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Synthesis of Fused Polycyclic Aromatics by Palladium-Catalyzed Annulation of Arynes Using 2-Halobiaryls

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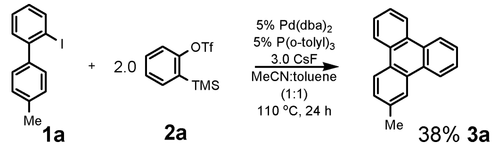
Transition metal-catalyzed annulation processes have proven very useful in organic synthesis.[1] Alkynes have been frequently used as substrates for Pd-catalyzed annulations with functionally substituted aryl and vinylic halides to synthesize a wide variety of carbocycles and heterocycles.[2] Arynes are very reactive substrates compared to ordinary alkynes, and they readily undergo cyclotrimerization under Pd catalysis to form polycyclic aromatic hydrocarbons.[3] The Pd-catalyzed cocyclotrimerizations of arynes with alkynes,[4] arynes with allylic halides,[4c,5] and arynes with alkynes and allylic halides[6] have also been reported. All examples of the carbopalladation of arynes reported so far have involved very stable π-allylpalladium intermediates.[4c,5,6] The inherent instability and high reactivity of aryl and vinylic palladium species obtained by oxidative addition to Pd(0) and the high reactivity and propensity of arynes to cyclotrimerize in the presence of Pd(0) do not bode well for annulation processes requiring these species to react with one another. Nevertheless, we have recently found that 2-halobenzaldehydes react with arynes generated from *o*-(trimethylsilyl)aryl triflates under Pd catalysis to generate fluoren-9-ones in high yields.[7] Herein, we wish to report a very efficient, high yielding synthesis of polycyclic aromatic hydrocarbons of potential interest as π-conjugated functional materials,[8] which involves the Pd-catalyzed annulation of arynes by aromatic and vinylic halides.

We first allowed 2-iodo-4′-methylbiphenyl (**1a**) to react with 2.0 equiv of *o*-(trimethylsilyl)phenyl triflate (**2a**), 5 mol % of Pd(dba)$_2$, 5 mol % of P(*o*-tolyl)$_3$, and 3.0 equiv of CsF in 2.0 mL of MeCN and 2.0 mL of toluene at 110 °C for 24 h. The desired annulation product **3a** was obtained in a 38% yield (eq 1; Table 1, entry 1). Subsequent work focused on optimization of this reaction (Table 1). During this process, we found that the slow generation of benzyne from treatment of **2a** with CsF is crucial to the success of this annulation chemistry (compare entries 1, 4, and 5). By increasing the amount of toluene in the solvent, we can slow the generation of benzyne and improve the yield of annulation product to a point. However, using toluene as the only solvent provided only a trace of arene **3a** (entry 6). So far, the optimal reaction conditions for this particular reaction are those shown in entry 5 in Table 1.



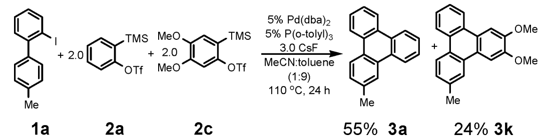
(1)

Table 1. Optimization of the Pd-Catalyzed Annulation of Benzyne (eq 1)[a]

entry	catalyst (0.05 equiv)	P(*o*-tolyl)$_3$ (equiv)	**2a** (equiv)	CsF (equiv)	solvent (MeCN/toluene)	% **3a**[b]
1	Pd(dba)$_2$	0.05	2.0	3.0	1:1	38
2	Pd(dba)$_2$	0.05	0.33	3.0	1:1	42
3	Pd(dba)$_2$	0.05	5.0	5.0	1:1	30
4	Pd(dba)$_2$	0.05	2.0	3.0	1:3	52
5	**Pd(dba)$_2$**	**0.05**	**2.0**	**3.0**	**1:9**	**92**
6	Pd(dba)$_2$	0.05	2.0	3.0	0:100	trace
7	Pd(dba)$_2$	0.10	2.0	3.0	1:9	82[c]
8	Pd(dba)$_2$	0.02	2.0	3.0	1:9	87[d]
9	Pd$_2$(dba)$_3$	0.05	2.0	3.0	1:9	73
10	Pd(PPh$_3$)$_4$	0	2.0	3.0	1:9	84[c]

[a] All reactions were run using substrate **1a** (0.30 mmol), 5 mol % of the Pd catalyst, 5 mol % of P(*o*-tolyl)$_3$, and the indicated amount of CsF in 4.0 mL of MeCN plus toluene at 110 °C for 24 h unless otherwise specified. [b] Isolated yield. [c] Approximately 5% of **1a** was recovered. [d] Pd(dba)$_2$ (0.02 equiv) was employed.

