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Cationic Palladium(II)-Catalyzed Highly Enantioselective [3 + 2] Annulation of 2-Acylarylboronic Acids with Substituted Alkynes

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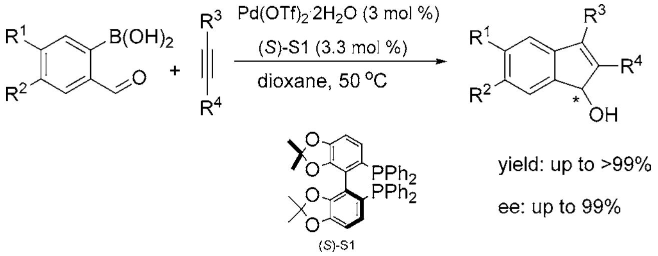
ABSTRACT



A cationic palladium(II)-catalyzed enantioselective tandem [3 + 2] annulation of 2-acylarylboronic acids with substituted alkynes to yield optically active 1-indenols was developed in high yields and excellent enantioselectivities.

The tandem annulation reaction catalyzed by transition metals is one of the most challenging processes of constructing carbo- and heterocyclic compounds.[1] The indenol moiety is an important structure unit in various biological active and pharmaceutical compounds.[2]

Despite various developments of the catalytic synthesis of these compounds,[3,4] only one example on the enantioselective formation of 1-indenol using $[RhCl(C_2H_4)_2]_2$/diene ligands as catalyst with 81% ee has been reported.[4b]

Among many transition metals used in organic synthesis, palladium is particularly useful as it provides the most versatile possibilities for the carbon−carbon bond formation.[5] Recently our group has developed a series of addition reactions of arylboronic acids to carbon−heteroatom multiple bonds catalyzed by Pd(II) species.[6−8] In all of these systems, Pd(II) species were used without the use of any redox system which is indispensable in many Pd(0)-catalyzed reactions. Compared to the neutral Pd(II) catalysts, cationic Pd(II)

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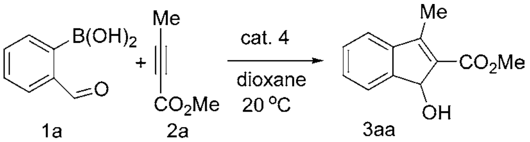
species have the following advantages: (1) vacant coordination sites for substrates or reagents, (2) stronger Lewis acidity, and (3) harder metal property.[9,10] Our results in the highly enantioselective formation of cycloalkanols led us to investigate the intermolecular [3 + 2] tandem reaction of 2-acylarylboronic acids with alkynes. Herein we report the synthesis of the optically active 1-indenol derivatives catalyzed by cationic palladium species with high yield and enantioselectivity.

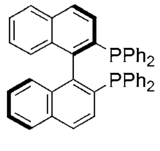
On the basis of our recent report on the intramoleclar enantioselective arylation of ketones,[7a] cationic palladium complex $[Pd(dppp)(H_2O)_2](OTf)_2$ (**4a**,[11a] 5 mol %) was first used to examine the annulation reaction of 2-formylphenylboronic acid (**1a**, 1.2 mmol) with methyl 2-butynoate (**2a**, 1 mmol) at 20 °C. The targeted 1-indenol **3aa** was obtained in 85% yield after 12 h. Control experiments indicated that no desired product was observed in the absence of the palladium catalyst. $[Pd(dppe)(H_2O)_2](OTf)_2$ (**4b**,[11b] 3 mol %) was found to be more effective than cat. **4a**, and **3aa** was furnished in quantitative yield. While neutral catalyst $Pd(OAc)_2$/dppp (**4c**) gave **3aa** in 59% yield, $Pd(TFA)_2$/dppp (**4d**)[9e] was completely inactive.

Then our attention was turned to the asymmetric version of the reaction. Initially, the easily prepared cationic palladium complex $[Pd((R)\text{-binap})(H_2O)_2](OTf)_2$ (**4e**,[11c] 3 mol %) was used as the catalyst, (−)-**3aa** was obtained in high yield (92%) with high ee (91%), (Table 1, entry 1). To further simplify the operation for the ligand screening, we tried to use the cationic palladium species prepared *in situ* to replace the prepared palladium complex. However, when $Pd(TFA)_2$/(*R*)-binap (**4f**)[9e] was used, the reaction was totally inhibited (Table 1, entry 2). This result prompted us to prepare $Pd(OTf)_2{\cdot}2H_2O$[11d] and investigate its reactivity. To our delight, when using $Pd(OTf)_2{\cdot}2H_2O$/(*R*)-binap (**4g**)[11e] as catalyst, (−)-**3aa** was obtained in 95% yield with 91% ee (Table 1, entry 3). After some optimization including the solvents and ligands, $Pd(OTf)_2{\cdot}2H_2O$/(*S*)-S1[11f] (**4h**)[11g] in dioxane at 20 °C provided the best result ((+)-**3aa**, quantitative yield, 98% ee; Table 1, entry 4).

