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Palladium-Catalyzed, Sequential, Three-Component Cross-Coupling of Aryl Halides, Alkynes, and Arynes**

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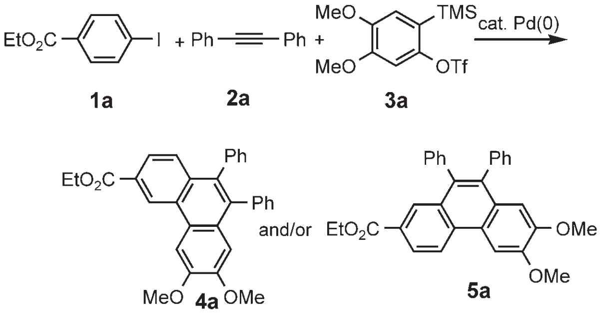
Alkynes have been frequently used as substrates for palladium-catalyzed carbopalladation by functionally substituted aryl and vinylic halides.[1] Aryl halides have also been treated with alkynes in the presence of a palladium catalyst to generate naphthalenes.[2] Arynes[3] are very reactive substrates compared to ordinary alkynes. Although there are a number of examples of stoichiometric transition-metal aryne complexes being employed creatively in organic synthesis,[4] arynes[5] have only recently been reported to undergo palladium-catalyzed conversion. Thus, the cyclotrimerization of arynes[6] and the co-cyclotrimerization of arynes with alkynes[7] are catalyzed by palladium. Yamamoto and coworkers have established that π-allylpalladium species are very effective for the intermolecular carbopalladation of arynes and can be employed in a three-component coupling with alkynes to produce naphthalenes.[8] Until the recent demonstration that an aryne can react with benzyl bromide in the presence of a palladium catalyst and undergo a subsequent Heck reaction,[9] all examples of the carbopalladation of arynes have involved very stable π-allylpalladium intermediates.[8,10] Recently, we reported that aryl and vinylic halides can be employed in the catalytic carbopalladation of arynes.[11] Our experience in aryne and alkyne chemistry led us to consider the possibility of using palladium to catalyze the stepwise carbopalladation of alkynes and arynes using aryl halides. Herein, we wish to report preliminary results on the palladium-catalyzed, three-component, sequential intermolecular coupling of aryl halides, alkynes, and arynes [Eq. (1); TMS = trimethylsilyl, OTf = $OS(O)_2CF_3$].



(1)

We first allowed ethyl 4-iodobenzoate (**1a**) to react with 2.0 equiv of diphenyl acetylene (**2a**), 2.0 equiv of the silylaryl triflate **3a**, 5 mol% of $[Pd(dba)_2]$ (dba = dibenzylideneacetone), 5 mol% of 1,1′-bis(diphenylphosphino)ferrocene (dppf), and 3.0 equiv of CsF in 2.0 mL of MeCN and 2.0 mL of toluene at 90 °C for 24 h. Surprisingly, we obtained only product **4a** in a 22% yield, and compound **5a** was not detected [Eq. (1); Table 1, entry 1]. The structure of compound **4a** was established by X-ray crystallography. Subsequent work focused on optimization of this process (Table 1). Changing the ligand from dppf to $P(o\text{-tolyl})_3$ had little effect (Table 1, entries 1 and 2). We subsequently found that the addition of TlOAc dramatically increased the yield from 18% to 79% (compare entries 2 and 3, Table 1).[12] No cyclotrimerization products of arynes or co-cyclotrimerization products of arynes with alkynes were detected in these reactions. The role of the TlOAc is unclear at this time, although it may be involved in removing the halide from solution. Interestingly, the yield was even higher in the absence of the phosphine ligand. The desired product **4a** can thus be obtained in 85% yield (Table 1, entry 4). Changing the amount of toluene in the solvent provided lower yields of the desired product, and the starting material **1a** was recovered both when an increased and when a decreased amount of toluene was used (Table 1, entries 5 and 6). When only 1.2 equiv of the aryne precursor **3a** were employed, the desired coupling product **4a** was isolated in 86% yield (Table 1, entry 7). Decreasing the amount of diphenyl acetylene (**2a**) from 2.0 to 1.5 equiv still afforded 83% yield (Table 1, entry 8). When only 0.5 equiv of TlOAc were used in this process, only a 68% yield of compound **4a** was obtained (Table 1, entry 9). Replacing TlOAc by $AgNO_3$ in this reaction proved ineffective (Table 1, entry 10). To date, the optimal reaction conditions for this particular reaction are those shown in entry 7 in Table 1.