However, when the 4,5-dimethoxy- and 4,5-dimethyl-substituted aryne precursors **2c** and **2d** (see Table 2 for these structures) were employed to this annulation process, we needed to decrease the amount of toluene in order to obtain good yields of the corresponding annulation products. We believe that generation of the arynes is significantly slower using the aryne precursors **2c** and **2d**. To obtain evidence for this hypothesis, we allowed 2-iodo-4′-methylbiphenyl (**1a**) to react with 2.0 equiv of **2a** and 2.0 equiv of **2c** under our "optimal" reaction conditions. Indeed, we obtained a 55% yield of **3a** and only a 24% yield of **3k** (eq 2).

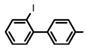
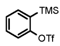
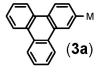
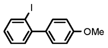
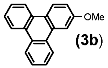
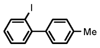
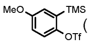
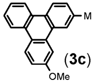
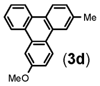
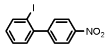
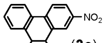
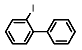
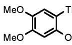
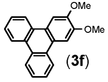
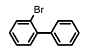
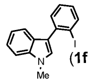
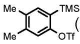
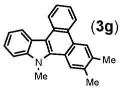
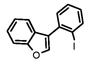
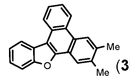
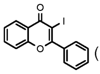
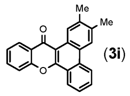
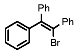
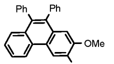


(2)

The scope and limitations of this Pd-catalyzed aryne annulation process were next examined using various aromatic and vinylic halides and aryne precursors. The results are summarized in Table 2. Substrates bearing both electron-donating and electron-withdrawing groups efficiently undergo this aryne annulation process to generate high yields of the corresponding polycyclic aromatics (Table 2, entries 1, 2, and 4). When the 4-methoxy-substituted aryne precursor **2b** was allowed to react with 2-iodo-4′-methylbiphenyl (**1a**), two isomers (**3c** and **3d**) were obtained in a 1:1 ratio, clearly suggesting the intermediacy of an aryne. Interestingly, relatively unreactive 2-bromobiphenyl also reacts well with aryne precursor **2c** to afford the corresponding annulation product in a 79% yield (entry 7). A number of heterocycles, including an indole, a benzofuran, and a chromone, have also successfully been employed in this process, affording excellent yields of the corresponding polycyclic materials (Table 2, entries 8−10). This latter chromone substrate is particularly interesting since it has been shown previously by us that this substrate reacts with diphenyl acetylene in the presence of a Pd catalyst to afford a furan product arising by alkyne insertion and attack of the resulting vinylpalladium intermediate on the carbonyl oxygen.[9] It is also particularly noteworthy that vinylic halides, such as chromone **1h** and the simple vinylic bromide **1i**, provide excellent yields of annulation products (entries 10 and 11).

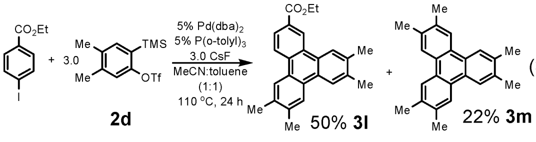
10.1021/ja055781o CCC: $30.25

Table 2. Pd-Catalyzed Annulation of Arynes[a]

entry	substrate	aryne precursor	product(s)	% yield[b]
1	 (**1a**)	 (**2a**)	 (**3a**)	92
2	 (**1b**)	**2a**	 (**3b**)	83
3	 (**1a**)	 (**2b**)	 (**3c**)  (**3d**)	86 (1:1)[c]
4	 (**1c**)	**2a**	 (**3e**)	75
5	 (**1d**)	 (**2c**)	 (**3f**)	94[d]
6	(**1d**)	**2b**	(**3b**)	83
7	 (**1e**)	**2c**	(**3f**)	79[d]
8	 (**1f**)	 (**2d**)	 (**3g**)	95[d]
9	 (**1g**)	**2d**	 (**3h**)	75[d]
10	 (**1h**)	**2d**	 (**3i**)	81[d]
11	 (**1i**)	**2c**	 (**3j**)	92[d]

