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Three-Component Coupling of Benzyne: Domino Intermolecular Carbopalladation

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The introduction of 2-(trimethylsilyl)phenyl triflate, **1**, as a benzyne precursor that operates under mild reaction conditions has enabled the development of a variety of transition-metal-mediated aryne carbon−carbon bond forming processes.[1−3] Intermolecular carbopalladation, in particular, stands out as a powerful methodology for the construction of diverse 1,2-functionalized arenes through multicomponent coupling processes (Scheme 1). Treatment of **1** with a fluoride source, usually CsF in acetonitrile, generates benzyne which can undergo carbopalladation with an organopalladium species to produce the arylpalladium intermediate **3**. Coupling with a third component gives the 1,2-functionalized benzene, **4**.[4]

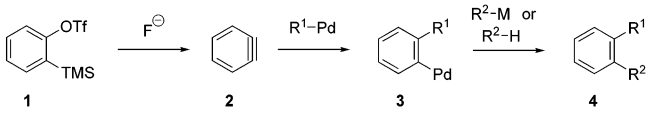
Pioneering work from Yamamoto established that π-allylpalladium complexes were particularly effective for intermolecular carbopalladation of benzyne and could be employed in three-component coupling (TCC) with alkynes to produce naphthalenes or with a second benzyne equivalent to give phenanthrenes.[5] Subsequently, Cheng demonstrated that initial carbopalladation with π-allylpalladium chlorides could be followed by a second intermolecular Stille coupling with alkynyl or allenyl stannanes to produce 1-allyl-2-alkynylbenzenes[6] or a second Suzuki coupling to give 1-allyl-2-arylbenzenes.[7] Larock has described the synthesis of polycyclic aromatics using the two-component coupling of benzyne with 2-halobiaryls.[8]

We are interested in developing new multicomponent benzyne carbopalladation processes for the rapid assembly of diverse 1,2-functionalized arenes. We wish to address two key points: first, the current lack of versatility in the electrophile component used in existing benzyne TCC reactions, where allyl chlorides predominate; and second, the introduction of new reactions to the second carbon−carbon bond forming step that can better exploit the vast array of nucleophiles available for palladium cross-coupling. This paper presents our preliminary results in the area, describing our development of a new benzyne TCC using carbopalladation followed by an intermolecular Heck reaction.

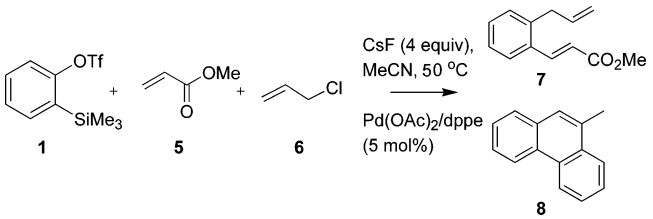
We began by studying the feasibility of the Heck reaction in the TCC of allyl chloride, benzyne, and methyl acrylate using CsF in MeCN, as shown in Scheme 2. Initial screening of catalysts revealed the formation of the phenanthrene product **8**[5c] at the expense of TCC product **7** to be a significant problem. For example, the Pd(OAc)$_2$/dppe catalyst system produced **7** in 28% yield along with 58% of **8** as the major product (based on benzyne).

The competitive formation of phenanthrenes is a major obstacle to the development of any palladium-mediated benzyne TCC strategy involving alkene components. To reduce the amount of **8** formed, we attempted to slow the rate of benzyne generation by switching to a solvent with reduced CsF solubility. A solvent screen established DME as the best choice, minimizing the formation of **8** and producing the TCC product **7** in an encouraging 50% yield.

Scheme 1. Carbopalladative Three-Component Coupling of Benzyne



Scheme 2. Three-Component Coupling of Benzyne, Allyl Chloride, and Methyl Acrylate[a]



[a] Ratio of reactants **1**:**5**:**6** = 1:2.4:1.2.

