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Cationic Pd(II)-Catalyzed Highly Enantioselective Arylative Cyclization of Alkyne-Tethered Enals or Enones Initiated by Carbopalladation of Alkynes with Arylboronic Acids

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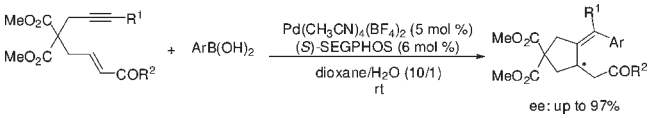
ABSTRACT



Cationic Pd(II)-catalyzed enantioselective arylative cyclization of alkyne-tethered enals or enones initiated by carbopalladation of alkynes was developed without the necessity of a redox system.

Transition-metal-catalyzed tandem reactions are powerful methods for the construction of structurally complex frameworks from relatively simple materials and have attracted great scientific interest from chemists.[1,2] Organoboronic compounds have been widely used in transition-metal-catalyzed transformations to construct carbon–carbon bonds because of their nontoxicity, commercial availability, and stability, especially in the area of multiple carbon–carbon bond-forming tandem reactions.[3,4]

Recently, our group has developed a variety of tandem reactions involving *ortho*-functionalized boronic esters or acids with internal alkynes or allenes catalyzed by cationic Pd(II) complexes.[5] Cationic Pd(II)-catalyzed arylative cyclization of alkyne-tethered aldehydes or ketones have also been reported.[6] In these reactions, vinylpalladium intermediates were generated by carbopalladation of alkynes followed by subsequent transformations. Compared with neutral Pd(II) species, cationic Pd(II) catalysts make the addition of aryl- or vinylpalladium to carbon–heteroatom multiple bonds or electron-deficient carbon–carbon double bonds more facile because of their vacant coordination sites and stronger Lewis acidity.[7] In these reactions, the

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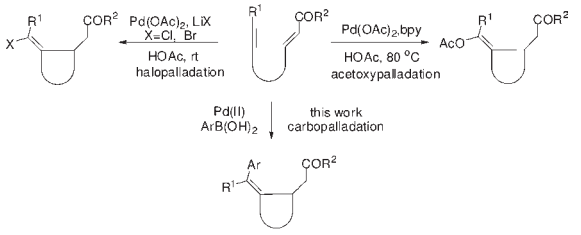
Pd(II) species was regenerated to complete the catalytic cycle without the necessity of a redox system.

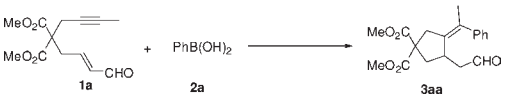
In our previous work, we reported Pd(II)-catalyzed intramolecular alkyne-α,β-unsaturated carbonyl coupling initiated by halopalladation or acetoxypalladation of alkynes[8] (Scheme 1). In the course of these reactions, halopalladation or acetoxypalladation of alkynes gives vinyl-palladium intermediate, which undergoes intramolecular carbon−carbon double bond insertion followed by protonolysis of the newly formed C−Pd bond to produce the product and regenerate the Pd(II) catalytic species. In these reactions, the use of excess halide ion or 2,2′-bipyridine ligand played a crucial role in inhibiting β-H elimination side reactions.[9] It is worth noting that β-H elimination side reactions were inhibited by using cationic Pd(II) as catalysts in our tandem reaction of *ortho*-boronate-substituted cinnamic ketones with alkynes[5c] and the conjugate addition reaction of arylboronic acids with enones reported by Miyaura.[7f,g] We are wondering if this enyne cyclization reaction is still possible when the reaction is initiated by carbopalladation of alkynes under the catalysis of cationic Pd(II) species.[10]

