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Cationic Pd(II)-Catalyzed Enantioselective Cyclization of Aroylmethyl 2-Alkynoates Initiated by Carbopalladation of Alkynes with Arylboronic Acids

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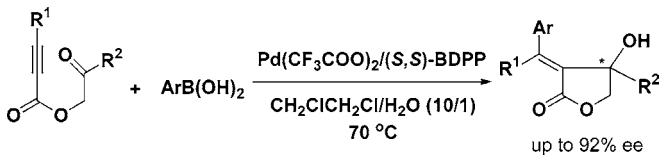
ABSTRACT



A cationic palladium(II)-catalyzed enantioselective intramolecular addition of vinylpalladium species to ketones initiated by the carbopalladation of alkynoates under mild conditions without a Pd(II)/Pd(0) redox system was developed with high yield and enantioselectivity. This cascade reaction provides an efficient method for the construction of optically active hydroxylactones.

Suffering from the less nucleophilic properties of the organopalladium species, the addition of carbon−palladium bond toward carbon−heteroatom multiple bonds has received scant attention compared with the numerous reports on the insertion of carbon−carbon multiple bonds.[1] Although, some reactions catalyzed by Rh,[2] Ni,[3] and others have been reported in this area, there were only a few examples on the addition of the organopalladium species to carbon−heteroatom multiple bonds.[4−7] Even so, most of them were catalyzed by Pd(0) species which involved a Pd(II)/Pd(0) redox system.[4,5]

In our earlier work, we reported a Pd(II)-catalyzed addition of a carbon−palladium species initiated by the acetoxypal-

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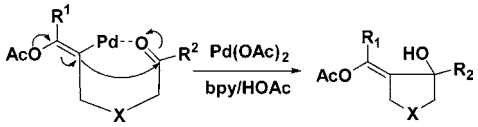
ladation of alkynes to a carbonyl group.[8] In the course of the reaction, vinylpalladium intermediates were generated by the acetoxypalladation of alkynes. The presence of the acetoxy group in the olefinic bond made the formed vinylpalladium species relatively more nucleophilic, and the nucleophilic addition to the carbonyl group became possible (Scheme 1). The question arises if this addition reaction is still possible when the reaction is initiated by carbopalladation of an alkyne.

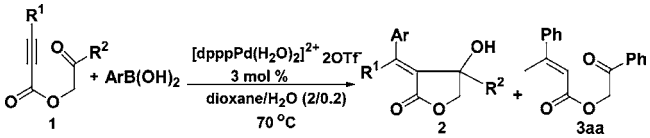
Scheme 1. Addition of 2-Acetoxyvinylpalladium Species to the Ketone Group



Organoboronic acids have been well-used in transition-metal-catalyzed carbon−carbon bond-forming reactions.[9] The carbopalladation of alkynes triggered by the addition of arylboronic acids is a promising way to generate vinylpalladium intermediates.[10] On the other hand, we have reported the addition of arylboronic acids to nitriles[6] and the intramolecular addition to ketones[7] catalyzed by cationic Pd complexes recently. It occurred to us that the cationic Pd catalyst may favor the addition of the vinylpalladium species to carbon−heteroatom bonds. Compared to the neutral Pd(II) species, there are two advantages for cationic Pd(II) species: [11,12] vacant coordination sites and stronger Lewis acidity. Herein, we wish to describe an unprecedented asymmetric cascade reaction which consists of the intermolecular carbopalladation of the alkynoates using arylboronic acids and subsequent intramolecular addition of vinylpalladium intermediates to the ketone group catalyzed by cationic Pd(II) complexes.

Our initial studies started by employing benzoylmethyl 2-butynoate as a model substrate in combination with $PhB(OH)_2$ to examine the reaction activity in the presence of different Pd(II) catalyst. When the neutral catalyst $Pd(OAc)_2$/dppp was employed, the protonolysis product **3aa** was obtained in 41% yield (Table 1, entry 1). Using $[(dppp)Pd(H_2O)_2](OTf)_2$[13a] as the catalyst, the reaction afforded **2aa** in 89% yield (Table 1, entry 4). However, the transformation was sluggish when the reaction was catalyzed by the two other cationic Pd catalysts $[(bpy)Pd(OH)]_2(OTf)_2$[6,13b] and $[(dppe)Pd(H_2O)_2](OTf)_2$[13c] (Table 1, entries 2 and 3). These results indicated that the acetoxy group is crucial in the addition of vinylpalladium species to ketones under neutral Pd(II) catalyst conditions. Meanwhile, the higher Lewis acidity of the cationic Pd(II) species might be the another reason for the success of the reaction.