The scope and limitations of this palladium-catalyzed, three-component coupling process were next examined using various aryl halides, acetylenes, and aryne precursors. The results are summarized in Table 2. We first allowed ethyl 4-iodobenzoate (**1a**) to react with diphenyl acetylene (**2a**) and several different aryne precursors (**3b–e**). All of the aryne precursors gave very high yields of the corresponding coupling products (Table 2, entries 1–4). It is noteworthy that aryne precursor **3e** affords two isomers, **4e** and **4f**, in a 1:1 ratio, clearly suggesting the intermediacy of an aryne

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Table 1: Optimization of the palladium-catalyzed three-component cross-coupling [Eq. (1)].[a]

Entry	Catalyst (0.05 equiv)	Ligand	TlOAc [equiv]	**2a** [equiv]	**3a** [equiv]	Solvent (MeCN:toluene)	**4a** [%][b]	**5a** [%]
1	$[Pd(dba)_2]$	dppf	0	2.0	2.0	1:1	22[c]	0
2	$[Pd(dba)_2]$	P(*o*-tolyl)$_3$	0	2.0	2.0	1:1	18[c]	0
3	$[Pd(dba)_2]$	P(*o*-tolyl)$_3$	1.2	2.0	2.0	1:1	79	0
4	$[Pd(dba)_2]$	–	1.2	2.0	2.0	1:1	85	0
5	$[Pd(dba)_2]$	–	1.2	2.0	2.0	100:0	51[d]	0
6	$[Pd(dba)_2]$	–	1.2	2.0	2.0	1:3	61[d]	0
7	**$[Pd(dba)_2]$**	–	**1.2**	**2.0**	**1.2**	**1:1**	**86**	**0**
8	$[Pd(dba)_2]$	–	1.2	1.5	1.2	1:1	83	0
9	$[Pd(dba)_2]$	–	0.5	2.0	1.2	1:1	68	0
10	$[Pd(dba)_2]$	–	1.2[e]	2.0	1.2	1:1	40	0

[a] All reactions were run using substrate **1a** (0.30 mmol), 5 mol% of $[Pd(dba)_2]$, 5 mol% of the ligand, if added, and 3.0 equiv of CsF in the solvent shown at 90 °C for 8 h, unless otherwise specified. The best result is highlighted in bold. [b] Yield of isolated product. [c] The reaction was run for 1 day. [d] Some starting material **1a** was left. [e] $AgNO_3$ was employed instead of TlOAc.

(Table 2, entry 4). Ethyl 4-bromobenzoate (**1b**) also affords good results in this process, providing a 79 % yield of **4a**, but only if P(*o*-tolyl)$_3$ was added (Table 2, entry 5). The reaction of ethyl 3-iodobenzoate (**1c**) gave **4g** as the only isomer (Table 2, entry 6). Other substrates bearing both electron-withdrawing and electron-donating groups, such as ketone, aldehyde, bromide, and methoxy groups, efficiently undergo this coupling process to generate good to excellent yields of the corresponding products (Table 2, entries 7–11). It is interesting to note that 4-iodobenzaldehyde (**1e**) affords a 91 % yield

Table 2: Palladium-catalyzed three-component cross-coupling.[a]

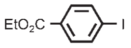
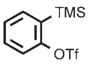
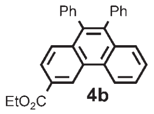
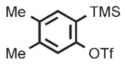
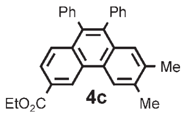
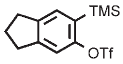
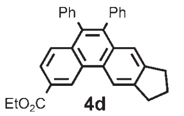
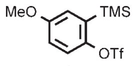
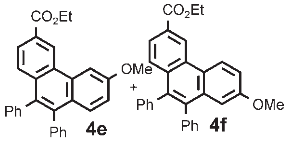
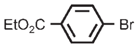
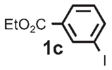
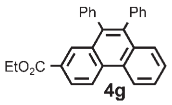
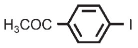
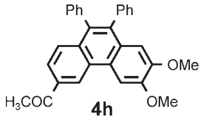
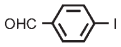
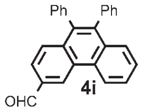
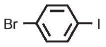
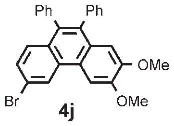
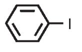
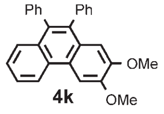
Entry	Substrate	Acetylene	Aryne precursor	Product(s)	Yield [%][b]
1	 **1a**	 **2a**	 **3b**	 **4b**	85
2	**1a**	**2a**	 **3c**	 **4c**	85
3	**1a**	**2a**	 **3d**	 **4d**	81
4	**1a**	**2a**	 **3e**	 **4e** + **4f**	80 (1:1)
5	 **1b**	**2a**	**3b**	**4b**	79[c]
6	 **1c**	**2a**	**3b**	 **4g**	76
7	 **1d**	**2a**	**3a**	 **4h**	91
8	 **1e**	**2a**	**3b**	 **4i**	91
9	 **1f**	**2a**	**3a**	 **4j**	78
10	 **1g**	**2a**	**3a**	 **4k**	75

