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Palladium-Catalyzed Domino Heck/Aryne Carbopalladation/C−H Functionalization: Synthesis of Heterocycle-Fused 9,10-Dihydrophenanthrenes

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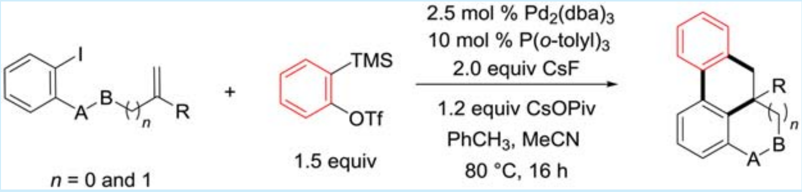
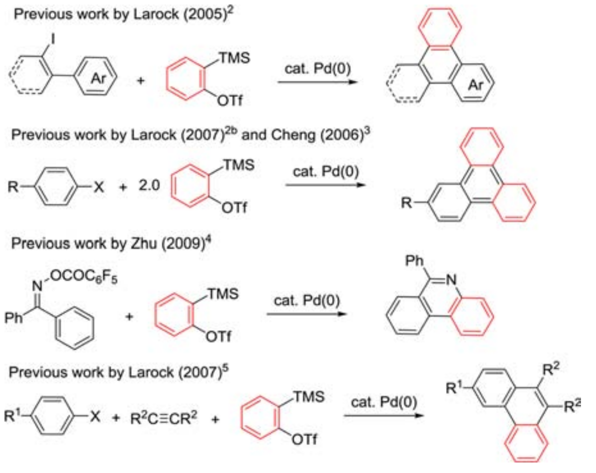
Supporting Information



ABSTRACT: A novel palladium-catalyzed domino Heck/aryne carbopalladation/C−H functionalization reaction using in situ generated arynes has been developed in which three new C−C bonds and a carbon quaternary center are formed. This methodology affords moderate to excellent yields of heterocycle-fused 9,10-dihydrophenanthrenes.

Arynes generated from the corresponding *o*-(trimethylsilyl)-aryl triflates have emerged as powerful synthons in organic synthesis.[1] Aryne annulation reactions with intramolecular C−H functionalization can be a powerful method for the synthesis of polycyclic compounds (Scheme 1). Larock reported the first palladium-catalyzed aryl halide annulation of arynes to generate fused polycyclic aromatics.[2] Aryl halide annulation of two arynes for the synthesis of triphenylenes has been reported by both Larock[2b] and Cheng.[3] Zhu has reported the palladium-catalyzed annulation of acyloximes with arynes to synthesize phenanthridines.[4] An interesting three-component cross-coupling reaction of aryl halides, internal alkynes, and arynes to form phenanthrenes has been reported by Larock.[5] That process involves the controlled insertion of an alkyne and an aryne into an arylpalladium complex. Until now, most of the reported aryne annulation processes have involved $C(sp^2)-Pd^{II}$ intermediates generated in situ by oxidative addition of Pd(0) to an aryl/vinylic halide. Reactions involving arynes and $C(sp^3)-Pd^{II}$ complexes remain unexploited.

Scheme 1. Aryne Annulation Reactions with Intramolecular C−H Functionalization



σ-Alkyl palladium(II) halide intermediates with no *syn-β*-hydrogen, which are generated by the intramolecular Heck reaction of 1,1′-disubstituted olefins, have been extensively explored in domino processes, since such intermediates can undergo trapping to form new bonds[6] and are often very efficient in constructing benzo-fused saturated heterocycles with a carbon quaternary center.[7] The transient neopentyl-type σ-Pd(II) complex can also undergo annulation to construct complex cyclic ring systems. The synthesis of polycyclic fused indolines and spiroindolines using diaziridinones has been reported by Shi.[8] Lautens reported an efficient synthesis of the dihydrodibenzoisochromene framework with two C−H functionalizations.[9]

Our interest in aryne chemistry and annulation chemistry prompted us to study the annulation reaction of arynes through in situ generated neopentyl-type σ Pd(II) complexes.[10] During the course of our study, García-López[11a] and Lautens[11b] reported the synthesis of spirobiaryls by trapping σ-alkylpalladium(II) intermediates with arynes (Scheme 2). Herein, we disclose our study of a palladium-catalyzed domino Heck/aryne carbopalladation/C−H functionalization reaction, which affords moderate to excellent yields of heterocycle-fused 9,10-dihydrophenan-