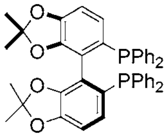
Table 1. Optimization of Cationic Pd(II)-Catalyzed Asymmetric Annulation of 2-Acylarylboronic Acids with Methyl 2-Butynoate[a]



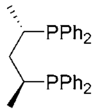
1a 2a 3aa



(*R*)-binap



(*S*)-S1



(*S*,*S*)-bdpp

entry	cat. (3 mol %)	yield[b]/ee[c] (%)/(%)
1	$[Pd((R)\text{-binap})(H_2O)_2](OTf)_2$ (**4e**)	92/91
2	$Pd(TFA)_2$/(*R*)-binap (**4f**)	–
3	$Pd(OTf)_2{\cdot}2H_2O$/(*R*)-binap (**4g**)	95/91
4	$Pd(OTf)_2{\cdot}2H_2O$/(*S*)-S1 (**4h**)	>99/98

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.25 mmol), cat. **4** (3 mol %), and dioxane at 20 °C. [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD-H column.

However, the conditions were not applicable to other alkynes. When **1a** and **2b** were mixed together in the presence of **4h** at 20 °C, no reaction occurred. Thus, reaction temperature was raised to 50 °C, and (+)-**3ab** was obtained in 84% yield with 86% ee (Table 2, entry 2). Finally, substituted alkynes (1.0 mmol), 2-acylarylboronic acids (1.2 mmol), and $Pd(OTf)_2{\cdot}2H_2O$/(*S*)-S1 (**4h,** 3 mol %) mixed in dioxane (2 mL) at 50 °C for 12 h were selected as the optimized conditions.

Under the optimized conditions, a variety of 2-acylarylboronic acids and alkynes could be used to afford corresponding 1-indenols in excellent yields with high enantioselectivities (Table 2, entries 2−6, 8, 9, and 14−18). The ligand (*S*)-S1 was not applicable to the alkyne **2f**, and benzaldyde was obtained as the major product. After screening, (*S*,*S*)-bdpp was found to be the better ligand (Table 2, entry 7). The substituents on the 2-acylarylboronic acids also affect the annulation reaction. The yields of the reaction of 2-formyl-4,5-methylenedioxyphenylboronic acid (**1c)** with corresponding alkynoates (**2a**−**c** and **e**) decreased sharply, and most of the arylboronic acid was hydrolyzed to piperonal under the above optimized conditions. On the basis of the results in the nonasymmetric reaction, the expected products were obtained in excellent yields and high enantioselectivities when cat. **4e** was used instead of **4h** (Table 2, entries 10−13).

Fortunately, excellent results could be also obtained when the corresponding arylboronic ester was used instead of the arylboronic acid under the optimal conditions (Scheme 1).

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(6) Pd(II)-catalyzed 1,2-addition of aldehydes and ketones initiated by acetoxypalladation of alkynes, see: (a) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed*. **2002**, *41*, 4343. (b) Lu, X. *Top. Catal*. **2005**, *35*, 73.

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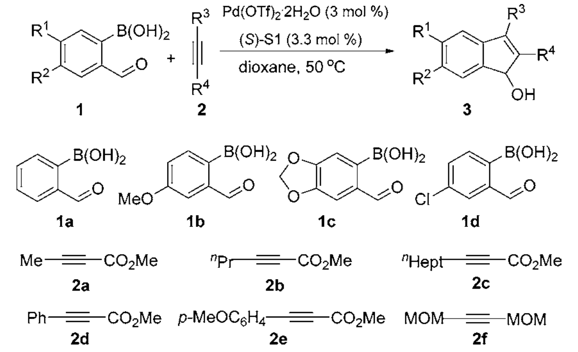
Table 2. Cationic Pd(II)-Catalyzed Enantioselective Tandem [3 + 2] Annulation Reaction of Acylarylboronic Acids and Substituted Alkynes[a]

