the Pd(II) catalyst impossible. Recently, Malinakova realized the intermolecular three-component coupling of an arylboronic acid with allenes and aldehydes using a β-pinene-derived π-allylpalladium dimer as the catalyst suggesting that a η^1-allylpalladium species was formed which can act as a nucleophile.[11]

Herein, we wish to report the cationic palladium complexes catalyzed [3 + 2] tandem reactions of 2-formylarylboronic acids with allenoates. First, the effect of different palladium catalysts was investigated. The reaction of boronic acid **1a** and allenoate **2a** catalyzed by $Pd(OAc)_2$ (5 mol %) provided **3aa** in 27% yield (Table 1, entry 1). Less efficient reactions occurred when a neutral palladium species was used in the presence of diphosphine ligands (Table 1, entries 2 and 3). Performing the reaction under $Pd(CF_3CO_2)_2$ (5 mol %) with dppp (6 mol %), only **3aa** was obtained in 33% yield. Gratifyingly, treatment of **1a** and **2a** with the cationic palladium complex $[(dppp)Pd(H_2O)_2]^{2+}(TfO^-)_2$ (3 mol %),[5,12] afforded chromatographically separable isomers **3aa′** (78%) and **3aa** (21%) (Table 1, entry 6), respectively. Surprisingly, when substituting TfO^- with BF_4^- as anion, the reaction proceeded smoothly and completely within 15 min, obtaining **3aa** as a single product in nearly quantitative yield (Table 1, entry 7). These examples showed that cationic palladium(II) complexes are usually excellent catalysts for the addition of arylboronic acids to carbon−heteroatom multiple bonds due to their higher Lewis acidity, more vacant sites, and harder palladium compared to the neutral palladium species.[5,6] It should be noted that the ligand of the cationic palladium has a large effect on the reaction. When $[(bpy)Pd^+(\mu\text{-}OH)]_2(OTf^-)_2$ (3 mol %) was used as the catalyst, the reaction was totally inhibited (Table 1, entry 5). On the basis of the above investigation, the optimal condition for this tandem annulation reaction was as follows: $[(dppp)Pd(H_2O)_2]^{2+}(BF_4^-)_2$ (3 mol %), boronic acid **1a** (1 equiv), and allenoate **2a** (1.2 equiv) in toluene at 50 °C.

Table 1. Pd(II)-Catalyzed [3 + 2] Tandem Annulation Reaction of 2-Formylphenylboronic Acid with Ethyl Buta-2,3-dienoate[a]



entry	catalyst (mol %)	temp (°C)/time	yield(%)[b] **3aa/3aa′**
1	$Pd(OAc)_2$ (5)	80/20 min	27/0
2	$Pd(OAc)_2$ (5) + dppp (6)	80/12 h	16/0
3	$Pd(OAc)_2$ (5) + dppe (6)	80/12 h	trace
4	$Pd(CF_3CO_2)_2$ (5) + dppp (6)	80/9 h	32/0
5	$[(bpy)Pd^+(\mu\text{-}OH)]_2(TfO^-)_2$ (5)	80/9 h	NR
6	$[(dppp)Pd(H_2O)_2]^{2+}(TfO^-)_2$ (3)	50/20 min	21/78
7	$[(dppp)Pd(H_2O)_2]^{2+}(BF_4^-)_2$ (3)	50/15 min	98/0
8	$[(dppp)Pd(H_2O)_2]^{2+}(BF_4^-)_2$ (3)	rt/3.5 days	21/0

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), toluene (2 mL). [b] Isolated yields.

Using the optimized conditions, we study the scope of the tandem reaction (Table 2). Under the optimal condition, using **1a** as a model substrate, a series of coupling partners bearing a 1,2-allene moiety were investigated. All different allenoates could react diastereoselectively to give the corresponding **3aa**−**3ag** in excellent yields (90−100%). The *cis* stereochemistry of **3aa** and **3ag** was determined by NOESY spectra. In the case of **2i** and **2j**, which have methyl groups at the γ-position of the allenoates, the reaction can also take place but with a lower yield. When allenoate **2k** has a methyl group at the α-position, the reaction was totally inhibited. Using more reactive allenyl ketones **2h** and **2l**, only **2h** could react with boronic acid (**1a**) resulting in a poor yield. As for the allenyl sulfones (**2m**) and an electron-rich allene (**2n**), no product was detected. These results showed that electron-deficient allenes were the best substrates for this reaction.