Scheme 1. Intramolecular Alkyne α,β-Unsaturated Carbonyl Coupling



In our initial study, alkyne-tethered enal **1a** was used as the model substrate in combination with $PhB(OH)_2$ to examine the effect of various cationic palladium catalysts. When $Pd(CF_3COO)_2$/dppp and $[Pd(dppp)(H_2O)_2](OTf)_2$ were used as catalysts, the reaction provided **3a** in 43% and 38% yields, respectively (Table 1, entries 1 and 2). A similar result was obtained when the reaction was catalyzed by $[Pd(dppe)(H_2O)_2](OTf)_2$ (40% yield, Table 1, entry 3). However, the reaction afforded **3aa** in a higher yield with $[Pd(dppp)(H_2O)_2](BF_4)_2$ as the catalyst (58% yield, Table 1, entry 4). By using toluene in the absence of H_2O as solvent, **3aa** was isolated only in 15% yield (Table 1, entry 5). Several kinds of additives were used to accelerate the transmetalation step. The good yields were achieved when 2 equiv of KF or 0.3 equiv of NaOH were added to the reaction (Table 1, entries 6 and 7). Nevertheless, when the reaction was performed in dioxane/H_2O, **3aa** was isolated in a very low yield (Table 1, entry 8). The yield of the product decreased as the temperature was lowered to 60 °C (Table 1, entry 9). On the basis of the above investigation, the optimal conditions for this tandem reaction were as follows: **1a** (0.2 mmol), phenylboronic acid **2a** (0.5 mmol, 2.5 equiv), $[Pd(dppp)(H_2O)_2](BF_4)_2$ (3 mol %), and NaOH (0.06 mmol, 0.3 equiv) in toluene/H_2O (2 mL/0.2 mL) at 80 °C.

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)/ time (h)	yield[b] (%)
1[c]	$Pd(CF_3COO)_2$ + dppp	toluene/H_2O	80/12	43
2	$[Pd(dppp)(H_2O)_2](OTf)_2$	toluene/H_2O	80/6	38
3	$[Pd(dppe)(H_2O)_2](OTf)_2$	toluene/H_2O	80/6	40
4	$[Pd(dppp)(H_2O)_2](BF_4)_2$	toluene/H_2O	80/5	58
5	$[Pd(dppp)(H_2O)_2](BF_4)_2$	toluene	80/12	15
6[d]	$[Pd(dppp)(H_2O)_2](BF_4)_2$	toluene/H_2O	80/3	67
7[e]	$[Pd(dppp)(H_2O)_2](BF_4)_2$	toluene/H_2O	80/0.5	79
8[e]	$[Pd(dppp)(H_2O)_2](BF_4)_2$	dioxane/H_2O	80/5	20
9[e]	$[Pd(dppp)(H_2O)_2](BF_4)_2$	toluene/H_2O	60/1	70

[a] Conditions: reactions were performed with **1a** (0.20 mmol), **2a** (0.50 mmol, 2.5 equiv), and catalyst (3 mol %) in toluene/H_2O (2 mL/0.2 mL), unless otherwise noted. [b] Isolated yield. [c] $Pd(CF_3COO)_2$ (5 mol %), dppp (6 mol %). [d] KF (2 equiv) was added. [e] NaOH (0.3 equiv) was added.

The reaction scope with a variety of arylboronic acids and alkyne-tethered enals or enones is summarized in Table 2. Generally, the reaction worked well with both electron-rich and electron-deficient arylboronic acids to give the corresponding products in moderate to good yields. However, aryboronic acids with electron-donating groups gave higher yields than those with electron-withdrawing groups (Table 2, entries 1−9). Arylboronic acids with halogen substituents, which offered opportunities for further transformations of the products, were compatible in this reaction (Table 2, entries 6 and 7). β-Naphthylboronic acid **2j** provided the highest yield in this reaction (Table 2, entry 10).