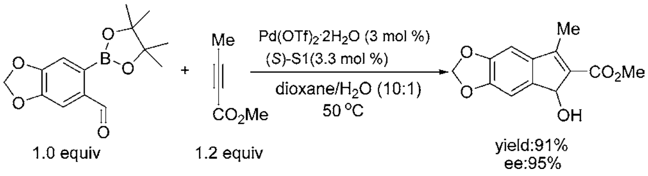


entry	1	2	3	yield (%)[b]	ee (%)[c]	entry	1	2	3	yield (%)[b]	ee (%)[c]
1[d]	**1a**	**2a**	**3aa**	>99	98(+)	10[g]	**1c**	**2a**	**3ca**	>99	76(−)
2	**1a**	**2b**	**3ab**	84	86(+)	11[g]	**1c**	**2b**	**3cb**	99	83(−)
3	**1a**	**2c**	**3ac**	88	89(+)	12[g]	**1c**	**2c**	**3cc**	>99	84(−)
4	**1a**	**2d**	**3ad**	58	90(+)	13[g]	**1c**	**2e**	**3ce**	71	89(−)
5	**1a**	**2e**	**3ae**	83	89(+)	14	**1d**	**2a**	**3da**	>99	96(+)
6[e]	**1a**	**2f**	**3af**	95	57(−)	15	**1d**	**2b**	**3db**	>99	99(+)
7[f]	**1b**	**2a**	**3ba**	83	99(+)	16	**1d**	**2c**	**3dc**	65	91(+)
8	**1b**	**2b**	**3bb**	92	84(+)	17	**1d**	**2d**	**3dd**	75	90(+)
9	**1b**	**2c**	**3bc**	94	87(+)	18	**1d**	**2e**	**3de**	55	87(+)

[a] Reaction conditions: **1** (1.2 mmol), **2** (1 mmol), Pd(OTf)$_2$•2H$_2$O (3 mol %), and (*S*)-S1 (3.3 mol %) in dioxane at 50 °C. [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD-H or OJ-H column. The sign of optical rotation is indicated in parentheses. [d] Reaction temperature was 20 °C. [e] (*S*,*S*)-bdpp as ligand. [f] **1b** (2.5 mmol) and **2a** (1 mmol) were used. [g] **4e** was used as catalyst.

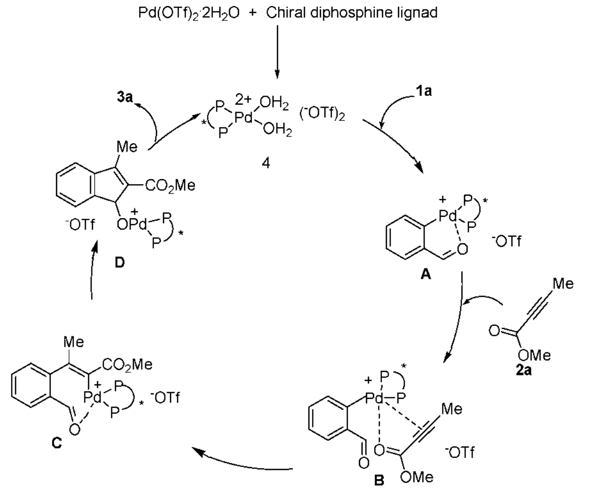
It should be noted that the asymmetric annulation reaction did not take place with 2-acetylphenylboronic acid under the optimized conditions. As to the alkynes, terminal alkynes and dialkylsubstituted alkynes failed to give annulation products in the presence of the cationic palladium species.

Scheme 1. Annulation Reaction of Arylboronic Ester with 2-Butynoate



A plausible mechanism for the asymmetric annulation is shown in Scheme 2. First, Pd(OTf)$_2$•2H$_2$O and the chiral diphosphine ligand form cationic Pd(II) catalyst **4**. The cationic nature of the transition-metal species makes the transmetalation of the catalyst with substrate **1a** easily to give intermediate **A**, in which the σ-coordination of the carbonyl group with the palladium center may stabilize the intermediate and make the transmetalation easier.[9,10,12] Next, the π-coordination of carbon–carbon triple bond or the σ-coordination of the oxygen in the alkynoates to the palladium center will occur to form the intermediate **B**.

Scheme 2. Plausible Mechanism for the Intermolecular Tandem Annulation Reaction of 2-Formylphenylboronic Acid with Substituted Akynes



Then the carbon–carbon triple bond inserts into the carbon–palladium bond to furnish vinylpalladium intermediate **C**, which undergoes nucleophilic addition to the carbonyl group at the ortho position resulting in the formation of a five-membered carbocycle D with alkoxypalladium species.[12,13] Finally, protonolysis occurs to form product **3aa** and regenerates the cationic palladium species **4**. The vacant coordination site and high Lewis acidity of the palladium center in **C** may activate the carbonyl group by coordination and enable the addition reaction to occur easily.[10] The coordination with the palladium center plays a key role in the enantiotopic discrimination of the aldehyde resulting in the high ee values.[7,14]

In conclusion, a cationic Pd(II)-catalyzed enantioselective tandem [3 + 2] annulation reaction of 2-acylarylboronic acids with substituted alkynes to yield optically active 1-indenols was developed in high yields and enantioselectivities. Further studies on the mechanism and applications of this reaction are underway.

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

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