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Biaryl Synthesis via Palladium-Catalyzed Aryne Multicomponent Coupling

Jaclyn L. Henderson,[†] Andrew S. Edwards,[‡] and Michael F. Greaney[*,†]

University of Edinburgh, School of Chemistry, Joseph Black Building, King's Buildings, West Mains Road, Edinburgh EH9 3JJ, U.K., and Organon Laboratories Ltd., Newhouse, Lanarkshire ML1 5SH, U.K.

michael.greaney@ed.ac.uk

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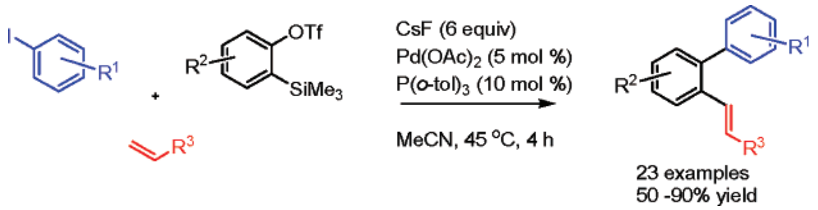
ABSTRACT



Aryl iodides have been introduced as electrophiles in the three-component Heck coupling of arynes. Following optimization studies to favor three- versus two-component coupling, the reaction proceeds in good yield to afford a variety of functionalized biaryls.

The biaryl motif occupies an iconic role in chemistry, being a key structural feature of natural products, novel optical and mechanical materials, drugs, agrochemicals, and other biologically active molecules. The assembly of functionalized biaryls using transition-metal-catalyzed tandem reactions, whereby multiple carbon−carbon or carbon−heteroatom bonds are formed in a single step, is a highly attractive approach to these valuable compounds that has widespread application.[1] The incorporation of arynes into such multicomponent coupling processes offers a unique entry point into functionalized aromatics and is a rapidly growing area of research.[2] Pioneering work from the Peréz/Guitián and Yamamoto groups used π-allyl palladium complexes, alkynes, and arynes to synthesize naphthalenes and phenanthrenes,[3,4] setting the stage for a series of developments in transition-metal-catalyzed aryne multicomponent couplings.[5−11] Until recently, a limitation of such aryne multicomponent coupling processes was the requirement for allyl halides as the electrophilic component. Work from our own laboratory

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[†] University of Edinburgh.
[‡] Organon Laboratories.

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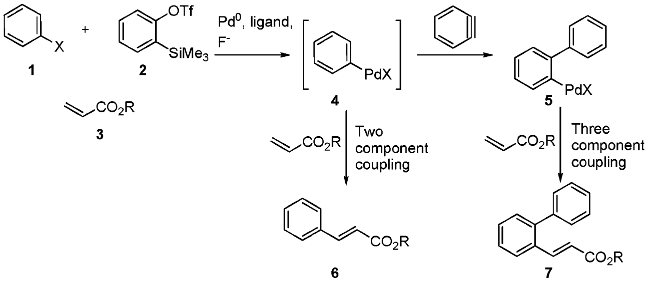
extended the reaction to include bromoacetates (heteroallyls) and benzyl bromides in a Heck reaction.[11] Biaryl synthesis via the use of aryl halide electrophiles, however, remains an unexplored area. The proposed reaction is set out in Scheme 1 for the insertion of benzyne, generated from the *O*-silyl aryl triflate **2**, into a Heck reaction to produce the biaryl **7**.