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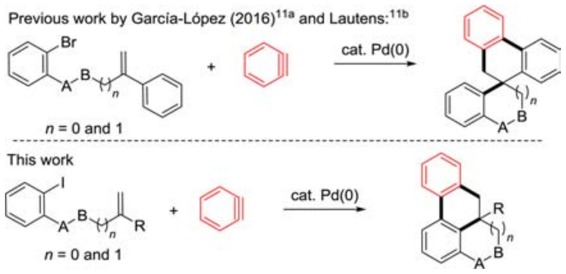
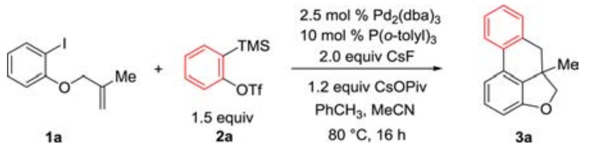
Scheme 2. Annulation Reactions with Intramolecular C−H Functionalization Involving a C(sp^3)−Pd^{II} Intermediate



threnes with high level of efficiency (Scheme 2).[12] This is a new strategy for the synthesis of polycyclic structures.

We commenced our studies by examining the effects of various reaction parameters on the yield of this palladium-catalyzed domino reaction using 1-iodo-2-[(2-methylallyl)oxy)]benzene (**1a**) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) (Table 1). Under the best conditions described in Table 1, the reaction afforded a 77% isolated yield of dihydrophenanthrofuran **3a** by employing 0.30 mmol of **1a**, 1.5 equiv of **2a**, 2.0 equiv of CsF, 1.2 equiv of CsOPiv, 2.5 mol % of $Pd_2(dba)_3$, and 10 mol % of P(*o*-tolyl)$_3$ in toluene/acetonitrile (v/v = 1:1, 3 mL) at 80 °C for 16 h. Using CsOPiv as the base is crucial for this palladium-catalyzed domino reaction, since other inorganic and organic bases afforded very poor yields of product **3a** (entries 2−6).[13] Bidentate phosphine ligands such as BINAP, dppm, and dppf afforded a moderate yield of **3a** (entries 7−9). Changing the ratio of toluene to acetonitrile led to lower yield, which implicated the rate of aryne generation was important (entries 10 and 11). Increasing the amount of the benzyne precursor **2a** to 2.0 equiv did not increase the yield of product **3a** (entry 12). Performing the reaction at 100 or 60 °C led to lower yields (entries 13 and 14). A lower loading of the catalyst (1.25 mol %) and ligand (5 mol %) still produced the desired product **3a** in a 52% yield (entry 15).

Table 1. Optimization of the Reaction Conditions[a]



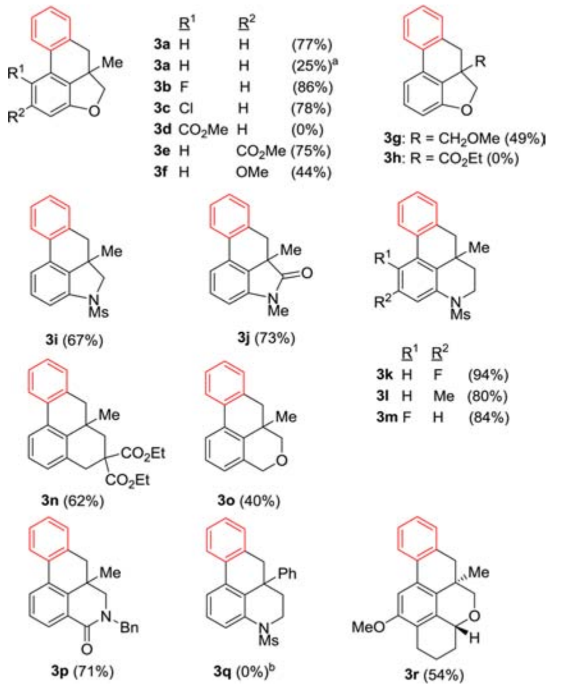
entry	change from standard conditions	yield[b] (%)
1	none	77
2	Et_3N instead of CsOPiv	8
3	NaOAc instead of CsOPiv	8
4	K_2CO_3 instead of CsOPiv	26
5	Cs_2CO_3 instead of CsOPiv	21
6	CsF instead of CsOPiv	7
7	5 mol % BINAP instead of 10 mol % P(*o*-tolyl)$_3$	50[c]
8	5 mol % dppm instead of 10 mol % P(*o*-tolyl)$_3$	34
9	5 mol % $PdCl_2$(dppf) instead of 2.5 mol % $Pd_2(dba)_3$ and 10 mol % P(*o*-tolyl)$_3$	66
10	$PhCH_3$ (2.0 mL) and MeCN (1.0 mL)	36
11	$PhCH_3$ (1.0 mL) and MeCN (2.0 mL)	52
12	2.0 equiv of **2a**	74
13	60 °C instead of 80 °C	38[d]
14	100 °C instead of 80 °C	56
15	1.25 mol % $Pd_2(dba)_3$ and 5 mol % P(*o*-tolyl)$_3$	52

[a] Representative procedure: **1a** (0.30 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, $Pd_2(dba)_3$, ligand, CsF, base, and the solvent were placed in a 4 dram vial, and the reaction was stirred at the desired temperature for 14 h. [b] Isolated yields. [c] 21% of **1a** was recovered. [d] 13% of **1a** was recovered.