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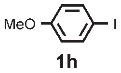
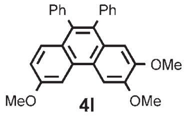
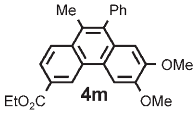
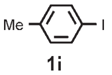
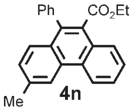
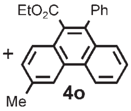
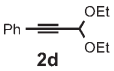
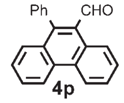
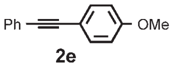
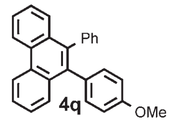
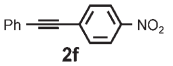
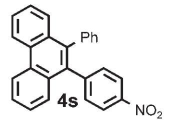
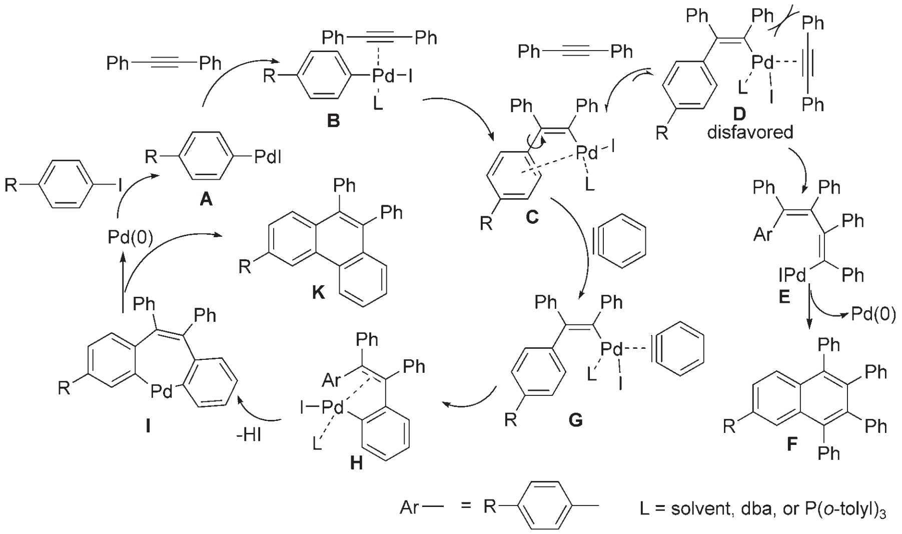
Table 1: (Continued)

Entry	Substrate	Acetylene	Aryne precursor	Product(s)	Yield [%][b]
11	 **1h**	**2a**	**3a**	 **4l**	49
12	**1a**	Ph—≡—Me **2b**	**3a**	 **4m**	56
13	 **1i**	Ph—≡—CO$_2$Et **2c**	**3b**	 **4n** +  **4o**	80 (1:6)
14	**1g**	 **2d**	**3b**	 **4p**	81
15	**1g**	 **2e**	**3b**	 **4q**	79
16	**1g**	 **2f**	**3b**	 **4s**	89

[a] All reactions were run using 0.30 mmol of organic halide, 0.60 mmol of alkyne, 0.36 mmol of aryne precursor, 5 mol% of [Pd(dba)$_2$], 0.36 mmol of TlOAc, and 3.0 equiv of CsF in 2.0 mL of MeCN and 2.0 mL of toluene at 90 °C for 8 h, unless otherwise specified. [b] Isolated yield. [c] 5 mol% of P(*o*-tolyl)$_3$ was added.