Scheme 1. Three-Component Coupling of Benzyne, Aryl Halide, and Heck Acceptor

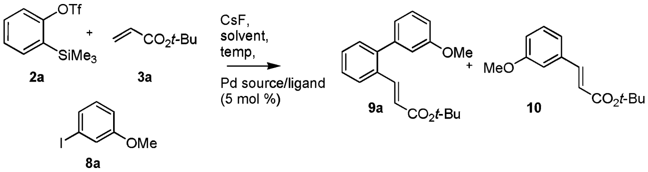


A major challenge concerns the *o*-arylpalladium(II) complex **4** generated after oxidative addition to the aryl halide **1**, being far more reactive than analogous benzyl or allylpalladium(II) species used with success in previous systems. Shepherding this reactive intermediate to undergo successful reaction with an aryne, another reactive intermediate, would seem to be a demanding requirement. An obvious side reaction is straight Heck coupling of **4** with acrylate to form the cinnamate derivative **6**. Selectivity for biaryl synthesis through three-component coupling (3CC, **7**) versus cinnamate formation through two-component coupling (2CC, **6**) is therefore expected to be a significant issue in this chemistry.

Two elegant solutions to multicomponent biaryl bond synthesis in this area have recently appeared: Larock described the three-component coupling of an aryl halide, an alkyne, and an aryne to produce polycyclic aromatics.[8d] Two-component coupling was not feasible with this monomer set, and bulky alkynes were used to prevent unwanted incorporation of multiple alkyne units. Cheng has reported the nickel-catalyzed union of arynes, acrylates, and boronic acids whereby the first two components undergo cyclization to a nickelacycle, followed by final biaryl bond formation.[7h] The formal carbopalladation of arynes with arylpalladium(II) intermediates, followed by intermolecular C−C bond formation with a third component (as shown in Scheme 1), has yet to be achieved and would represent a very direct and convenient method for accessing highly functionalized biaryls. Our previous experience in catalyst optimization for incorporating arynes into the Heck reaction suggested that it may be possible to engineer the reaction toward this goal.[11]

Initial studies on coupling *m*-iodoanisole (**8a**), benzyne, and *tert*-butyl acrylate (**3a**) produced low yields of the desired 3CC product **9a** (Table 1). Using a catalyst system that had been effective for benzyl bromide coupling ($Pd(OAc)_2$/dppe 5 mol %) in the presence of CsF in MeCN, we isolated the 2CC product **10** (74%), along with a very small amount (6%) of the desired 3CC biaryl **9a**. Yields were not improved using either aryl bromides or chlorides, both proving unproductive in the reaction.

Table 1. Three-Component Coupling of Aryne, Aryl Iodide, and Heck Acceptor; Optimization Data



entry	Pd/ligand	time (h)	temp (°C)	ratio **2**:**3**:**8**	yield of **9a**	yield of **10**
1	$Pd(OAc)_2$/dppe	48	50	1:1:1	6	74
2	$Pd(OAc)_2$/P(*o*-tol)$_3$	2	50	1:1:1	34	15
3	$Pd(OAc)_2$/P(*o*-tol)$_3$	4	50	2:1:1.5	55	36
4	$Pd(OAc)_2$/P(*t*-Bu)$_3$·HBF_4	4	50	2:1:1.5	48	29
5	$Pd(OAc)_2$/P(*o*-tol)$_3$	4	45	2:1:1.5	62	30

We began an optimization study, aiming to control the critical 3CC versus 2CC dichotomy.[12] An initial coarse catalyst screen identified $Pd(OAc)_2$/P(*o*-tol)$_3$ and a shortened reaction time of 2 h as producing **9a** as the major product, albeit in low overall yield. (Table 1, entry 2).

