Multicomponent Coupling

Synthesis of Highly Substituted 1,3-Butadienes by Palladium-Catalyzed Arylation of Internal Alkynes**

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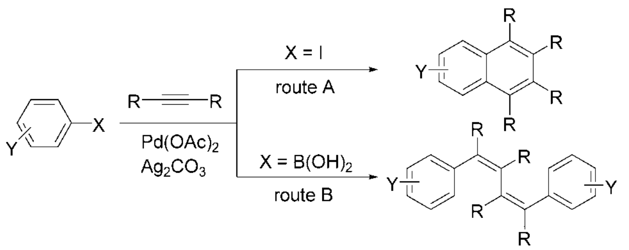
The transition-metal-catalyzed arylation of alkynes by halogenated or metalated aromatic reagents through carbometalation is a powerful tool for constructing π-conjugated molecules.[1] Some of these reactions are conducted in the presence of terminators such as hydrogen sources or organometallic reagents to give rise to three-component coupling products. In other cases, the reactions involve cyclometalation in the termination step to yield cyclic compounds.

As examples for the latter case, we reported rhodium-,[2a] iridium-,[2b] and palladium-catalyzed[2c] coupling reactions of alkynes with aroyl chlorides or aryl iodides to afford the corresponding indenones or naphthalenes. In the palladium-catalyzed reaction of aryl iodides, the use of silver(I) salts as base was essential for the effective sequential insertion of two alkyne molecules and the successive ring closure (Scheme 1, route A).[2c,3]

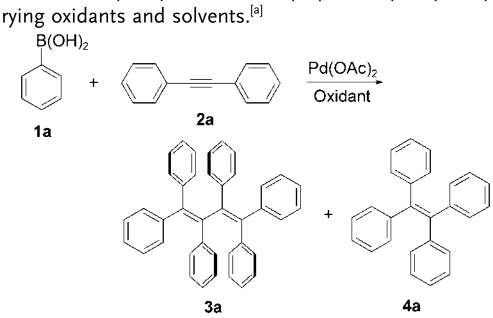


Scheme 1. Coupling of aryl iodides and aryl boronic acids with alkynes.

Silver(I) salts are known to act not only as base, but also as oxidant, in palladium-catalyzed coupling reactions.[4] Consequently, we have undertaken alkyne arylation reactions with aryl boronic acids instead of aryl iodides under similar conditions to those employed in route A.[2c] We found that the predominant products were not the expected naphthalenes, but rather 1,4-diaryl-1,3-butadienes by a 2:2 coupling reaction with the formation of three carbon–carbon bonds (Scheme 1, route B). Furthermore, it was revealed that the addition of iodobenzene as the third component allows the construction of 1,3-dienes that bear two different aryl groups at C1 and C4. Among the related reactions reported to date[5–12] are the palladium-catalyzed and -promoted arylations of alkynes with aryl tin[5] and aryl magnesium[6] reagents, respectively, in each of which 2:1 coupling occurs to give 1,2-diaryl ethenes selectively.[7] Meanwhile, the palladium-catalyzed three-component coupling of aryl iodides, alkynes, and aryl boronic acids was also examined with $KHCO_3$ as base.[11] In this case, 1:1:1 coupling takes place to give 1,2-diaryl ethenes effectively. This contrasts markedly with the present 1:2:1 coupling.[12]

When phenylboronic acid (**1a**) was treated with diphenylacetylene (**2a**) (1 equiv) in the presence of $Pd(OAc)_2$ (2.5 mol%) and Ag_2CO_3 (1 equiv) in 1-propanol/H_2O (9:1) at 120 °C for 0.5 h, 1,1,2,3,4,4-hexaphenyl-1,3-butadiene (**3a**) was formed in 70% yield along with a minor amount of 1,1,2,2-tetraphenylethene (**4a**) (Table 1, entry 1). The yield of **3a** was somewhat lower in the absence of H_2O, but the formation of **4a** was suppressed (Table 1, entry 2). The reaction also proceeded smoothly in 1,4-dioxane/H_2O, whereas MeCN/H_2O and DMF/H_2O were not effective (Table 1, entries 3–5). Ag_2O and AgOAc could be used as oxidants instead of Ag_2CO_3, albeit with lower efficiency (Table 1, entries 6 and 7). $Cu(OAc)_2$ did not catalyze the reaction (Table 1, entry 8).

