



PdCl₂-catalyzed cross-coupling reaction of arylacetylene iodides with arylboronic acids to diarylacetylenes

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ABSTRACT

A new Suzuki-type cross-coupling reaction between 1-iodo-2-arylkynes and arylboronic acids to afford a wide variety of functionalized diarylacetylenes in a mild reaction condition was developed. The reaction was catalyzed by a small amount of a structurally simple, commercially available, and stable PdCl₂. This unique sp²–sp² carbon–carbon bond formation provides a new protocol for the synthesis of diarylacetylenes, which is a new addition to the Suzuki cross-coupling reaction.

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The Suzuki coupling is one of the most versatile and widely used reactions for the selective construction of a carbon–carbon bond between organoboron and organic halides or triflates.¹ The original version included the Pd-catalyzed coupling of the vinyl boronate with an aromatic halide (Br or I) to form the sp²–sp² C–C bond. Later, it became the most powerful tool for aryl–aryl cross-coupling. Recently its scope has gradually extended, and the ability to couple with the sp³-hybridized alkyl halides to form sp²–sp³ and sp³–sp³ C–C bonds has been extensively explored.² In general, aryl, alkenyl, and even alkyl halides were employed in the organoboron involved reactions, which all use sp² or sp³ C–X (X = halogen) substrates to couple with organoboron derivatives. In contrast, it is quite rare to report the sp²–sp C–C bond formation by the use of sp C–X bonds and arylboronic acids to afford the diarylacetylenes due mainly to cross-homo scrambling, although the sp²–sp alkenyl–alkynyl coupling has been occasionally reported³ (Scheme 1). In this Letter, we disclose a new type of Suzuki cross-coupling (sp²–sp) from iodoalkynes and arylboronic acids to form the diarylacetylenes.

In our previous studies for the synthesis of 2,3,4-trisubstituted pyrroles, pyrrole **3** was obtained by iodination of one of the two

TMS groups and coupling with *p*-methoxyphenylboronic acid (Scheme 2). The structure of compound **3** was established by X-ray crystallography (CCDC 768902), although the original structure was incorrectly defined by routine spectra.⁴ Obviously it was formed by iodination of the alkynyltrimethylsilane and then transformed through Suzuki cross-coupling. Selective iodination and the arylboronic acid coupling with the iodide on the sp carbon atom were two significant features for such a transformation. As we know this is the first case of 1-iodo-2-arylkynes to couple with arylboronic acid to form diarylacetylene under Suzuki-type condition. Based on this unexpected result, we were very interested to see if more reaction examples could be involved under this condition.

To find the optimal reaction conditions, the 4-iodoethynyl benzoic acid methyl ester (**4**) was used as the electrophile and *p*-methoxyphenyl boronic acid (**5**) as the nucleophile to perform the Suzuki reaction under a variety of conditions (Table 1). The reaction was first tried under the typical Suzuki conditions (entry 1), which have been used to proceed from pyrrole **2** to pyrrole **3**, but the yield was no more than 50%, and the homo-coupling product **7** was obtained in a yield of 20%. When the reaction was carried out in MeOH



Scheme 1. The Pd-catalyzed alkynylation by Suzuki cross-coupling.

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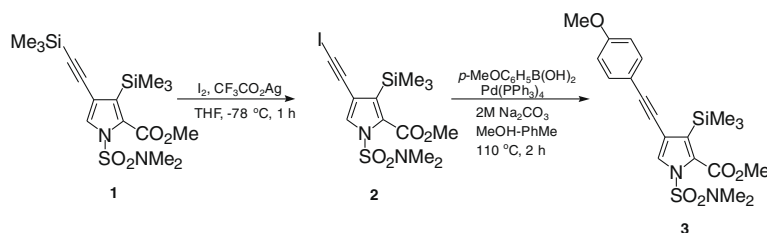
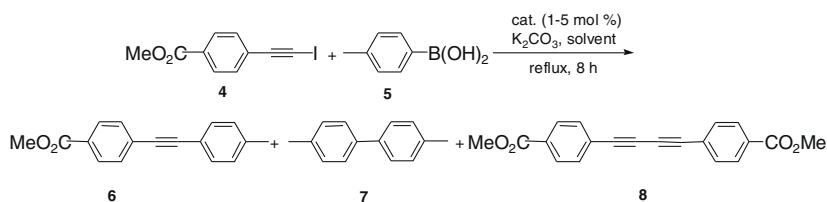
Scheme 2. The transformation of pyrrole **1** to pyrrole **3**.

Table 1

The coupling of 4-iodoethynyl benzoic acid methyl ester and *p*-methylphenylboronic acid as the optimization of reaction conditions

Entry	Catalyst	Temp (°C)	Base	Solvent	Isolated yield (%)		
					6	7	8
1	Pd(PPh ₃) ₄ ^a	80	K ₂ CO ₃	Toluene/MeOH/H ₂ O ^d	49	20	—
2	Pd(PPh ₃) ₄ ^a	70	K ₂ CO ₃	MeOH	17	Trace	33
3	Pd(PPh ₃) ₄ ^a	60	K ₂ CO ₃	THF	Trace	Trace	71
4	Pd(PPh ₃) ₄ ^a	60	K ₂ CO ₃	THF/H ₂ O ^e	39	25	—
5	Pd(PPh ₃) ₄ ^a	60	K ₂ CO ₃	THF/MeOH/H ₂ O ^d	45	15	—
6	Pd(PPh ₃) ₂ Cl ₂ ^a	80	K ₂ CO ₃	Toluene/MeOH/H ₂ O ^d	16	69	—
7	Pd(OAc) ₂ ^a	80	K ₂ CO ₃	Toluene/MeOH/H ₂ O ^d	12	75	—
8	PdCl ₂ ^b	80	K ₂ CO ₃	Toluene/MeOH/H ₂ O ^d	88	8	0
9	PdCl ₂ ^c	25	K ₂ CO ₃	Toluene/MeOH/H ₂ O ^d	15	58	0
10	NiCl ₂ ^c	80	K ₂ CO ₃	Toluene/MeOH/H ₂ O ^d	—	—	—
11	PdCl ₂ ^b	80	CH ₃ ONa	Toluene/MeOH/H ₂ O ^d	85	10	0
12	PdCl ₂ ^b	80	NaOH	Toluene/MeOH/H ₂ O ^d	88	7	0
13	PdCl ₂ ^b	80	Et ₃ N	Toluene/MeOH/H ₂ O ^d	85	8	0
14	PdCl ₂ ^b	80	K ₃ PO ₄	Toluene/MeOH/H ₂ O ^d	80	10	0