It was envisaged that changing the allyl chloride for a heteroallyl halide, such as methyl bromoacetate, might improve the efficiency of the domino carbopalladative TCC further, as benzyne/benzyne/allyl-derived phenanthrene side product formation would no longer be feasible. A brief catalyst screen proved this to be the case, with benzyne, methyl bromoacetate, and methyl acrylate undergoing clean reaction at 50 °C in DME using 5 mol % of PdCl$_2$dppf to give the TCC product **12a** in 75% yield as the only benzyne-derived product (Chart 1).

The reaction proved effective for a small selection of acrylates as well as for a methyl-substituted benzyne precursor **9**. Here, the isolation of TCC product **12c** as a 1:1 mixture of regioisomers supports the intermediacy of benzyne in the TCC mechanism, as the unsymmetrical aryne undergoes nonselective carbopalladation to produce equal amounts of regioisomeric *o*-palladium intermediates for Heck reaction.

Encouraged by the success of the double carbopalladation reaction in TCC, we decided to introduce benzyl halides to the reaction. The resulting phenylbenzyl products would contain a versatile enoate group for further manipulation in addition to displaying a variety of aryl functionality derived from commercially available benzyl halides. Application of the optimized TCC reaction conditions developed previously was not immediately successful. Treatment of **1**, *tert*-butyl acrylate, and benzyl bromide with Pd(dppf)Cl$_2$ and CsF in DME produced the desired TCC benzylphenyl product **15** in low yields with comparable amounts of a phenanthrene derived from benzyne/benzyne/acrylate insertion as a difficult to remove contaminant (Chart 2). A screen of catalyst systems showed the bidentate ligands dppb, dppp, and xantphos to be ineffective when used in combination with Pd(OAc)$_2$. The combination of dppe and Pd(OAc)$_2$, however, proved efficacious, providing adduct **15a** in 65% yield with much reduced levels of the phenanthrene byproduct. It proved convenient to isolate the TCC

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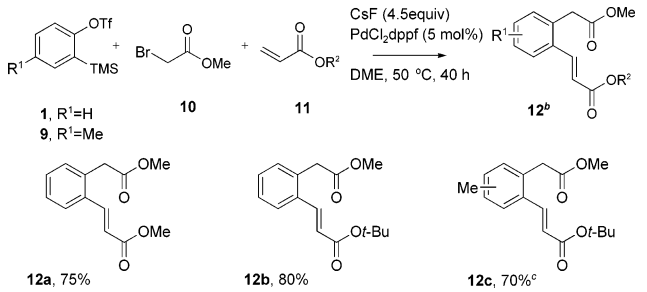
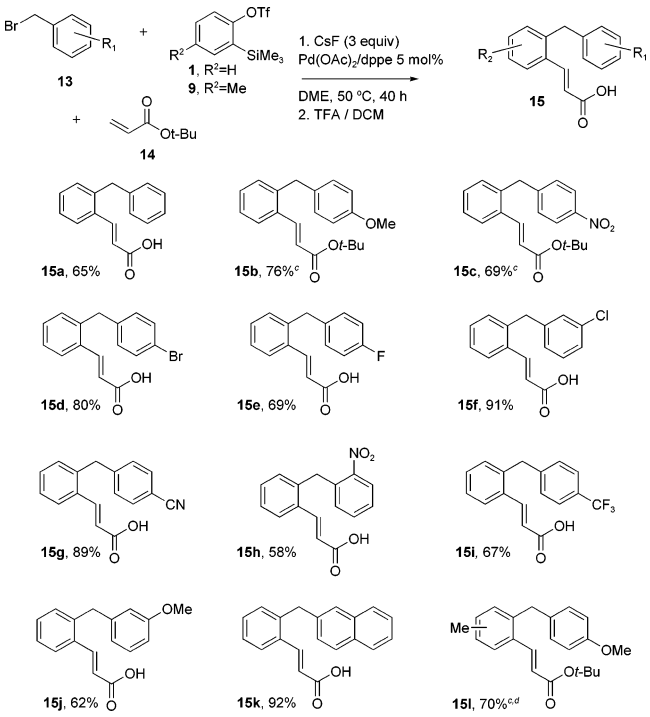
Chart 1. Three-Component Coupling of Benzyne, Methyl Bromoacetate, and an Acrylate[a]