Table 1. Cationic Pd(II)-Catalyzed Cyclization of Aroylmethyl 2-Alkynoates[a]

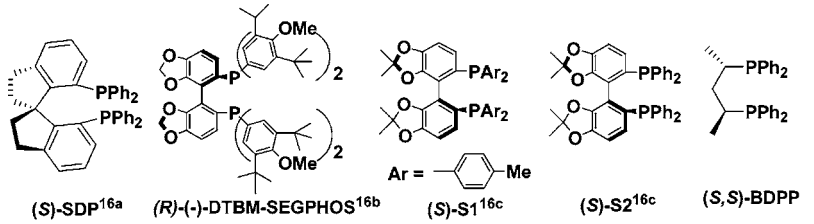


entry	**1**	R^1	R^2	Ar	**2**	yield (%)[b]
1[c]	**1a**	CH_3	Ph	Ph	**2aa**	
2[d]	**1a**	CH_3	Ph	Ph	**2aa**	39
3[e]	**1a**	CH_3	Ph	Ph	**2aa**	30
4	**1a**	CH_3	Ph	Ph	**2aa**	89
5	**1a**	CH_3	Ph	4-$MeOC_6H_4$	**2ab**	92
6	**1a**	CH_3	Ph	4-MeC_6H_4	**2ac**	90
7	**1a**	CH_3	Ph	4-FC_6H_4	**2ad**	94
8	**1a**	CH_3	Ph	3-$NO_2C_6H_4$	**2ae**	96
9	**1a**	CH_3	Ph	3-$MeOC_6H_4$	**2af**	85
10	**1a**	CH_3	Ph	2-naphthyl	**2ag**	88
11	**1b**	n-C_3H_7	Ph	Ph	**2ba**	81
12	**1c**	n-C_7H_{15}	Ph	Ph	**2ca**	79
13	**1d**	Ph	Ph	Ph	**2da**	84
14	**1e**	CH_3	4-$MeOC_6H_4$	Ph	**2ea**	82
15	**1f**	CH_3	4-ClC_6H_4	Ph	**2fa**	90
16	**1g**	CH_3	4-BrC_6H_4	Ph	**2ga**	89
17	**1h**	CH_3	CH_3	Ph	**2ha**	76

[a] Reaction conditions: Substrate (0.2 mmol), arylboronic acid (0.3 mmol) $[(dppp)Pd(H_2O)_2](OTf)_2$ (0.006 mmol) in dioxane/H_2O (2 mL/0.2 mL) at 70 °C. [b] Isolated yield. [c] Catalyzed by $Pd(OAc)_2$/dppp. [d] Catalyzed by $[(bpy)Pd(OH)]_2(OTf)_2$; **3aa** was obtained also in 33% yield. [e] Catalyzed by $[(dppe)Pd(H_2O)_2](OTf)_2$; **3aa** was obtained also in 21% yield.

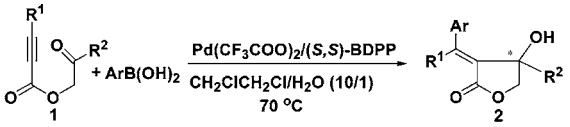
A series of α-alkylidene-β-hydroxy-γ-lactones were obtained in good to excellent yields (Table 1, entries 4−17) when a variety of arylboronic acids and aroylmethyl 2-alkynoates were employed. However, ortho-substituted arylboronic acid gave no cyclization product probably because of the steric hindrance. The stereochemistry of the exocyclic double bond in products **2** was assigned as (*E*)-configuration on the basis of the lower field chemical shift

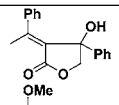
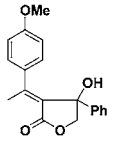
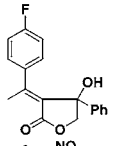
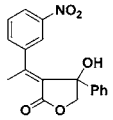
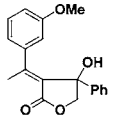
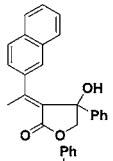
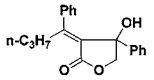
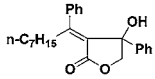
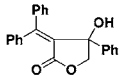
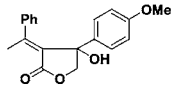
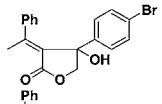
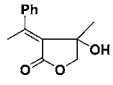
Scheme 2. Chiral Bidentate Phosphorus Ligands Screened in the Asymmetric Cyclization of Aroylmethyl 2-Alkynoates



(*S*)-SDP[16a] 16% (52% ee) | (*R*)-(-)-DTBM-SEGPHOS[16b] 23% (26% ee) | (*S*)-S1[16c] 78% (37% ee) | (*S*)-S2[16c] 71% (50% ee) | (*S,S*)-BDPP 87% (82% ee)