Table 1: Reaction of phenylboronic acid (**1a**) with diphenylacetylene (**2a**) with varying oxidants and solvents.[a]



Entry	Oxidant (mmol)	Solvent	Yield [%][b] 3a	4a
1	Ag_2CO_3 (2)	1-propanol/H_2O (9:1)	70 (67)	6
2	Ag_2CO_3 (2)	1-propanol	63	2
3	Ag_2CO_3 (2)	1,4-dioxane/H_2O (9:1)	65	3
4	Ag_2CO_3 (2)	MeCN/H_2O (9:1)	14	27
5	Ag_2CO_3 (2)	DMF/H_2O (9:1)	42	9
6	Ag_2O (2)	1-propanol	59	7
7	AgOAc (4)	1-propanol	40	2
8	$Cu(OAc)_2$ (2)	1-propanol	6	trace

[a] The reaction of **1a** (2 mmol) with **2a** (2 mmol) was conducted with $Pd(OAc)_2$ (0.05 mmol) in the solvent (5 cm^3) at 120 °C for 0.5 h. [b] Yield determined by GC. The value in parenthesis indicates the yield of the isolated product.

(4-Methylphenyl)boronic acid (**1b**) was treated with **2a** under the conditions used for the reaction in Table 1, entry 1 Although the coupling took place similarly to give 1,4-di(4-methylphenyl)-1,2,3,4-tetraphenyl-1,3-butadiene in 60% yield, its NMR spectra indicated that it consists of at least

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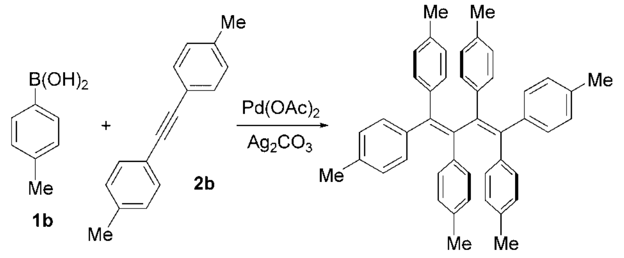
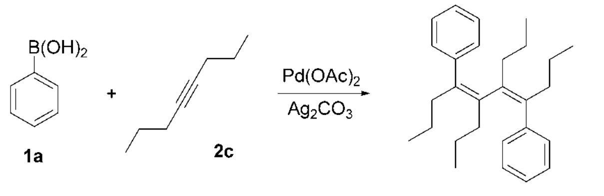
two geometrical isomers. As expected, the reaction of **1b** with di(4-methylphenyl)acetylene (**2b**) gave 1,1,2,3,4,4-hexa(4-methylphenyl)-1,3-butadiene (**3b**) in 58% yield as the single major product (Scheme 2). Interestingly, the reaction of **1a** with 4-octyne (**2c**) afforded only (4*Z*,6*Z*)-4,7-diphenyl-5,6-dipropyl-4,6-decadiene (**3c**) without contamination with any other isomers (Scheme 3). The purity and structure of **3c** were confirmed by NMR spectroscopic studies and X-ray[13] crystal-structure analysis (see Supporting Information).[14]



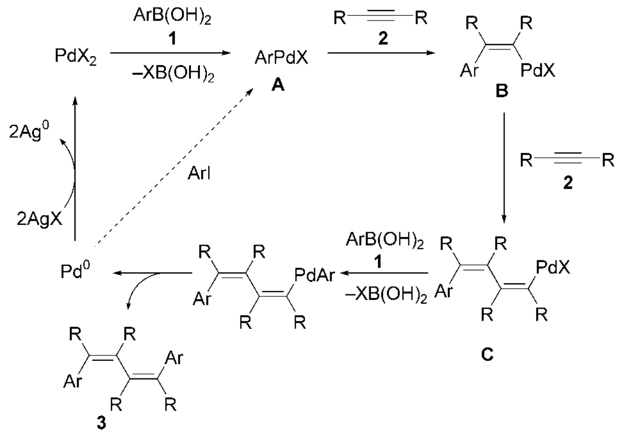
Scheme 2. Reaction of **1b** with **2b**. Reaction conditions: **1b** (2 mmol), **2b** (2 mmol), $Pd(OAc)_2$ (0.05 mmol), Ag_2CO_3 (2 mmol), 1-propanol/H_2O (9:1), 120°C, 0.5 h.



Scheme 3. Reaction of **1a** with **2c**. Reaction conditions: **1a** (2 mmol), **2c** (2 mmol), $Pd(OAc)_2$ (0.05 mmol), Ag_2CO_3 (2 mmol), 120°C, 0.5 h. Yield of **3c**: 41% in 1,4-dioxane/H_2O (9:1); 36% in 1-propanol.