[a] Ratio of reactants **1**:**10**:**11** = 1.5:1:1.5. [b]Isolated yields. [c]Isolated as a 1:1 mixture of 4- and 5-methyl-substituted regioisomers.

Chart 2. Three-Component Coupling of Benzyl Bromides, Benzyne, and *tert*-Butyl Acrylate[a,b]

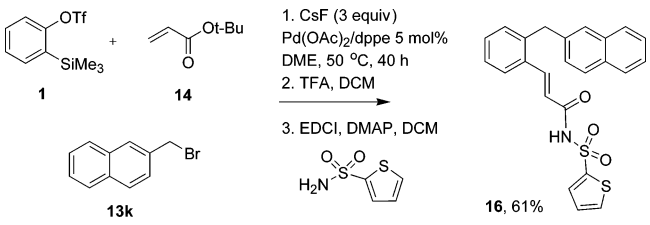


[a] Ratio of reactants **1**:**13**:**14** = 1:1.5:1. [b]Isolated yields quoted over two steps. [c]Isolated yield over one step (TFA hydrolysis not carried out). [d]Product isolated as a 1:1 mixture of 3- and 4-methyl-substituted regioisomers.

product **15a** as the carboxylic acid, following treatment of the crude reaction mixture with TFA.

We were pleased to observe that the $Pd(OAc)_2$/dppe catalyst system proved to be general, and a variety of commercially available benzyl bromides were successfully incorporated into the TCC with benzyne and *tert*-butyl acrylate in good to excellent yield (Chart 2).[9] Electron-withdrawing and -donating groups on the benzyl bromide component are equally well-tolerated, and no complications arise from aryl halide functionality. The TCC works for *o*-, *m*-, and *p*-substituted benzyl bromides, with the *o*-nitrobenzyl bromide **13h** being the least efficient substrate (58% yield) and the naphthyl bromide **13k** being the best (92% yield). As with the bromoacetate system, we used the unsymmetrical benzyne precursor **9** to support the intermediacy of the aryne (product **15l** isolated as a 1:1 mixture of regioisomers).

Scheme 3



To demonstrate the power of the carbopalladation TCC for the rapid assembly of biologically active compounds, we synthesized the prostenoid EP_3 receptor antagonist **16** recently reported by Merck (Scheme 3).[10] TCC of naphthyl bromide **13k** with *tert*-butyl acrylate and benzyne proceeded in excellent yield, affording the acid **15k** following treatment of the crude reaction mixture with TFA. Coupling to thiophene-2-sulfonamide then gave the EP_3 antagonist in an overall yield of 61% for the three steps.

In conclusion, we have developed a new TCC reaction of benzyne based upon two successive intermolecular carbopalladation reactions. The methodology presents alternatives to simple allyl chlorides as the initial carbopalladation electrophile, introduces the Heck reaction to benzyne TCC, and provides rapid and efficient access to diverse 1,2-functionalized arenes. The use of benzyl bromides as coupling partners is notable, providing a quick and easy route to various benzylphenyl compounds of the type used in medicinal chemistry screening programs. Work is underway on the application of this methodology to the synthesis of biologically active target molecules.

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Supporting Information Available: Experimental procedures, catalyst screening details, 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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(9) The direct Heck reaction between the electrophile and acrylate was never observed in this or the preceding systems. A control experiment using **13b** and **14** under TCC reaction conditions in the absence of **1** produced no isolatable amounts of Heck coupled product.

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