Table 2. Asymmetric Cyclization of Aroylmethyl 2-Alkynoates under the Catalysis of $Pd(CF_3COO)_2$/(S, S)-BDPP[a]



entry	product		yield (%)[b]	ee (%)[c]
1		**2aa**	87	82 (+)
2		**2ab**	87	74 (+)
3		**2ad**	87	78 (+)
4		**2ae**	83	92 (-)
5		**2af**	92	81 (+)
6		**2ag**	85	89 (+)
7		**2ba**	83	83 (+)
8		**2ca**	82	62 (+)
9		**2da**	65	79 (+)
10		**2ea**	90	75 (+)
11		**2ga**	85	76 (+)
12		**2ha**	82	84 (-)

[a] Reaction conditions: Substrate (0.2 mmol), arylboronic acid (0.5 mmol), $Pd(CF_3COO)_2$ (0.006 mmol), (S, S)-BDPP (0.0066 mmol) in CH_2ClCH_2Cl/H_2O (2 mL/ 0.2 mL) at 70 °C. [b] Isolated yield. [c] The ee values were determined by chiral HPLC. The sign of optical rotation was indicated in parentheses (for details see Supporting Information).

of the methyl or alkyl group for the *E* isomer in ^{1}H NMR spectra[14] and compared with the data in the literature.[15] Again, the structure of **2af** was confirmed by X-ray crystallography.

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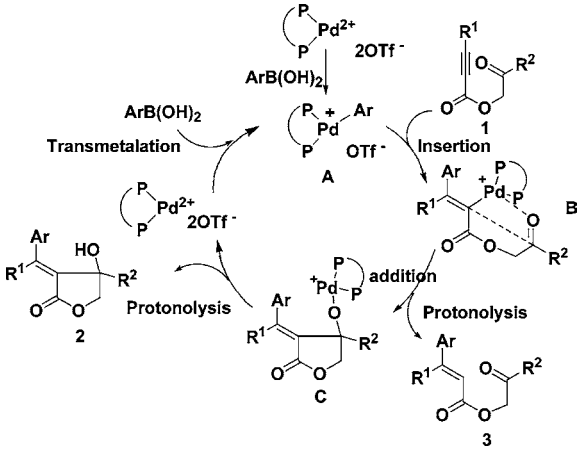
Subsquently, the asymmetric version of this cascade cyclization was studied. Unexpectedly, [(*R*)-(binap)$Pd(H_2O)_2$]-$(OTf)_2$ which was effective in cationic palladium-catalyzed intramolecular addition of arylboronic acid to ketones[7] showed low reactivity in the present reaction in dioxane (25% yield). Although the yield was improved to 71% in CH_3NO_2, low enantioselectivity (34% ee) was still observed. Some other chiral bidentate phosphorus ligands[16] also gave negative results (Scheme 2). Fortunately, enlightened by the structure of dppp, (*S*,*S*)-BDPP[16d] was tested, and good yields with moderate to excellent ee values were obtained (Table 2). It is important to note here that to simplify the experimental manipulation, $Pd(CF_3COO)_2$/(*S*,*S*)-BDPP was used directly in the reaction to generate cationic palladium-(II) species in situ.[17]

The possible mechanism is proposed as shown in Scheme 3.[18] First, arylpalladium species **A** is formed by transmetalation of the cationic Pd(II) species with arylboronic acids. Regioselective insertion of **1** to **A** affords vinylpalladium intermediate **B** (carbopalladation). High Lewis acidity of the

Scheme 3. Proposed Mechanism of the Asymmetric Cyclization of Aroylmethyl 2-Alkynoates under the Catalysis of Cationic Palladium(II) Initiated by Carbopalladation



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Pd center in cationic species **B** may activate the carbonyl group by coordination to the unshared electron pairs on the oxygen atom, facilitating the formation of the intermediate **C**.[11e] It is also proposed that this coordinated intermediate **B** is helpful to the enantioface discrimination of ketones resulting in high ee values.[19] A competitive reaction is the protonolysis of the vinyl palladium species producing byproduct **3**. After the addition of the Csp^2 carbon to the activated carbonyl group in B generates C, the product **2** is formed by protonolysis of the palladium alkoxide intermediate C with regeneration of the palladium species to make the catalytic cycle possible. Of course, another pathway to form intermediate C by the insertion of carbonyl group coordinated to palladium via the π-electrons to carbon−palladium bond in B could not be excluded.

In summary, we have developed a cationic palladium(II)-catalyzed enantioselective addition of vinylpalladium species to ketones initiated by carbopalladation of the alkynes without a Pd(II)/Pd(0) redox system. This cascade reaction provided an efficient way for the construction of optically active hydroxylactones.

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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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