A variety of 2-formylarylboronic acids were investigated using allenoate **2a** as another component. It turned out that different boronic acids can be used to give products in moderate to good yields. The electronic properties of the aromatic system have some influence on the yield of the reaction. For highly electron-rich boronic acid **1c**, it is better to carry out the reaction at room temperature because of the

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(10) Palladium(0)-catalyzed arylative cyclization with aryl iodides and distannane or In:(a) Ha, Y.-H.; Kang, S.-K. *Org. Lett.* **2002**, *4*, 1143. (b) Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376. See also silylative and stannylative cyclization: (c) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 343. (d) Yu, C.-M.; Youn, J.; Lee, M.-K. *Org. Lett.* **2005**, *7*, 3733. (e) Anwar, U.; Grigg, U.; Rasparini, M.; Savic, V.; Sridharan, V. *Chem. Commun.* **2000**, 645.

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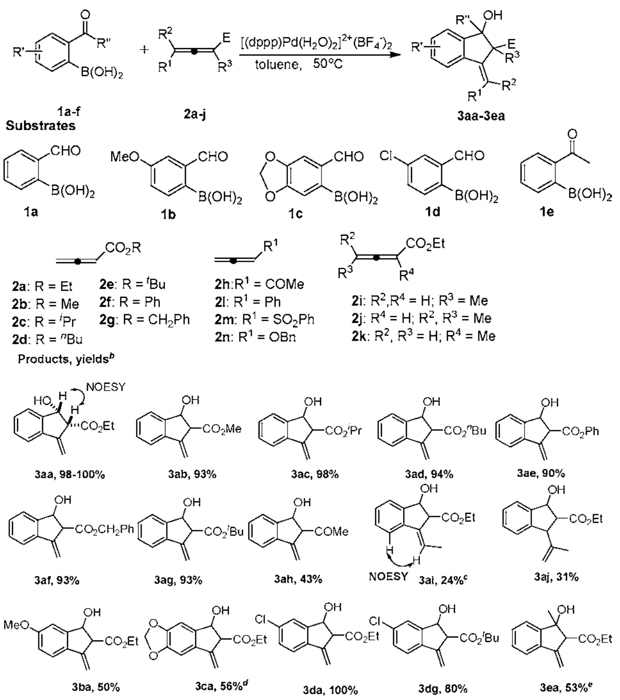
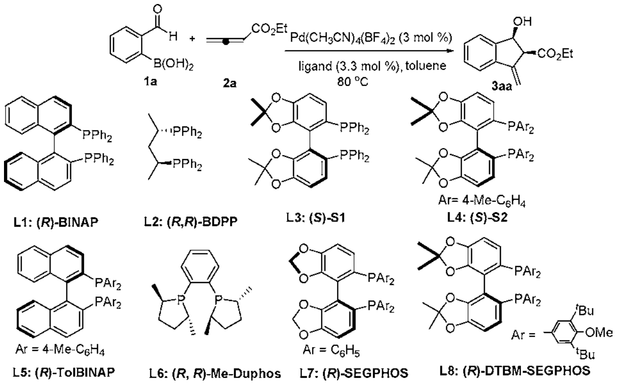
(12) Selected example catalyzed by $[(dppp)Pd(H_2O)_2]^{2+}(TfO^-)_2$, see: (a) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (b) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450. (c) Hamashima, Y.; Hotta, D; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (d) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, *6*, 1861. (e) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525.

Table 2. Cationic Palladium Complex Catalyzed Tandem Annulation Reaction of 2-Formylarylboronic acid with Substituted Allenes[a]



[a] Reaction conditions: **1** (0.24 mmol), **2** (0.2 mmol), toluene (2 mL), catalyst $[(dppp)Pd(H_2O)_2]^{2+}(BF_4^-)_2$ (3 mol %). [b] Cited yields are of products isolated by silica gel chromatography. [c] The configuration of double bond was comfirmed by NOESY spectra. [d] The reaction was carried out at 25 °C. [e] The reaction was carried out at 80 °C.