Enals bearing other substituted alkynes were treated with phenylboronic acid. Slightly lower yields were obtained with **1b** (R = *n*-Pr) and **1c** (R = Ph) than with **1a** (R = Me) (Table 2, entries 1, 11, and 12). While alkyne-tethered enones **1d** and **1e** worked well in this reaction (Table 2, entries 13 and 14), the reaction of alkyne-tethered enoate **1f** did not occur (Table 2, entry 15). Five-membered heterocycles could also be synthesized using this method (Table 2, entries 16 and 17). The stereochemistry of the exocyclic double bond in the products was assigned as the *E* configuration as confirmed by the X-ray crystallography of 2,4-dinitrophenylhydrazone derivative of **3af**.

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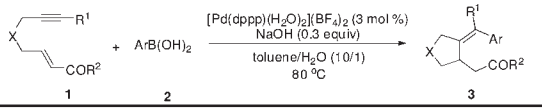
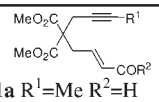
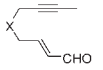
Table 2. Cationic Pd(II)-Catalyzed Arylative Cyclization of Alkyne-Tethered Enals or Enones[a]



entry	substrate **1**	$ArB(OH)_2$	product	yield[b](%)
		Ar		
1	**1a** R^1=Me R^2=H	**2a** Ph	**3aa**	79
2	**1a**	**2b** 4-Me-C_6H_4	**3ab**	83
3	**1a**	**2c** 3-Me-C_6H_4	**3ac**	72
4	**1a**	**2d** 4-^{i}Pr-C_6H_4	**3ad**	70
5	**1a**	**2e** 4-MeO-C_6H_4	**3ae**	84
6	**1a**	**2f** 4-Br-C_6H_4	**3af**	58
7	**1a**	**2g** 4-Cl-C_6H_4	**3ag**	62
8	**1a**	**2h** 4-F-C_6H_4	**3ah**	64
9	**1a**	**2i** 4-Ph-C_6H_4	**3ai**	74
10	**1a**	**2j** β-naphthyl	**3aj**	85
11	**1b** R^1=n-Pr R^2=H	**2a** Ph	**3ba**	67
12	**1c** R^1=Ph R^2=H	**2a** Ph	**3ca**	56
13	**1d** R^1=Me R^2=Me	**2a** Ph	**3da**	82
14	**1e** R^1=Me R^2=Ph	**2a** Ph	**3ea**	77
15	**1f** R^1=Me R^2=OMe	**2a** Ph	-	0
				
16	**1g** X=NTs	**2a** Ph	**3ga**	64
17[c]	**1h** X=O	**2a** Ph	**3ha**	35

[a] The reaction was carried out with **1** (0.2 mmol) and **2** (0.5 mmol) in toluene/H_2O (2 mL/0.2 mL) in the presence of $[Pd(dppp)(H_2O)_2](BF_4)_2$ (3 mol %) and NaOH (0.3 equiv) at 80 °C, unless otherwise noted. [b] Isolated yield. [c] The reaction was performed at 60 °C.

From the literature, it is known that γ-butyrolactone frameworks widely exist in some natural products and bioactive molecules.[11] We then wondered whether our new method was suitable for the synthesis of these compounds from the easily available acyclic allylic 2-alkynoate precursors. However, when substrates **1i** and **2a** were conducted under the standard reaction conditions, the desired product **3ia** was obtained in 41% yield together with another uncyclized product **3ia′** (48%) (Scheme 2). The stereochemistry of the newly formed double bond in products **3ia** and **3ia′** was assigned as the (*E*)-configuration on the basis of the lower field chemical shift of the methyl group resulting from the deshielding effect of the same side carbonyl group in ^{1}H NMR spectra and compared with the data in the literature.[12]

Subsequently, the asymmetric version of this cyclization reaction was studied. Various chiral ligands, solvents, and palladium species were screened to improve the yield and

