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Palladium-Catalyzed Tandem Reactions of β-(2-Bromophenyl)-α,β-Unsaturated Carbonyl Compounds with 2-Hydroxyphenylboronic Acid: A New Route to Benzo[*c*]chromenes

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Palladium-catalyzed tandem reactions of β-(2-bromophenyl)-α,β-unsaturated carbonyl compounds with 2-hydroxyphenylboronic acid for the synthesis of benzo[*c*]chromenes are presented. This mild reaction allows formation of one carbon–carbon bond and one carbon–oxygen bond in one pot.

Introduction

Benzo[*c*]chromenes are important structural units which are widespread in many naturally and biologically active compounds. For example, 5*H*-dibenzo[*c*,*g*]chromen-3-ol has been reported to be an estrogen receptor agonist.[1,2] They are also the basic structure of cannabinols.[3] Although diverse synthetic approaches toward benzo[*c*]chromenes have been developed,[4,5] convenient and efficient methodologies to synthesize these compounds are still in need.

Recently, Motti[6] reported the preparation of benzo[*c*]-chromenes through palladium- and norbornene-catalyzed reactions of *ortho*-substituted aryl iodides, *o*-bromophenols, and activated olefins. Li et al.[7] reported that benzo[*c*]-chromenes could be obtained by palladium-catalyzed annulations of 2-(2-iodophenoxy)-1-arylethanones and 1-(2-iodophenoxy)propan-2-one with arynes. They had exploited palladium-catalyzed aryl–aryl cross-coupling reactions to form palladium-bonded biphenylyl structures containing an *ortho*-phenolic moiety.

The synthesis of biaryls through C–C bond-formation reactions is of great interest because of their presence in many natural products and functional materials.[8] The transition-metal-catalyzed formation of C–C bonds by cross-coupling reactions has thus been developed in the past decades.[9] Among the various biaryl coupling methods, the Suzuki–Miyaura coupling has attracted attention due to its high substrate tolerance and the lower toxicity of boronic acids compared to that of other organometallic reagents.[10] Therefore, the homocoupling of arylboronic acids is a valuable method to obtain asymmetrical biaryls.

We herein describe a new strategy involving a palladium-catalyzed Suzuki–Miyaura aryl–aryl bond formation reaction for the synthesis of benzo[*c*]chromenes in high yield. Compared with existing procedures, this methodology has several advantages, including operational simplicity, high yields, short reaction times, and simple materials.

Results and Discussion

In this reaction, β-(2-bromophenyl)-α,β-unsaturated carbonyl compounds were coupled with 2-hydroxyphenylboronic acid to form an aryl–aryl bond by a Suzuki–Miyaura reaction. Attack of the hydroxy group of the resulting intermediate at the olefinic carbon atom then afforded the benzo[*c*]chromenes. Reaction between **1a** and **2** was chosen as a model reaction to optimize the reaction conditions. Several Pd sources were investigated (Table 1, Entries 1–5), and $Pd(PPh_3)_4$ exhibited the highest efficiency (Table 1, Entry 2). Subsequently, a series of solvents, including acetonitrile, toluene, 1,4-dioxane, DMF, DMA, and DME, were screened, and it was found that DME was the best solvent. With the optimal reaction conditions in hand, the scope of this transformation was investigated by studying the reaction of β-(2-bromophenyl)-α,β-unsaturated carbonyl compounds with 2-hydroxyphenylboronic acid, $Pd(PPh_3)_4$, and 2 M Na_2CO_3 in DME.

Reactions of β-(2-bromophenyl)-α,β-unsaturated carbonyl compounds **1b**–**l** with **2** under the optimal conditions were then examined (Table 2, Entries 2–12). We were pleased to find that the reaction between **1** containing either electron-withdrawing or -donating functional groups on the aromatic ring and **2** proceeded smoothly under the optimal conditions (Table 2, Entries 2–12) and provided the desired products in excellent yields. For example, substrate **1h** and **1l**, both bearing a nitro group at the 5-position of the aromatic ring, were treated with **2** to efficiently provide the products in good yield (Table 2, Entries 8 and 12). Substrate

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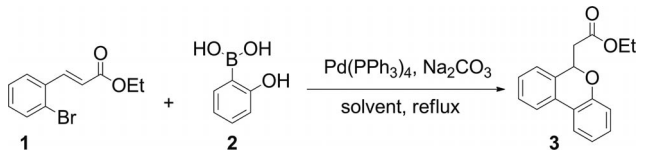
Table 1. Optimization of reaction conditions for the formation of **3**.[a]