A key parameter proved to be the benzyne stoichiometry. Assuming a carbopalladation mechanism (vide infra), we reasoned that 3CC works through successful aryne interception of the arylpalladium intermediate formed from oxidative addition of Pd(0) with the aryl iodide. Clearly, an insufficient concentration of aryne present in the reaction medium will lead to high yields of unwanted 2CC. However, simply adding a large excess of **2** to the reaction in order to promote 3CC is not feasible, as excessive concentrations of benzyne lead to triphenylene formation via Pd-catalyzed trimerisation.[13] A balance between the two limiting stoichiometries was struck as **2a**:**3a**:**8a** = 2:1:1.5, with the aryne precursor **2** being added in two equal batches at $t = 0$ and $t = 1$ h (Table 1, entry 3). Although a slow, steady addition of benzyne via syringe pump could be envisioned to give further improvements, we found that this did not significantly enhance the production of **9a**. In our previous work we also found that the rate of benzyne generation could be controlled by solvent, and thus a selection of solvents and solvent mixtures were tested, none giving a better ratio or yield than 100% acetonitrile. Addition of Ag_2CO_3 to the reaction did not have any affect on the yield, ruling out any inhibitory role for the iodide anion. After some additional optimization of reaction temperature we could isolate the desired 3CC product **9a** in a good 62% yield using the final conditions shown in entry 5, Table 1. Additional fine-tuning of the catalyst system did not reveal a superior combination to $Pd(OAc)_2$/P(*o*-tol)$_3$, although $Pd(OAc)_2$/P(*t*-Bu)$_3$·HBF_4 proved similarly effective.

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(12) See Supporting Information.

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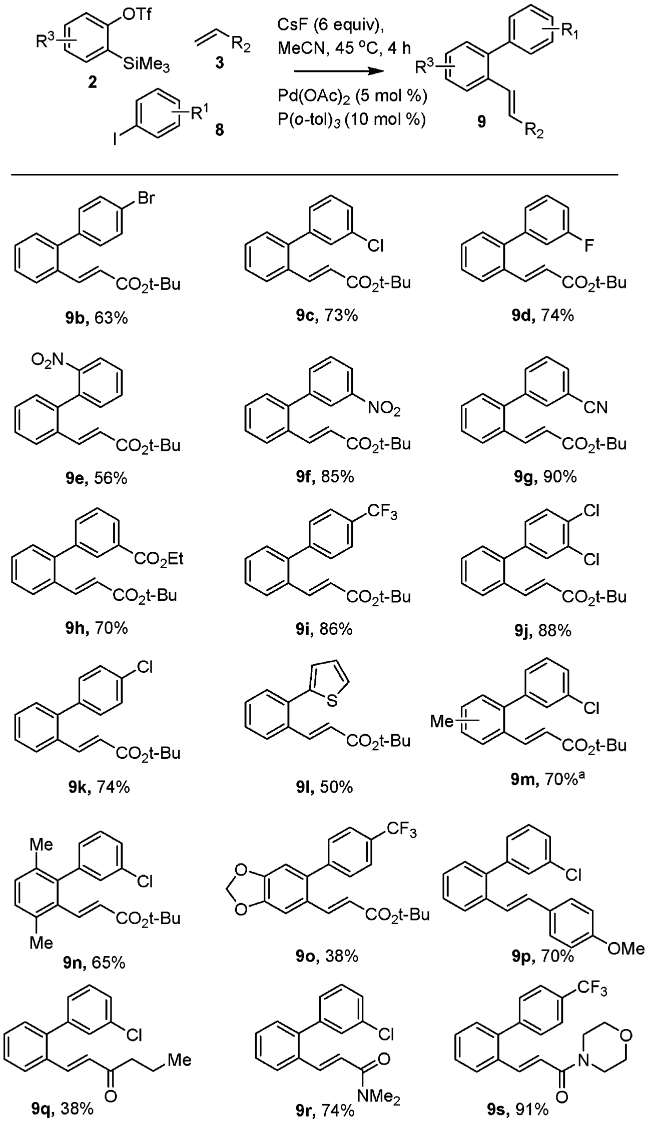
The scope and limitations of this palladium-catalyzed 3CC process were next examined, and we were pleased to observe that the reaction conditions had good generality and could be applied to a wide variety of aryl iodides for the synthesis of diverse biaryls. The results are summarized in Scheme 2.

Scheme 2. 3CC of Aryl Iodides, Arynes and Heck Acceptors



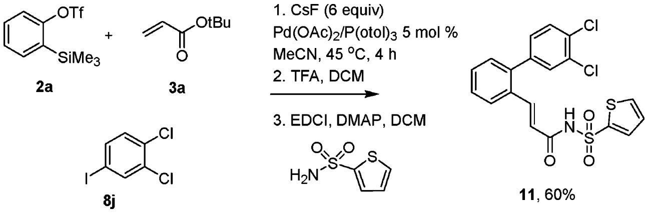
[a] Product isolated as a 1:1 mixture of 3- and 4-methyl substituted regioisomers.