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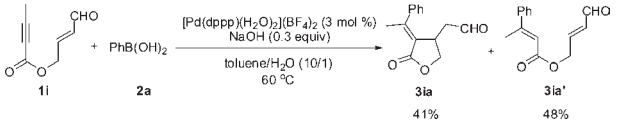
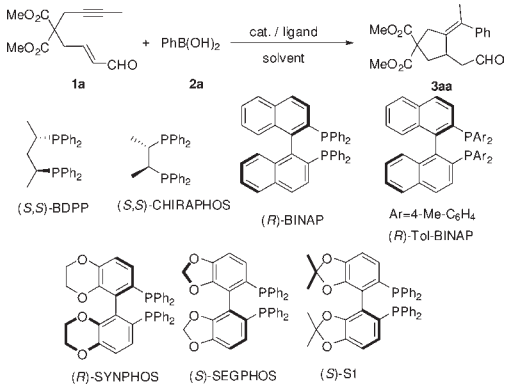
Scheme 2. Arylative Cyclization of **1i** with **2a**



the enantioselectivity (Table 3). High enantioselectivities were obtained by using bisphosphine ligands with biphenyl or binaphthyl motifs (Table 3, entries 1−7), and the best result (66% yield, 93% ee) was achieved with (*S*)-SEGPHOS (Table 3, entry 6). Elevating the reaction temperature to 40 °C resulted in a decreased enantioselectivity (Table 3, entry 8). When the reaction was performed in the absence of water, both the yield and the enantioselectivity

Table 3. Optimization of the Asymmetric Arylative Cyclization[a]



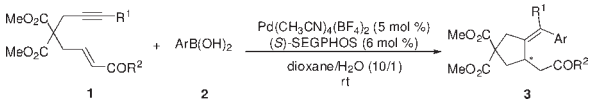
entry	ligand	solvent	yield[b] (%)	ee[c] (%)
1	(*S*,*S*)-BDPP	dioxane/H_2O	58	3
2	(*S*,*S*)-CHIRAPHOS	dioxane/H_2O	52	53
3	(*R*)-BINAP	dioxane/H_2O	48	92
4	(*R*)-Tol-BINAP	dioxane/H_2O	36	73
5	(*R*)-SYNPHOS	dioxane/H_2O	58	85
6	(*S*)-SEGPHOS	dioxane/H_2O	66	93
7	(*S*)-S1	dioxane/H_2O	65	93
8[d]	(*S*)-SEGPHOS	dioxane/H_2O	61	79
9	(*S*)-SEGPHOS	dioxane	28	74
10	(*S*)-SEGPHOS	MeOH	0	
11	(*S*)-SEGPHOS	THF/H_2O	52	35
12	(*S*)-SEGPHOS	toluene/H_2O	64	76
13	(*S*)-SEGPHOS	DCE/H_2O	40	93
14[e]	(*S*)-SEGPHOS	dioxane/H_2O	24	30
15[e,f]	(*S*)-SEGPHOS	toluene/H_2O	70	5
16[g]	(*S*)-SEGPHOS	dioxane/H_2O	trace	
17[h]	(*S*)-SEGPHOS	dioxane/H_2O	40	46

[a] Conditions: reactions were performed with **1a** (0.10 mmol), **2a** (0.15 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (5 mol %), ligand (6 mol %) in dioxane/H_2O (1 mL/0.1 mL) at room temperature for 2 days, unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The reaction was performed at 40 °C for 1 day. [e] NaOH (0.03 mmol, 0.3 equiv) was added. [f] The reaction was performed for 6 h. [g] $Pd(CF_3COO)_2$ (5 mol %) was used. [h] $Pd(OAc)_2$ (5 mol %) was used.

were sharply reduced (Table 3, entry 9). Other solvents were also tested (Table 3, entries 10–13). No desired product was observed in MeOH (Table 3, entry 10), and the ee value decreased in THF/H_2O or toluene/H_2O (Table 3, entries 11 and 12). A high ee value was also achieved in DCE/H_2O, while the yield was low (Table 3, entry 13). The ee value was sharply reduced when 0.3 equiv of NaOH was used as an additive (Table 3, entries 14 and 15). $Pd(CF_3COO)_2$ could not catalyze the reaction efficiently (Table 3, entry 16), and neutral palladium species $Pd(OAc)_2$ gave low yield and ee (Table 3, entry 17).