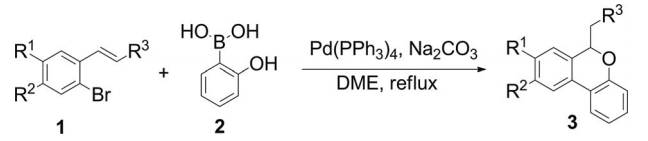


Entry	Catalyst	Solvent	Temperature [°C]	Yield [%][b]
1	$Pd(dppf)_2Cl_2$	DME	reflux	80
2	$Pd(PPh_3)_4$	DME	reflux	95
3	$Pd(dba)_2$	DME	reflux	23
4	$Pd(PPh_3)_2Cl_2$	DME	reflux	34
5	$Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$	DME	reflux	83
7	$Pd(PPh_3)_4$	DMF	102	33
8	$Pd(PPh_3)_4$	1,4-dioxane	reflux	60
9	$Pd(PPh_3)_4$	acetonitrile	reflux	30
10	$Pd(PPh_3)_4$	DMA	102	56

[a] Reaction conditions: **1** (0.78 mmol), **2** (1.0 equiv.), [Pd] (10 mol-%), 2 M Na_2CO_3 (2 mL). [b] Isolated yield.

1 with a methoxy group also exhibited high reactivity. Moreover, it was found that **1d** and **1i**, both containing a fluorine atom on the benzene ring, were also suitable substrates for this tandem reaction, and they afforded the corresponding products in excellent yields (Table 2, Entries 4 and 9).

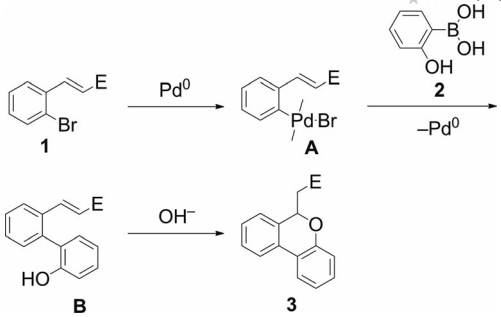
Table 2. Palladium-catalyzed tandem reactions of β-(2-bromophenyl)-α,β-unsaturated carbonyl compounds with 2-hydroxyphenylboronic acid to form benzo[*c*]chromenes.[a]



Entry	**1**	R^1	R^2	R^3	Yield [%][b]
1	**1a**	H	H	CO_2Et	95
2	**1b**	OMe	H	CO_2Et	90
3	**1c**	OMe	OMe	CO_2Et	92
4	**1d**	H	F	CO_2Et	91
5	**1e**	H	H	COMe	90
6	**1f**	OMe	H	COMe	91
7	**1g**	OMe	OMe	COMe	95
8	**1h**	NO_2	H	COMe	92
9	**1i**	H	F	COMe	93
10	**1j**	H	H	COPh	95
11	**1k**	OMe	OMe	COPh	90
12	**1l**	NO_2	H	COPh	92

[a] Reaction conditions: **1** (0.78 mmol), **2** (1.0 equiv.), [Pd] (10 mol-%), and 2 M Na_2CO_3 (2 mL) in DME at reflux for 4 h. [b] Isolated yield.

A possible mechanism is speculated and described in Scheme 1. Oxidative addition of Pd^0Ln with **1** affords intermediate **A**. The intermediate **A** selectively reacts with 2-hydroxyphenyl boronic acid (**2**) to give species **B**. Intramolecular attack of the hydroxy group on the activated double bond leads to final product **3**. Further study on this mechanism is still in process.



Scheme 1. The possible reaction mechanism.

Conclusions

In summary, we have developed a mild method for the synthesis of 6*H*-benzo[*c*]chromenes by palladium-catalyzed tandem reactions of β-(2-bromophenyl)-α,β-unsaturated carbonyl compounds with 2-hydroxyphenylboronic acid. This new route allows formation of one carbon–carbon bond and one carbon–oxygen bond in one pot. Importantly, we provide a convenient approach for the preparation of 6*H*-benzo[*c*]chromenes. Efforts to extend the applications of this transformation in organic synthesis and screening of these types of compounds for biological activity are currently underway.

Experimental Section

General Procedure for the Synthesis of 6*H*-Benzo[*c*]chromenes: To a Schlenk-type flask containing a DME solution of a β-(2-bromophenyl)-α,β-unsaturated carbonyl compound (0.78 mmol) and (2-hydroxyphenyl)boronic acid (0.78 mmol) was added 2 M Na_2CO_3 (2 mL) and $Pd(PPh_3)_4$ (0.1 g, 10%mmol) under an atmosphere of N_2. The resulting mixture was heated at reflux for 4 h. After cooling to room temperature, the solid was filtered. The filtrate was concentrated under reduced pressure. The crude was purified immediately by flash chromatography (silica gel 60, particle size 200–300 mesh, petroleum ether/EtOAc, 15:1).

Supporting Information (see footnote on the first page of this article): Characterization data for compounds **1a**–**l**; copies of the ^1H NMR, ^{13}C NMR, and HRMS spectra for all new compounds.

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