The model reaction was also tested under the reaction conditions used in García-López's synthesis of spirobiaryls (10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, 3.0 equiv of CsF in toluene/acetonitrile at 90 °C for 16 h), which afforded only about 10% of the desired product **3a**.

The scope and limitations of this palladium-catalyzed aryne annulation process were next examined (Scheme 3). Under our standard conditions, aryl iodide **1a** with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) as the benzyne precursor gave a 77% isolated yield of the desired product **3a**. The less reactive bromo analogue of **1a** (1-bromo-2-((2-methylallyl)oxy)-benzene) could be used in this process but produced **3a** in a lower yield of 25%. While the presence of F or Cl at the *meta*-position of the aryl iodide is well tolerated (**3b** and **3c**), a more bulky ester group at the *meta*-position of the aryl iodide did not afford the desired product **3d**. This might be attributed to the increased steric hindrance in the C−H functionalization step (see Scheme 5). The chloro group in **3c** could be a handle for further elaboration.[14] The presence of an electron-withdrawing group or -donating group at the *para*-position of aryl iodide is tolerated (**3e** and **3f**). In general, electron-withdrawing substituents on the aryl iodide result in higher yields compared to their electron-donating counterparts, which implicates a base-induced palladation in the C−H functionalization step.[15] The substrate with a *β*-OMe group underwent the reaction smoothly to furnish the corresponding product **3g** in a 49% yield. Unfortunately, a substrate with a conjugated carbon−carbon double bond did not

Scheme 3. Scope of the Aryl Halide Bearing the Alkene Moiety

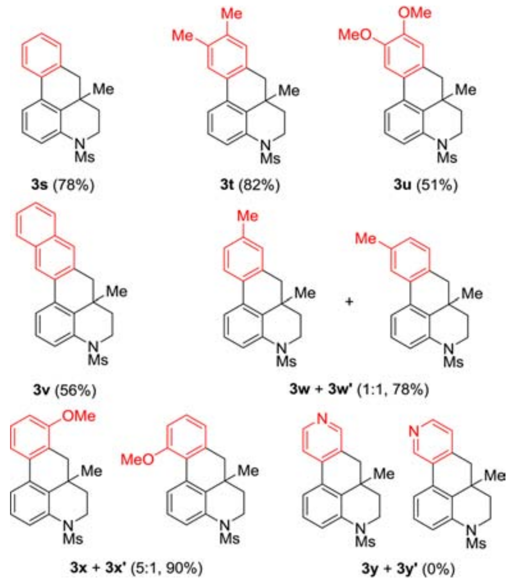


[a] 1-Bromo-2-((2-methylallyl)oxy)benzene was used. [b] 50% of *N*-(2-iodophenyl)-*N*-(3-phenylbut-3-en-1-yl)methanesulfonamide (**1q**) was recovered, and 10% of 1′-(methylsulfonyl)-2′,3′-dihydro-1′*H*,10*H*-spiro[phenanthrene-9,4′-quinoline] was obtained.

afford the product **3h**. Other five-membered ring products, such as tetrahydronaphthoindole **3i** and dihydronaphthoindolone **3j**, can be efficiently prepared in good yields. The versatility of this domino reaction was further demonstrated by the synthesis of six-membered ring products. This process has successfully been applied in the synthesis of tetrahydronaphthoquinoline **3k**, tetrahydrobenzoanthracene **3l**, dihydrodibenzoisochromene **3m**, and tetrahydrodibenzoisoquinolinone **3n**. A substrate with a phenyl group on the carbon−carbon double bond did not afford product **3q**, and 50% of the starting material **1q** was recovered. A small amount of the spirobiaryl product as in García-López's chemistry was observed. Thus, our conditions and those of García-López complement each other. The fused 9,10-dihydrophenanthrene **3r** was obtained in good yield, which further illustrates the efficiency of this Pd-catalyzed domino reaction for the construction of complex heterocycles.