Yields were good for aryl iodides having halogenated functionality in the *meta* (**9c**, **9d**, **9j**; 73−88%) and *para* (**9b** and **9k**, 63% and 74%) position of the aryl iodide component. The production of the bromo-compound **9b** is noteworthy as it provides a facile handle for further elaboration of the biaryl ring system. Electron-poor aryl iodides were particularly effective, producing some of the highest yields of 3CC, e.g., the *m*-nitro and cyano compounds **9f** and **9g** in 85% and 90% yields and the *p*-trifluoromethyl compound **9i** in 86% yield. 2CC was not a noticeable problem for this set of substrates, in hindsight suggesting that we chose a difficult aryl iodide in **8a** for initial studies. In point of fact, the reaction proved less tolerant than previous systems of electron-rich electrophilic components, with the 2- and 4-iodomethoxy benzenes failing to produce isolable yields of 3CC products.

The aryne component was varied to include the 1,4-dimethyl, 5-methyl, and 4,5-methylenedioxy functionalities. The methyl-substituted arynes worked well (**9m** and **9n**, 70% and 65% yield), with the formation of **9m** as a 1:1 mixture of regioisomeric biaryls supporting the intermediacy of benzyne in the coupling process. Methylenedioxy aryne was less effective, producing **9o** in a low 38% yield. It is likely that focused optimization would improve 3CC of this electron-rich aryne precursor. The Heck acceptor could be altered to an enamide without problems, producing the dimethyl amide and morpholine amide compounds **9r** and **9s** in high yields. *p*-Methoxystyrene was also effective as the nucleophilic component, affording the novel tricyclic arene **9p** in a good 70% yield. It is also worth noting that no products of either palladium migration[14] or benzyne/benzyne/acrylate trimerization[6b] were observed during the course of these investigations.

To demonstrate the power of the biaryl 3CC for the rapid assembly of biologically active compounds, we synthesized the prostenoid EP3 receptor antagonist **11** recently reported by Merck-Frosst (Scheme 3).[15] 3CC of 1,2-dichloro-4-iodobenzene with *tert*-butyl acrylate and benzyne proceeded in an excellent 88% yield. Subsequent ester hydrolysis and amide bond formation with thiophene-2-sulfonamide then gave the EP3 antagonist in an overall yield of 60% for the three steps.

Scheme 3. 3CC for the Synthesis of EP_3 Receptor Antagonist



Three possible mechanistic pathways for the reaction are set out in Scheme 4. Pathways A and B involve Pd^0 complexing benzyne as a first step, either in concert with the acrylate to form a palladacycle **12** (path A),[6b] or directly to form the η^2-metallocyclopropene **15** (path B).[8a−c] Path C shows the conventional carbopalladation of the aryne with the oxidative addition product **18**, followed by a Heck reaction.