Table 3. Screening of the Asymmetric Reaction Conditions of **1a** and **2a** with Different Ligands[a]



entry	ligand	time (h)	yield (%)[b]	ee (%)[c]
1	(*S*, *S*)-BDPP	14	50	15
2	(*R*)-Tol-BINAP	2	99	81
3	(*R*)-BINAP	0.75	94	73
4	(*R*, *R*)-Me-DUPHOS	18	34	50
5	(*R*)-SEGPHOS	2	100	75
6	(*R*)-DTBM-SEGPHOS	1	48	--
7	(*S*)-S1	0.75	92	79
8	(*S*)-S2	0.5	92	82
9	(*S*)-S2	6	100	84

[a] Reaction conditions: **1a** (0.24 mmol, 1.2 equiv), **2a** (0.2 mmol, 1.0 equiv), cat. (3 mol %), ligand (3.3 mol %), and toluene (2 mL). [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD-H column. [d] The reaction temperature was 60 °C.

easy protonolysis of the boronic acid group (Table 2, product **3ca**). For ketone-substituted phenylboronic acid **1e**, a higher temperature was required to give the desired product in moderate yield (Table 2, product **3ea**).

Having developed the successful results for this tandem reaction, we turned our attention to the asymmetric version of the reaction. Cationic palladium complex $Pd(CH_3CN)_4(BF_4^-)_2$ combined with chiral ligands was used as the catalyst.[13] To improve the yield and the enatioselectivity of **3aa**, various axially chiral bisphosphine ligands were screened (Table 3). Finally, it was found that L4 ((*S*)-S2) and L5 ((*R*)-TolBINAP) were the best ligands for these asymmetric reactions.

Several 2-formylarylboronic acids were subjected to the reaction with allenoates **2a**−**2i** in the presence of $Pd(CH_3CN)_4(BF_4)_2$ (3 mol %)/(*R*)-TolBINAP (3.3 mol %) or $Pd(CH_3CN)_4(BF_4)_2$ (3 mol %)/(*S*)-S2 (3.3 mol %) (Table 4). All the allenoates **2a**−**2g** could participate in this reaction except **2i**. All reactions furnished excellent yields and high diastereoselectivity resulting in constructing two stereocenters in one pot.

The possible mechanism of this tandem reaction is shown in Scheme 2. The Pd hydroxo complex **C** was supposed to be the active catalytic species.[14−18] After transmetalation, owing to the vacant coordination site on the cationic palladium complex, substrate **2a** could easily coordinate to the palladium center to give intermediate **F**. Then, η^1-allylpalladium complex **G** was formed when the allenoate **2a** inserted into the palladium−carbon bond. High Lewis acidity of cationic palladium species **G** may activate the carbonyl group by coordination, and high nucleophilic property of the cationic η^1-allylpalladium complex **G** may result in intramolecular 1,2-addition to produce intermediate **H**.[17,18] The subsequent hydrolysis of **H** would afford product **3aa** and complete the catalytic cycle. It is worth noting that the more stable η^3-allyl complex cannot be formed immediately due to the orthogonal orbitals of the allene. The η^1-allyl complex lacking the conjugation with the other double bond is always formed first, then η^3-coordination is possible to be formed after a rotation around the σ-C−C bond.[2] The highly active cationic η^1-allylpalladium complex will react with the aldehyde immediately once it is formed

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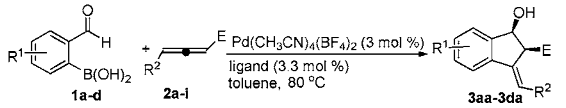
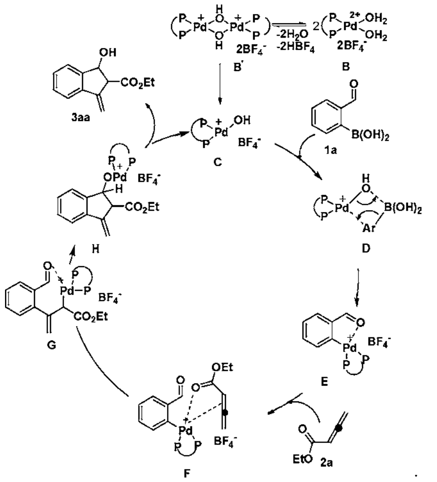
Table 4. $Pd(CH_3CN)_4(BF_4)_2$/(*R*)-TolBINAP or (*S*)-S2-Catalyzed Tandem Reaction of 2-Formylarylboronic Acids and Allenoates[a]