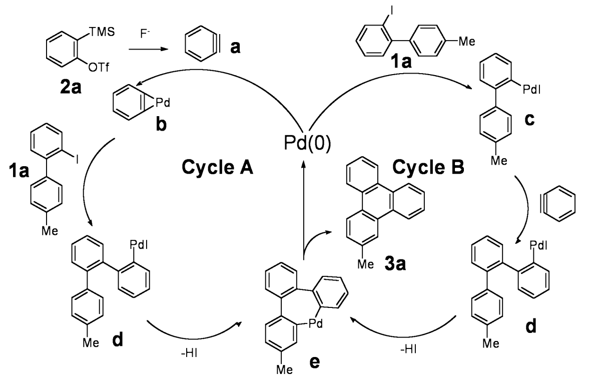
[a] All reactions were run using 0.30 mmol of organic halide, 0.6 mmol of aryne precursor, 5 mol % of Pd(dba)$_2$, 5 mol % of P(*o*-tolyl)$_3$, and 3.0 equiv of CsF in 4.0 mL of 1:9 MeCN:toluene at 110 °C for 24 h unless otherwise specified. [b] Isolated yield. [c] The ratio of products was determined by ^{1}H NMR spectral analysis. [d] MeCN:toluene = 1:3.

Our success using 2-halobiaryls to annulate arynes and previous Pd-catalyzed cyclotrimerizations suggested to us that we might also be able to generate polycyclic aromatics by the reaction of an aryl iodide and two arynes.[10] Indeed, the reaction of ethyl 4-iodobenzoate and 3 equiv of triflate **2d** afforded a 50% yield of arene **3l** alongside 22% of cyclotrimer **3m** (eq 3).

 (3)

Based on the known chemistry of arynes and previous work on the Pd-catalyzed annulation of alkynes,[2] we suggest two possible mechanisms (cycles **A** and **B**) to account for the present aryne annulation processes (Scheme 1). The main difference between these two mechanisms is the first Pd oxidative addition step. In cycle **A**, the Pd(0) complex initially undergoes oxidative cyclization with the aryne **a** to generate palladacycle **b**.[11] Subsequent reaction with **1a** affords intermediate **d** [or perhaps initially an organopalladium-(IV) intermediate], which undergoes intramolecular C−H activation to generate the palladacycle **e**. Subsequent reductive elimination yields the observed annulation product **3a** and regenerates the Pd(0) catalyst. Cycle **B** involves initial oxidative addition of 2-iodo-4′-methylbiphenyl (**1a**) to Pd(0) to generate arylpalladium intermediate **c**, which then reacts with the aryne to afford intermediate **d**, which goes on to product. The improbability of two very reactive intermediates (the aryne and the arylpalladium intermediate **c**) present in only very low concentrations at any one time reacting with each other to afford excellent yields of annulation products seems to favor the process described in cycle **A**, although the successful reaction of an aryl iodide and two arynes (eq 3) suggests that cycle **B** is also possible. Other mechanistic possibilities are also under consideration.

Scheme 1



In summary, we have developed a novel, high yielding synthesis of fused polycyclic aromatics, which involves the Pd-catalyzed carboannulation of arynes by aryl and vinylic halides. This methodology provides an exceptionally efficient route to a wide variety of substituted polycyclic aromatic and heteroaromatic compounds from readily available starting materials. Further studies on the reaction mechanism and the scope of the double aryne annulation process are in progress.

Acknowledgment. We are grateful to the National Science Foundation for partial support of this research. Thanks are also extended to Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donating the Pd salts, and Frontier Scientific Co. for donating the arylboronic acids used to prepare the starting materials.

Supporting Information Available: Detailed experimental procedure and characterization data for all previously unknown products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For the Pd-catalyzed formation of naphthalenes from an aryl halide and two alkynes, see: (a) Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 6836. (b) Wu, G.; Rheingold, A. L.; Geib, S. L.; Heck, R. F. *Organometallics* **1987**, *6*, 1941.
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JA055781O