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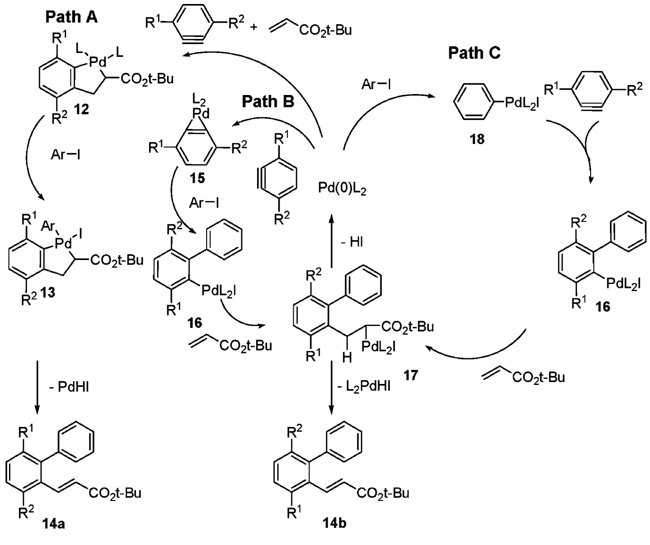
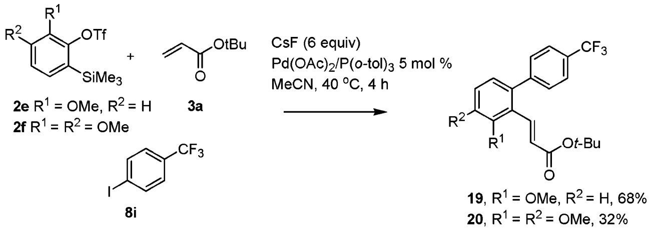
Scheme 4. Possible Three-Component Coupling Mechanisms



Addition of aryl iodides to palladacycles analogous to **12** is precedented in the norbornene shuttle work of Catellani and Lautens and implies the formation of a Pd(IV) species **13**.[16] Subsequent reductive elimination/β-hydride elimination processes furnish the biaryl **14a**. A similar addition of Ar-I is required for Path B, producing the biaryl σ-palladium species **16**, which undergoes Heck reaction as in path C. The biaryl **14b** is identical to **14a** for the symmetrical arynes employed in our studies thus far. If an unsymmetrical aryne is used, however, then **14a** and **14b** will be isomeric. We have investigated this possibility via the 3CC of 3-methoxy and 3,4-dimethoxy benzyne precursors **2e** and **2f** (Scheme 5). The exclusive formation of products **19** and **20**, corresponding to the **14b** connectivity, allow us to rule out the cycloisomerization pathway A. Palladacycle formation from 3-methoxy benzyne would be expected to be highly selective for intermediate **13** having $R^1 = OMe$ and $R^2 = H$ (Scheme 3), due to the methoxy group providing inductive[17] and dative[7h,8b] stabilization to the neighboring palladium atom, subsequently forming product **14a**.

Scheme 5. 3CC of *o*-Methoxy-arynes



Carbopalladation mechanism C has been implicated in several aryne multicomponent couplings.[4,5,7b,d,8a−c,9,11] Studies from Larock have established that stoichiometric amounts of a preformed arylpalladium complex will produce 2CC products with benzyne in a related reaction (albeit in lower yield), giving support to the mechanism.[8c]

Our own stoichiometric studies have been inconclusive in the aryl iodide series, with the preformed (p-$CF_3C_6H_4$)-$PdI(PPh_3)_2$ complex providing the three-component-coupled product **9i** in a low 27% yield after extended reaction times of 24 h. The benzyl complex $BnPdCl(PPh_3)_2$ was more effective, however, giving a 40% yield of the analogous phenylbenzyl 3CC product. Given sufficient lifetime in solution of complex **18**, the carbopalladation−Heck pathway C appears reasonable. In the catalytic manifold, however, we would favor the alternative pathway B. We have observed that straight 2CC between aryl iodide and acrylate is sluggish under the optimized 3CC reaction conditions, giving yields of 16−22% when no aryne is present over the 4 h reaction time course.[12] If oxidative addition−Heck reaction is slow, it seems unlikely that oxidative addition−aryne carbopalladation−Heck reaction would be substantially faster, suggesting that the aryne is having a significant effect on the catalytic pathway in regard to 2CC versus 3CC coupling. Whether this is through the formation of the η^2-metallocyclopropene **15** or through another pathway will form the basis of our future mechanistic studies in this area.

In conclusion, we have introduced aryl iodides to the 3CC insertion of arynes into the Heck reaction for the synthesis of highly functionalized biaryl compounds. The reaction is effective across a range of structures in each component, producing diverse, multifunctional arenes in a single step from commercially available starting materials.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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