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Cationic Palladium(II)-Catalyzed Highly Enantioselective Tandem Reactions of *ortho*-Boronate-Substituted Cinnamic Ketones and Internal Alkynes: A Convenient Synthesis of Optically Active Indenes

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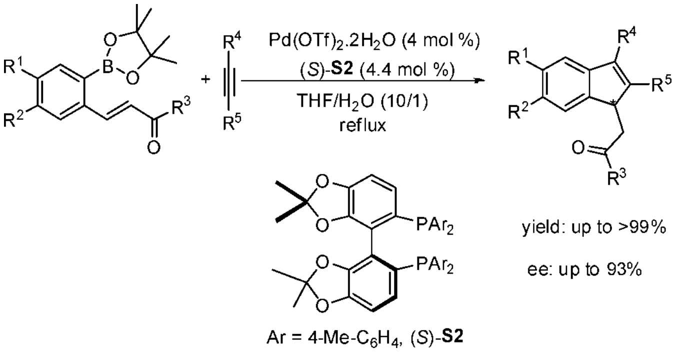
ABSTRACT



Cationic palladium(II)-catalyzed tandem reactions of *ortho*-boronate-substituted cinnamic ketones and internal alkynes to yield optically active indenes were developed in high yields and good enantioselectivities.

Indenes, especially the multiply substituted indenes, have been attractive as drug candidates possessing biological activities,[1] functional materials,[2] and metallocene complexes utilized in catalyzing olefin polymerization.[3] Although many methods related to the synthesis of indenes were reported,[4] most of them are only useful in synthesizing simple indenes. In view of synthetically useful methods, tandem cyclization reactions catalyzed by transition metals have been proven highly useful, especially when the highly substituted indene derivatives and their yields are concerned.[1b,5]

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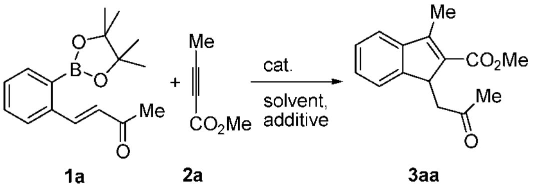
Table 1. Optimization of Cationic Palladium Complex-Catalyzed Tandem Addition of *ortho*-Boronate-Substituted Cinnamic Ketones and Interanl Alkynes[a]

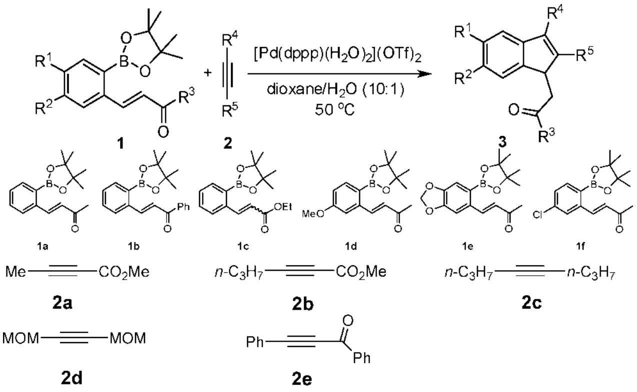


entry	cat. (mol %)	solvent	temp (°C)	time (h)	yield (%)[b]
1	A (3)	MeOH	50	48	NR
2[c]	A (3)	MeOH	50	48	NR
3	B (3)	MeOH	50	48	NR
4[c]	B (3)	MeOH	50	48	NR
5	B (3)	dioxane/H_2O	50	48	NR
6	C (1.5)	dioxane/H_2O	80	48	NR
7	D (3)	dioxane	80	48	NR
8[d]	D (3)	dioxane	80	48	NR
9[e]	D (3)	dioxane	80	48	NR
10[f]	D (3)	dioxane	80	48	NR
11	D (3)	dioxane/H_2O	25	48	96
12	D (3)	dioxane/H_2O	50	20	>99

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.18 mmol). [b] Isolated yield. [c] KF (1.5 equiv) was added. [d] $Ba(OH)_2$ (1.5 equiv) was added. [e] K_3PO_4 (1.5 equiv) was added. [f] Amberlite IRA-400 (OH) (1.5 equiv) was added.