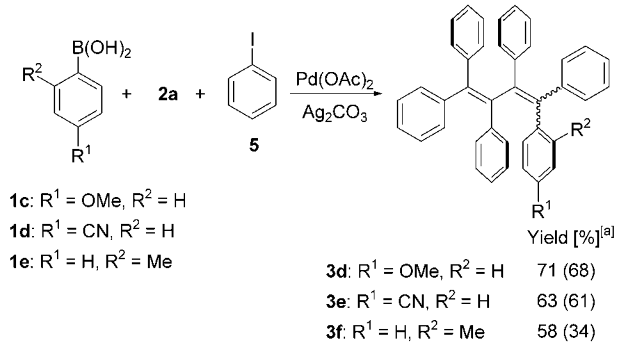
The first step of the present reaction may involve transmetalation to give an aryl palladium species **A** (Scheme 4).[8,9b–d] Subsequently, the insertion of two alkyne molecules forms a dienylpalladium intermediate **C**. The successive second transmetalation and reductive elimination give 1,4-diarylated 1,3-diene **3**.[15] The palladium(0) species generated in the last step may be reoxidized by the silver(I) species to close the catalytic cycle.[16] The result of the reaction of **1b** with **2a** implies that *E*/*Z* isomerization in **B** and **C** may take place.[17] However, the reason why it did not occur in the coupling of **1a** with **2c** is not clear.

The intermediate **A** may be generated directly through oxidative addition of aryl halides to a palladium(0) species (dotted arrow in Scheme 4). Thus, we next examined three-component reaction of aryl boronic acids, alkynes, and iodobenzene. When a mixture of (4-methoxyphenyl)boronic acid (**1c**; 1 mmol), **2a** (1 mmol), and iodobenzene (**5**; 1 mmol) was treated in the presence of $Pd(OAc)_2$ (0.05 mmol) and



Scheme 4. A plausible mechanism for the coupling of aryl boronic acids and aryl iodides with alkynes.

Ag_2CO_3 (1 mmol) in 1-propanol/H_2O at 120°C for 0.5 h, 1-(4-methoxyphenyl)-1,2,3,4,4-pentaphenyl-1,3-butadiene (**3d**) was produced in 71% yield (Scheme 5).[18] Only a minor amount of 1,4-di(4-methoxyphenyl)-1,2,3,4-tetraphenyl-1,3-butadiene (5%), which may be the result of an oxidative 2:2 coupling of **1c** with **2a**, was detected by GC–MS. The use of the substrates in the ratio **1c**/**2a**/**5** = 1:2:1 resulted in a decrease in the yield of **3d** (45%). (4-Cyanophenyl)- and (2-methylphenyl)boronic acids, **1d** and **1e** respectively, also reacted with **2a** and **5** to afford the corresponding dienes **3e** and **3f**. In these cases, the oxidative 2:2 coupling products were not detected. In each case, the major product **3** was found to consist of two possible isomers (≈2:1) by NMR spectroscopic analysis.



Scheme 5. Reaction of **1** with **2a** and **5**. Reaction conditions: **1** (1 mmol), **2a** (1 mmol), **5** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), Ag_2CO_3 (1 mmol), 1-propanol/H_2O (9:1), 120°C, 0.5 h. [a] Yield determined by GC (The value in parenthesis indicates the yield of the isolated product).

In summary, we have demonstrated that the coupling reactions of aryl boronic acids with alkynes in the absence and presence of iodobenzene can be performed with a palladium catalyst and a silver salt to give selectively 2:2 and 1:2:1 coupling products, respectively. These reactions offer a straightforward route to multiarylated butadienes, which are of interest for their photochemical, electrochemical, and biological properties.[19]

Experimental Section

Typical procedure: A mixture of **1** (2 mmol), **2** (2 mmol), $Pd(OAc)_2$ (0.05 mmol, 11 mg), and Ag_2CO_3 (2 mmol, 550 mg) in 1-propanol/H_2O (9:1, 5 mL) was stirred under N_2 at 120 °C. After 0.5 h, the mixture was cooled to room temperature, Et_2O (100 mL) was added, and insoluble materials were removed by filtration through filter paper. The product was isolated by recrystallization from toluene/hexane and/or column chromatography on silica gel with hexane/EtOAc as eluent. Characterization data of products are summarized in the Supporting Information.

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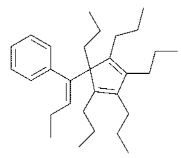

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