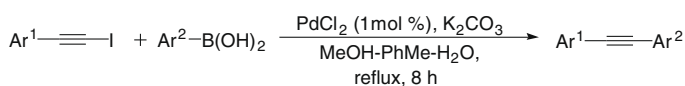
^a The catalyst amount was 2.5 mol %.^b The catalyst amount was 1 mol %.^c The catalyst amount was 5 mol %.^d The ratio of the solvents was 3:3:1.^e The ratio of the solvent was 4:1.

(entry 2), another homo-coupling product **8** was discovered in a yield of 33%, with the desired product **6** in poor yield. In the case of THF, the situation was even worse, with trace desired molecule and a substantial amount of homo-coupling product **8** (entry 3). When more polar solvent (THF/H₂O) was used, a better result was observed with an increased yield of **6** and less **7** (entry 4). We can see that H₂O plays an important role to facilitate the cross-coupling reaction and restrain the homo-coupling of arylacetylene iodides. The effective solvent system (THF/MeOH/H₂O) was observed to afford more desired **6** and less by-product **7** (entry 5), but this was still inferior to Toluene/MeOH/H₂O (entry 1). Therefore the original solvent system was utilized, in which the catalyst screening in the solvent mixture was conducted. When the reaction was carried out with catalysts PdCl₂(PPh₃)₂ (entry 6) or Pd(OAc)₂ (entry 7), the major product was **7** with yields of 69% and 75%, respectively. When the simple and stable PdCl₂ was employed as the catalyst with the increased amount of *p*-methylphenylboronic acid (1.5 equiv), surprisingly, the yield of cross-coupled product **6** was raised to 88% (entry 8). Different amounts of PdCl₂ (1, 2, 5, 10 mol %) afforded almost the same yield of product **6** (88%, 85%, 88%, 86%), respectively. Thus, the subsequent coupling reaction was undertaken with 1–5 mol % of PdCl₂. A higher

reaction temperature improved the coupling significantly, whereas the reaction could not be finished in 24 h, and the major product was **7** at room temperature (entry 9). Other bases such as CH₃ONa, NaOH, Et₃N, and K₃PO₄ were also employed in parallel reactions, and the results indicated that the differences of the base hold little influence over the reaction (entries 11–14). It should be pointed out that NiCl₂ has no catalytic activity (entry 10).

Having optimized the reaction conditions, the experimental scope was extended to include more Suzuki coupling substrates, resulting in the successful reactions of various substituted arylacetylene iodides and arylboronic acids (Table 2). The phenyl subunit on arylethynyl iodide can tolerate different types of substituents: not only the electron-deficient substrates with –CO₂Me, –CHO, –COMe, and –CN (entries 1–4), but also the electron-rich substrates with Me and –OMe (entries 6 and 7) reacted smoothly with arylboronic acid. This method is also suitable for many substituted arylboronic acids such as naphthyl, 4-methoxyphenyl, 2-hydroxyphenyl, phenyl, and 4-fluorophenylboronic acids (entries 8–13). It should be noted that in the case of arylboronic acid with an electron-withdrawing group (F), the reaction proceeded as well in good yield (entry 13). This catalytic system seems to allow diverse electron density around the aromatic rings. The

Table 2
The coupling of arylacetylene iodides and arylboronic acids



Entry	Ar ¹	Ar ²	Isolated yield (%)
1			88
2			84 ^a
3			92
4			85 ^a
5			74 ^{b,c}
6			82 ^d
7			79 ^d
8			69
9			82
10			84
11			73
12			78
13			84

^a The solvent is THF/MeOH/H₂O.

^b Yield determined by ¹H NMR.

^c The catalyst amount was 2.5 mol %.

^d The catalyst amount was 5 mol %.

yields for most of the products are comparable to those by Sonogashira reaction.⁵ However for the preparation of 4-[2-(4-methylphenyl)ethynyl] benzaldehyde (entry 2), much improved yield (84%) was achieved compared to that of the literature method (31%) by ordinary Sonogashira coupling.⁶ Although high conversion of this product was recently reported, an abnormal N-heterocyclic carbenes precatalyst was required, which has complicated structure and need multi-step synthesis.⁷ All the compounds synthesized were characterized by ¹H, ¹³C NMR, and mass spectrometry.

In summary, we have developed a novel coupling reaction for the Pd-catalyzed alkylation from iodoalkynes and arylboronic

acids, which extends the scope of the Suzuki-coupling reaction. This reaction takes place efficiently with the -CHO group-containing substrate compared to ordinary Sonogashira coupling reaction. Although it is two steps longer than the Sonogashira reaction, this method provides an alternative synthetic pathway for diarylacetylenes.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.011.

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