Under optimized conditions as shown in Table 3, entry 6, a variety of enyne substrates and arylboronic acids were subjected to asymmetric arylative cyclization (Table 4). The reactions furnished in high enantioselecivities with moderate yields which were probably due to the competive conjugate addition side reactions.[7f,g] Again, the β-naphthylboronic acid **2j** gave the highest yield with 97% ee (Table 4, entry 8).

Table 4. Asymmetric Arylative Cyclization Reaction of Alkyne-Tethered Enals Catalyzed by $Pd(CH_3CN)_4(BF_4)_2$/(*S*)-SEGPHOS System[a]

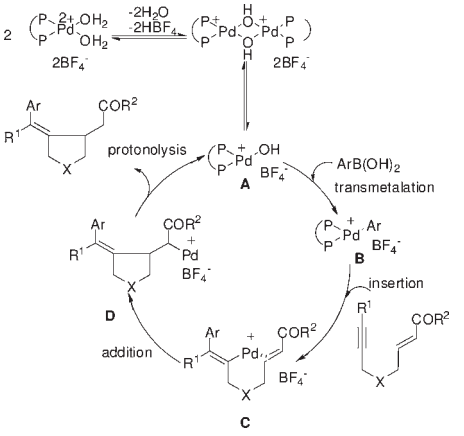


entry	substrate	product	yield[b] (%)	ee[c] (%)
1	**1a**, **2a**	**3aa**	66	93 (–)
2	**1a**, **2b**	**3ab**	61	93 (–)
3	**1a**, **2c**	**3ac**	65	93 (–)
4	**1a**, **2d**	**3ad**	61	92 (–)
5	**1a**, **2e**	**3ae**	68	85 (–)
6	**1a**, **2f**	**3af**	57	95 (–)
7	**1a**, **2i**	**3ai**	64	94 (–)
8	**1a**, **2j**	**3aj**	70	97 (–)
9	**1b**, **2a**	**3ba**	52	80 (–)
10	**1d**, **2a**	**3da**	67	93 (–)
11	**1e**, **2a**	**3ea**	65	92 (–)

[a] The reaction was carried out with **1** (0.1 mmol) and **2** (0.15 mmol) in dioxane/H_2O (1 mL/0.1 mL) in the presence of $Pd(CH_3CN)_4(BF_4)_2$ (5 mol %) and (*S*)-SEGPHOS (6 mol %) at room temperature for 2–3 days, unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis.

A possible mechanism of this tandem reaction is shown in Scheme 3. The Pd hydroxo complex **A** is supposed to be the active catalytic species.[13] Arylpalladium species **B** is formed by transmetalation of **A** with arylboronic acids. Carbopalladation of the substrate affords vinylpalladium intermediate **C**. Subsequent carbon–carbon double bond insertion gives intermediate **D**. The protonolysis of the newly formed C–Pd bond generates the product and regenerates the Pd(II) species **A**. While Pd(0) catalyst has been reported to be effective in this kind of arylative cyclization reaction through a cyclometalation pathway involving Pd(II)/Pd(0) catalytic cycle,[14] Pd(II) catalytic cycle is a plausible mechanism for this cationic Pd(II) catalyzed transformations based on the following results: (1) Halogen-substituted phenylboronic acids can be used as the substrates for this reaction (Table 2, entries 6 and 7). (2) Allylic esters can be used as the substrates for this reaction (Scheme 2). Both the aryl–halogen bond and the allylic ester group will be cleaved first in the presence of Pd(0).

Scheme 3. Proposed Mechanism for the Tandem Reaction



In conclusion, a cationic Pd(II)-catalyzed enantioselective arylative cyclization of alkyne-tethered enals or enones initiated by carbopalladation of alkynes was developed. This newly developed tandem reaction proceeds through a Pd(II) catalytic cycle without the necessity of a redox system.

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Supporting Information Available. Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.