of the desired compound **4i** (Table 2, entry 8), because benzaldehyde can react with arynes directly under mild reaction conditions.[13] The presence of a bromide in the aryl iodide is readily tolerated under our reaction conditions, affording the corresponding cross-coupled product in 78% yield (Table 2, entry 9). Unsymmetrical acetylenes can also be employed in this process (Table 2, entries 12–16). When ethyl 4-iodobenzoate (**1a**) was allowed to react with 1-phenylpropyne (**2b**) and aryne precursor **3a**, only one isomeric phenanthrene was obtained in 56% yield (Table 2, entry 12). Similar regioselectivity for this alkyne has been observed in our earlier work.[14] Ethyl 3-phenylpropiolate (**2c**) afforded two isomers, **4n** and **4o**, in a 1:6 ratio (Table 2, entry 13). When phenylpropynal diethyl acetal (**2d**) was employed, the corresponding aldehyde was obtained in an 81% yield after work-up (Table 2, entry 14). Diphenyl acetylenes bearing either a methoxy (**2e**) or a nitro (**2f**) group also gives excellent results in this three-component coupling process, affording the corresponding products **4q** and **4s** in very high yields (Table 2, entries 15 and 16).

Based on work on the palladium-catalyzed carbopalladation of alkynes,[1] we propose the mechanism illustrated in Scheme 1 for this process, which consists of the following key steps: oxidative addition of the aryl halide to Pd^0 and subsequent carbopalladation of the internal alkyne to generate intermediate **C** or a five-membered ring palladacycle, which can either undergo carbopalladation of another alkyne



Scheme 1. Possible mechanism of the palladium-catalyzed three-component cross-coupling (see text for details).

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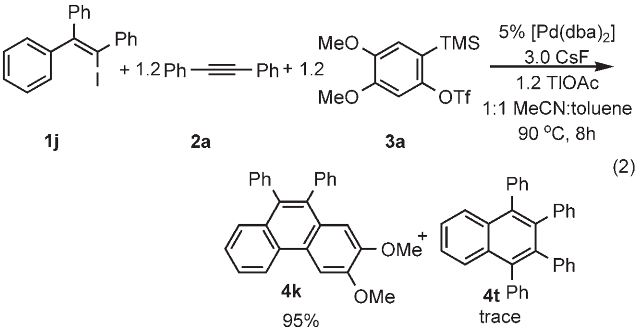
to generate intermediate **E**[2] or carbopalladation of the aryne to generate intermediate **H**. Considering the steric hindrance created when placing two phenyl groups next to each other in intermediate **D**, it seems reasonable that intermediate **C** would preferentially undergo carbopalladation of the less hindered aryne to generate **H**, which undergoes cyclization and reductive elimination to regenerate Pd^0 and the phenanthrene product **K**.

To obtain further evidence for this mechanism, we allowed vinylic halide **1j** to react with 1.2 equiv of diphenyl acetylene and 1.2 equiv of **3a** under our usual reaction conditions. Indeed, we obtained a 95 % yield of the product of carbopalladation of the aryne, **4k**, and only a trace amount of the product expected from carbopalladation of the diphenyl acetylene, **4t** [Eq. (2)].[15]



In summary, we have developed a novel, palladium-catalyzed, sequential, three-component cross-coupling of aryl halides with acetylenes and arynes, which affords excellent yields of substituted phenanthrenes. This process appears to involve the stepwise regio- and chemoselective palladium-catalyzed carbopalladation of an internal alkyne and subsequent carbopalladation of the aryne. This methodology provides an exceptionally efficient route to a wide variety of substituted polycyclic aromatic compounds from readily available starting materials. Further studies on the reaction mechanism and the scope of this synthesis of polycyclic aromatic hydrocarbons with regard to the use of various alkynes, alkenes and arynes are in progress.

Experimental Section

General procedure for the palladium-catalyzed, three-component cross-coupling: CsF (0.9 mmol) was added to a mixture of the haloarene (0.3 mmol), the alkyne (0.60 mmol), $[Pd(dba)_2]$ (0.015 mmol), TlOAc (0.36 mmol), and silylaryl triflate (0.36 mmol) in MeCN (2 mL) and toluene (2 mL). The reaction mixture was stirred at 90 °C for 8 h. The resulting reaction mixture was washed with brine (20 mL) and extracted with CH_2Cl_2 (20 mL) twice. The combined CH_2Cl_2 fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

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Keywords: alkynes · arynes · cross-coupling · palladium · polycycles

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