However, no methods have been reported for the control of the C-1 stereogenic center. Thus far, the synthesis of optically active indenes is limited to a few examples.[6] An expedient and promising method for the synthesis of indenes is the rhodium-catalyzed tandem reactions of *ortho*-boronate-substituted cinnamic ketones and alkynes.[1b] However, much less attention has been paid to the asymmetric version of this tandem reaction. Recently, cationic palladium species has been shown to be highly active catalysts in the arylboronic acid initiated conjugate addition reaction by Miyaura's group[7] and in several tandem reactions by our group.[8] These results prompted us to investigate the tandem reactions of *ortho*-boronate-substituted cinnamic ketones and alkynes under the catalysis of cationic palladium species. Herein we report our results of the successful synthesis of the optically active indenes.

Table 2. Cationic Palladium Complex-Catalyzed Tandem Addition of *ortho*-Boronate-Substituted Cinnamic Ketones and Internal Alkynes[a]



entry	1	R^4≡ R^5	Product	Yield (%)[b]
1	**1a**	**2a**	**3aa**	>99
2	**1a**	**2b**	**3ab**	93
3[c]	**1a**	**2c**	**3ac**	78
4	**1a**	**2d**	**3ad**	82
5[c]	**1a**	**2e**	**3ae**	85
6	**1b**	**2a**	**3ba**	>99
7	**1b**	**2b**	**3bb**	>99
8[c]	**1b**	**2c**	**3bc**	57
9	**1b**	**2d**	**3bd**	89
10[c]	**1b**	**2e**	**3be**	75
11[d]	**1c**	**2a**	**3ca**	NR
12	**1d**	**2a**	**3da**	>99
13	**1e**	**2a**	**3ea**	>99
14	**1f**	**2a**	**3fa**	81

[a] Reaction conditions: **1** (0.15 mmol), **2** (0.18 mmol), $[Pd(dppp)(H_2O)_2](OTf)_2$ (3 mol %) and dioxane/H_2O (10/1), reaction time (24− 48 h). [b] Isolated yield. [c] $[Pd(dppp)(H_2O)_2](OTf)_2$ (4 mol %). [d] Reaction temperature was 80 °C.

First, neutral and cationic palladium complexes with 2,2-bipyridine (bpy) as ligand were chosen as the catalysts to examine the tandem reactions of arylboronic ester **1a** with methyl 2-butynoate (**2a**). No reaction occurred even in the case using dioxane/H_2O as the solvent (Table 1, entries 1−6). Then reactions of cationic palladium complex $[Pd(dppp)(H_2O)_2](OTf)_2$ (3 mol %) as catalyst in dioxane (2 mL) were examined. These reactions were also inactive even when bases, which are believed to facilitate the transmetalation of arylboronic compounds,[7a] were added at 80 °C (Table 1, entries 8−10). When a dioxane/H_2O (10/1) solvent mixture was used instead of dioxane, the coupling product **3aa** was obtained in quantitative yield after 20 h (Table 1, entry 12). Thus, arylboronic ester (0.15 mmol), alkyne (0.18 mmol), $[Pd(dppp)(H_2O)_2](OTf)_2$ (0.0045 mmol, 3 mol %), and dioxane/H_2O (10/1) at 50 °C were chosen as the optimized conditions.

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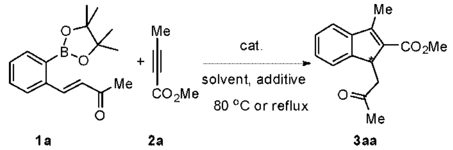
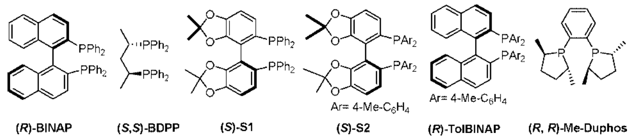
Table 3. Optimization of Chiral Cationic Palladium Complex-Catalyzed Tandem Addition of *ortho*-Boronate-Substituted Cinnamic Ketones and Internal Alkynes[a]