entry	substrate	ligand	product	yield (%)[b]	ee (%)[c]
1	**1a**,**2a**	**L5**	**3aa**	99	81(−)
2	**1a**,**2b**	**L5**	**3ab**	98	77(−)
3	**1a**,**2c**	**L5**	**3ac**	91	80(−)
4	**1a**,**2g**	**L5**	**3af**	18	65(−)
5	**1a**,**2a**	**L4**	**3aa**	92	82(−)
6	**1a**,**2b**	**L4**	**3ab**	96	77(−)
7	**1a**,**2c**	**L4**	**3ac**	93	82(−)
8	**1a**,**2d**	**L4**	**3ad**	97	81(−)
9	**1a**,**2e**	**L4**	**3ae**	81	70(−)
10	**1a**, **2f**	**L4**	**3af**	98	67(−)
11	**1a**,**2g**	**L4**	**3ag**	93	77(−)
12	**1a**, **2i**	**L4**	**3ai**	54	5(−)
13[d]	**1b**,**2a**	**L4**	**3ba**	52	80(−)
14	**1d**,**2a**	**L4**	**3da**	100	84(−)

[a] Reaction condition: **1a** (0.24 mmol, 1.2 equiv), **2a** (0.2 mmol, 1 equiv), catalyst (3 mol %), ligand (3.3 mol %), and toluene (2 mL). [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD column. The sign of optical rotation is indicated in parentheses. [d] The reaction temperature was 60 °C.

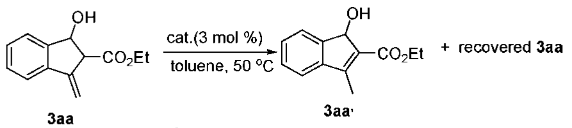
Scheme 2. Proposed Mechanism for the Tandem Reaction



without the formation of the η^3-allyl complex. The success for the tandem cyclization of allenes without the use of umpolung reagents showed the advantage of the use of cationic palladium complex as a catalyst for allenes.

The counteranions of the cationic palladium catalysts are particularly important as shown in the selectivity in the cationic $[(dppp)Pd(H_2O)_2]^{2+}(TfO^-)_2$ (**A**) and $[(dppp)Pd(H_2O)_2]^{2+}(BF_4^-)_2$ (**B**) catalyst (Table 1, entries 6 and 7). It is presumed that HOTf and HBF_4 generated from **A** and **B** would have a different impact on the final product. The control experiments showed that only HOTf or HBF_4 could not turn **3aa** into **3aa′**.

Scheme 3



cat. A	$[(dppp)Pd(H_2O)_2]^{2+}(TfO^-)_2$:	24 h	48%	50%
cat. B	$[(dppp)Pd(H_2O)_2]^{2+}(BF_4^-)_2$:	20 h	0%	90%

Subsequently, we probed the detailed effect of **A** and **B** employing product **3aa** under standard conditions (Scheme 3). In contrast to **B**, catalyst **A** favored the formation of the thermodynamic stable product **3aa′**. The reason for the difference in reactivity of these two cationic complexes is not clear. Several papers reported that the difference in reactivity of the cationic complexes with these two counteranions is due to their coordinating ability to the transition metals, and BF_4^- is less coordinating than TfO^-.[19] Thus, catalyst **B** has the more vacant sites for coordinating with the exocyclic double bond making the product **3aa** more stable.

In summary, we have uncovered the diastereo- and enantioselective, highly efficient tandem annulation reaction of 2-formylarylboronic acids and allenes catalyzed by cationic palladium complex $[(dppp)Pd(H_2O)_2]^{2+}(BF_4^-)_2$ which can suppress the generation of the π-allylpalladium complex without the presence of any additives. The use of cationic palladium species is crucial for this reaction. In addition, the selectivity made by the different counterions of the catalyst is noticeable. The detailed mechanism of this reaction is now underway in our laboratory.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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