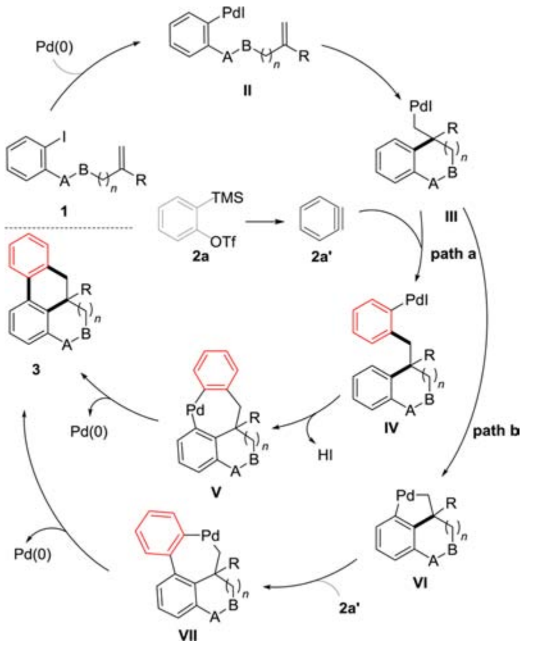
The scope of this palladium-catalyzed domino reaction was also established by examining the reaction of *N*-(2-iodophenyl)-*N*-(3-methylbut-3-en-1-yl)methanesulfonamide (**1s**) and various *o*-silylaryl triflates (Scheme 4). Silylaryl triflates with two methyl or two methoxy groups furnished the desired tetrahydronaphthoquinolines **3t** and **3u** in good yields. Additionally, the symmetrical naphthalyne furnished the expected product **3v** in a 56% yield. The reaction of an unsymmetrically substituted silylaryl triflate, namely the reaction of 4-methylbenzyne, took place smoothly, giving a 1:1 mixture of regioisomers **3w** and **3w′** in a 78% overall yield. A reaction with 3-methoxybenzyne afforded a 5:1 mixture of the two possible isomers **3x** and **3x′** in an excellent overall yield. The regioselectivity of the aryne is consistent with previous observations in the study of spirobiaryl synthesis, which also involves a C(sp^3)−Pd^{II} intermediate.[11] The reaction of 3,4-pyridyne from Garg's 3,4-pyridine precursor[16] did not afford any of the desired products due to its instability at the elevated temperature.[10b]

Scheme 4. Scope of the Silylaryl Triflates



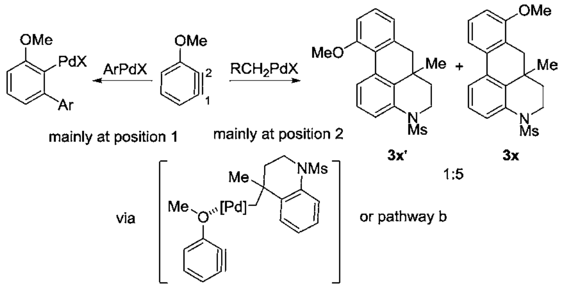
We propose the mechanisms illustrated in Scheme 5 for this domino process (ligands are omitted for simplicity). Pd(0) adds oxidatively to the aryl halide **1** to generate the arylpalladium(II) intermediate **II**, which in turn undergoes 5-*exo-trig* (n = 0) or 6-*exo-trig* (n = 1) cyclization to form neopentyl-type σ Pd(II) complex **III**. In pathway a, the aryne intermediate **2a′** generated in situ from aryne precursor **2a** undergoes carbopalladation with C(sp^3)−Pd^{II} intermediate **III** to afford arylpalladium intermediate **IV**. The C−H functionalization via base-induced palladation generates palladacycle **V**, which undergoes reductive elimination to regenerate Pd(0) and the product **3**. In pathway b, neopentyl-type σ Pd(II) complex **III** performs C−H functionalization first to generate palladacycle **VI**, followed by aryne carbopalladation and reductive elimination to form product **3**. Although the related five-membered palladacycle [Pd(CH$_2$CMe$_2$C$_6$H$_4$)] has been reported,[17] the ring strain arising from a five−five ring conjunction (when n = 0) in intermediate **VI** makes this less likely to happen. Thus, pathway a is favored at the time being, but we can not exclude the possibility of pathway b.

Scheme 5. Proposed Mechanism



The carbopalladation of 3-methoxybenzyne by ArPdX mainly occurred at position 1, which is more reactive than position 2 (Scheme 6).[10b,18] This observation is explained by the charge-controlled model, steric model,[19] and more recently, the aryne distortion model.[20] If this domino reaction indeed proceeds through pathway a, the reverse regioselectivity is an indication of a difference between C(sp^3)−Pd^{II} and C(sp^2)−Pd^{II} intermediates in their reactions with arynes. The methoxy group might serve as a directing group by coordination with a σ-alkyl Pd(II) complex. The regioselectivity can also be explained by pathway b,

Scheme 6. Regioselectivity of Aryne Carbopalladation



in which the carbopalladation occurs at the more reactive position 1 of the 3-methoxyaryne.[21]

In summary, we have developed a novel palladium-catalyzed domino Heck/aryne carbopalladation/C−H functionalization reaction in which three new C−C bonds and a carbon quaternary center are formed. This aryne annulation reaction is an efficient and convergent method for the synthesis of heterocycle-fused 9,10-dihydrophenanthrenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03833.

Detailed experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all previously unknown products (PDF)

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Notes

The authors declare no competing financial interest.

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