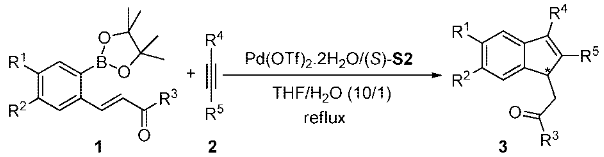
entry	cat.	solvent	yield (%)[b]	ee (%)[c]
1	[Pd((*R*)-BINAP)(H_2O)$_2$] (OTf)$_2$[d]	Dioxane/H_2O	NR	–
2	Pd(OTf)$_2$.2H_2O/(*R*)-BINAP	Dioxane/H_2O	NR	–
3	Pd(TFA)$_2$/(*R*)-BINAP	Dioxane/H_2O	NR	–
4	[Pd((*R*)-BINAP)(H_2O)$_2$] (OTf)$_2$[d]	CH_3NO_2/H_2O	89	60
5	Pd(OTf)$_2$.2H_2O/(*R*)-BINAP	CH_3NO_2/H_2O	96	60
6	Pd(OTf)$_2$.2H_2O/(*R*-BINAP)	THF/H_2O	55	76
7	Pd(OTf)$_2$.2H_2O/(*S,S*)-BDPP	THF/H_2O	92	75
8	Pd(OTf)$_2$.2H_2O/(*S*-**S1**)	THF/H_2O	44	70
9	Pd(OTf)$_2$.2H_2O/(*S*-**S2**)	THF/H_2O	99	91
10	Pd(OTf)$_2$.2H_2O/(*S*-**S2**)	Dioxane/H_2O	85	75
11	Pd(OTf)$_2$.2H_2O/(*R*-Tol-BINAP)	THF/H_2O	89	79
12	Pd(OTf)$_2$.2H_2O/(*R,R*-Me-Duphos)	THF/H_2O	trace	–

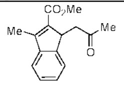
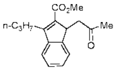
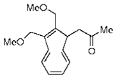
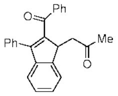
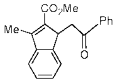
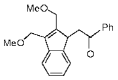
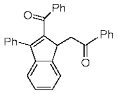
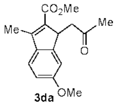
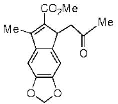
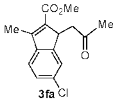
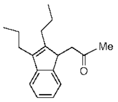
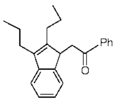
[a] Reactions were run in a solvent mixture containing Pd(OTf)$_2$•2H_2O (4 mol %), chiral ligands (4.4 mol %), substrate **1a** (0.12 mmol) and **2a** (0.14 mmol) under nitrogen atmosphere at reflux. The mixture was stirred until **1a** disappeared as monitored by TLC. [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD-H column. [d] Using isolated complex as catalyst.

With these results in hand, the scope of the annulation reaction was investigated. Using **1a** as the model substrate, a series of alkynes were screened. Alkynes with an electron-withdrawing group on one side (**2a**, **2b**, and **2e**) gave products in excellent yields (Table 2, entries 1−2, and 5). Alkynes with increasing electron density of the triple bond, for example, hepta-4-yne (**2c**) and the bis(methoxymethyl) substituted alkyne (**2d**), still gave yields around 80% (Table 2, entries 3−4). Similar reactivity was observed in the ketones with different substitutents (Table 2, entries 6−10). When the ketone group in **1a** was changed to an ester group (**1c**) (Table 2, entry 11), no reaction occurred. The effect of substituents on the aromatic ring of the boronate-substituted cinnamic ketones was also examined. The reactions all gave excellent yields (Table 2, entries 12−14).

Subsquently, the asymmetric version of this tandem cyclization was studied. For simplifying the operation of the ligand screening, the cationic palladium species used for screening were prepared in situ by adding the ligand directly to the Pd(OTf)$_2$.2H_2O without isolation of the palladium complexes.[9] At first, the annulation reaction of **1a** with **2a** in dioxane/H_2O (10/1) was examined using chiral cationic palladium complexes as the catalyst. No annulation product

Table 4. Chiral Cationic Palladium Complex-Catalyzed Asymmetric Tandem Addition of *ortho*-Boronate-Substituted Cinnamoyl Compounds and Internal Alkynes[a]



entry	product	yield(%)[b]	ee(%)[c]
1	 3aa	>99	91(+)
2[d]	 3ab	95	81(+)
3[e]	 3ad	>99	92(-)
4[f,h]	 3ae	83	55(+)
5	 3ba	>99	82(+)
6	 3bd	89	80(-)
7	 3be	72	78(+)
8	 3da	94	92(+)
9	 3ea	94	93(+)
10	 3fa	88	85(+)
11[g,h]	 3ac	88	11(+)
12[h]	 3bc	55	5(+)

[a] Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), Pd(OTf)$_2$.2H_2O (4 mol %) and (*S*)-**S2** (4.4 mol %). Reaction time (24−48 h) monitored by TLC. [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD, AD, OJ-H column. [d] **1a** (0.12 mmol), **2b** (0.14 mmol). [e] **1a** (0.12 mmol), **2d** (0.14 mmol). [f] **1a** (0.12 mmol), **2e** (0.14 mmol). [g] **1a** (0.12 mmol), **2c** (0.24 mmol). [h] Pd(OTf)$_2$.2H_2O (6 mol %) and (*S*)-**S2** (6.6 mol %).

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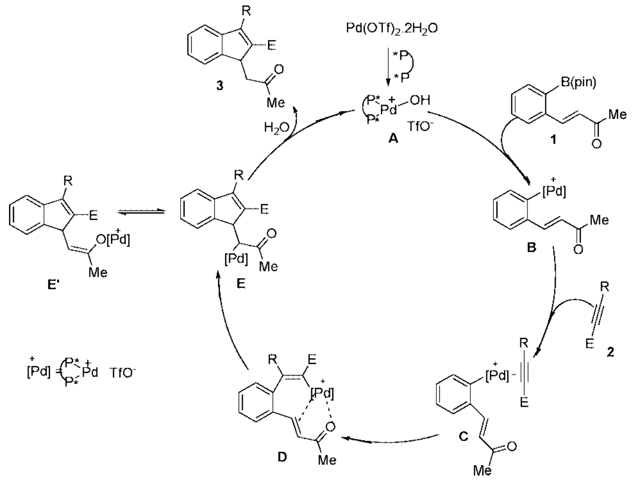
Scheme 1. Proposed Mechanism for the Tandem Annulation Reaction



was detected (Table 3, entries 1−3). Then a solvent mixture of CH_3NO_2/H_2O (10/1), THF/H_2O (10/1) with (*R*)- BINAP as the ligand was applied, and the reactions gave moderate to excellent yields with moderate to good enantioselectivity (Table 3, entries 4−6). Finally, THF/H_2O (10/1) was chosen as the solvent. Our investigations then focused on the examination of different chiral diphosphine ligands, and the ligand (*S*)-**S2** was found to give the best result (Table 3, entries 7−11). With the optimization of the solvents and ligands, $Pd(OTf)_2.2H_2O$/(*S*)-**S2** in THF/H_2O (10/1) under reflux conditions was found to be the best reaction conditions to obtain (+)-**3aa** in quantitative yield with 91% ee (Table 3, entry 9).

The results of the asymmetric version of this tandem cyclization reaction are summarized in Table 4. All reactions took place smoothly under the optimized conditions in good yields ranging from 55% to 99%. Alkynes with an electron-withdrawing group on one side (**2a**, **2b**, and **2e**) gave products in good ee (Table 4, 1−2, 4−5, and 7−10) except for the result of entry 4. Whereas hepta-4-yne (**2c**) was subjected to the reaction conditions, the ee declined to a low value (Table 4, entries 11−12). In the case of bis(methoxymethyl) substituted alkyne (**2d**), the product with the opposite sign of optical rotation was obtained (Table 4, entries 3 and 6).

A plausible mechanism of this tandem reaction is shown in Scheme 1. First, the monohydroxo cationic palladium species **A** with vacant sites might be formed from the in situ reaction of $Pd(OTf)_2.2H_2O$ and the chiral ligand.[9,10] **A** is believed to be the active catalyst and enables smooth transmetalation with the substrate **1** to yield a cationic arylpalladium(**II**) species **B**.[7a,9,11,12] Next, π-coordination of the carbon−carbon triple bond to the cationic palladium center occurs to form **C**, followed by the regioselective insertion of the alkyne into the carbon−palladium bond, affording the vinylpalladium intermediate **D** (carbopalladation). Then, conjugate addition of the vinylpalladium species to the cinnamic ketones occurs to yield the product **3**. It is also proposed that the coordinated intermediate **D** is helpful to the enantioface discrimination of α, β-unsaturated ketones, resulting in high ee values.[8] It is also worth mentioning that this tandem cyclization through transmetalation-alkyne insertion-enantioselective conjugate addition under the chiral cationic palladium complexes did not afford the Heck-type coupling products via β-hydride elimination.[13,14]

In conclusion, we have developed a cationic palladium-catalyzed enantioselective tandem reaction of *ortho*-boronate-substituted cinnamic ketones and internal alkynes. The use of the cationic palladium complexes as the catalyst is crucial for the high selectivity of the reaction. This tandem reaction provided an efficient way for the construction of optically active, multiply substituted indene derivatives.

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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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